Lone Atrial Fibrillation

Toward a Cure – Volume IV

By

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Introduction

Since the publication of *Lone Atrial Fibrillation: Towards a Cure* in December 2002 research into atrial fibrillation has grown exponentially. This emphasis on AF research is not coincidental. Recent studies conclude that more than 5.5 million Americans and Europeans now suffer from atrial fibrillation and that the incidence of the disorder increased by 300% between 1986 and 1996. Another study reached the sobering conclusion that one out of every four men and women over the age of 55 years will develop atrial fibrillation during their lifetime. It is estimated that about 20% of all AF patients have lone atrial fibrillation, that is, atrial fibrillation without any underlying heart disease. Truly an epidemic of enormous proportions.

Over the past year **The AFIB Report** has kept subscribers informed of new developments in atrial fibrillation research as reported in the leading journals such as *Journal of Cardiovascular Electrophysiology, Pacing and Clinical Electrophysiology, Circulation*, etc. The subjects covered in our journal summaries range from details of the latest ablation procedures, their outcome and potential complications, to the safety and efficacy of antiarrhythmic drugs. The latest insights into the mechanism of atrial fibrillation as well as important information about stroke risk and prevention are also covered. In addition, *The AFIB Report* has, in detail, covered the results of our most recent LAF survey dealing with the effectiveness of ablation and surgical procedures for eliminating LAF. Numerous afibbers who have found ways of controlling their afib have shared their experience for the benefit of others and specific approaches to AF management and stroke prevention have been thoroughly researched and the results disseminated in *The AFIB Report*.

Truly, the 2006 issues of *The AFIB Report* are a treasure trove of immensely valuable information. Unfortunately the vast volume of data contained in the newsletter makes it very difficult to quickly and conveniently locate a particular piece of information. My new book ***Lone Atrial Fibrillation: Toward a Cure – Volume IV***, hopefully, solves this problem. Its 230 pages contain all the information published in the 2006 issues arranged in logical sections. The comprehensive subject index makes it easy to find the elusive, but important information you know is there – somewhere! In addition, the wealth of important new LAF information contained in *Lone Atrial Fibrillation: Toward a Cure – Volume IV* makes it an ideal and essential companion to *Lone Atrial Fibrillation: Towards a Cure* and *Lone Atrial Fibrillation: Toward A Cure – Volumes II and III*.

This book would not have been possible without the whole-hearted support of my wife Judi who was instrumental in seeing it come to fruition. Without her word processing skills, editing advice, and encouragement I couldn't have accomplished it. Anthony Bestwick, Michael Coleman, and David Booth deserve my special thanks for taking the time to put their own personal afib experience into words for others to share. Also my heartfelt thanks to Patrick Chambers for his excellent article *LAF vs AF: Shape Matters* and to Jackie Burgess for her concise summary and observations from the October 2005 Atrial Fibrillation Summit. My gratitude also to the many afibbers who participated in the 2006 Ablation/Maze Survey and thereby helped other afibbers find a way to manage their condition. Finally, a huge thank you to the many enthusiastic and caring contributors to the Bulletin Board and to the subscribers to *The AFIB Report* without whose support my research would not have been possible.

Hans R. Larsen
Victoria, BC, Canada
April 2007

AFIB Journeys

My AF Story – Or How it Zaps You When You're Not Looking

Anthony Bestwick

My story starts some 12 years ago in those heady days when the world didn't seem to have quite so many problems as it does now. I was a 50 year old silversmith with my own small business in a small town on the coast of Devon, in the south west peninsula of the United Kingdom, and spent my leisure time collecting rocks, exploring the old tin and copper mines of Devon and Cornwall, playing the melodeon and bodhran in the local pubs, and flying small aeroplanes from nearby Dunkeswell aerodrome, a one-time US Navy wartime bomber base flying Liberators across the Bay of Biscay.

I had been divorced for a few years after a long marriage and was, emotionally, on the fragile side of neutral, though I doubt I would have agreed with that if you'd mentioned it then! As is the way of these things I'd eventually found myself with a new girlfriend and that, dear reader, is where my story really starts.

We split up. Nothing really unusual about that, although it was as always painful, but this split coincided with one of my frequent bright (or, in this case, not-so-bright) ideas. I'd lose weight. Go on a diet. Not eat very much. In fact, not eat at all. I certainly was not overweight at 13 stone (184Lb) but summer was coming and I was determined to lose a few pounds to be able to get into my summer shorts.

Now, I don't know whether you've tried not eating but I don't recommend it. In my case it brought on quite persistent pangs of hunger and a distant rumbling from down-under which, try as I might, I could not ignore. I cast around for some way to lessen the noise and my gaze fell on ..... the coffee maker, with its usual welcoming smile, in the corner of my office-cum-workshop.

And so it came to pass that, in the same week as the emotionally draining split from my girlfriend, I came to live on strong black coffee – as black as the night and as strong as the bond between miser and dollar. The coffee machine happily worked overtime, spewing out great mugs of the stuff in response to my ever-increasing hunger pangs until I looked more like a coffee picker than an English silversmith.

By the third day I began to suffer bouts of what I fondly thought was indigestion, a general rumbling and banging inside which reminded me

very much of an old car I once had. I ignored it, and carried on with the coffee therapy but by the following Monday, a full seven days after the start of my crash diet, I felt unwell enough to take the monumental plunge of visiting my local doctor, to complain about my indigestion.

I duly arrived at the appointed hour, expecting – indeed resigned – to be given some indigestion medicine and be sent on my way with a flea in my ear for wasting his time. But no! 'Come in' he said 'you don't look terribly well'. 'No' I said 'I think I've overdosed on coffee and it's given me indigestion'. 'Well' he said 'let's just listen to your …… Nurse!' he shouted 'get the ECG equipment ready'.

And that, fellow afibber, was the first time I knew I'd got a problem!

To cut a long story short, my ECG showed the usual and I was whisked off to the hospital in nearby Exeter, a rather grand place smelling of disinfectant and full of ill people. I say 'whisked' but in the absence of any form of public transport including an ambulance I was apologetically asked if I would make my own way there, which I did.

On arrival at the hospital I was taken to a ward, made a fuss of, given a loading dose of sotalol and asked to get into bed. Now, I have to confess that I don't like hospitals. Even less do I like wearing pyjamas or getting into bed in the daytime – and anyway, I only had indigestion – so this now became a battle of wills. 'I'm not taking my jeans off' I said. 'You must' they said. 'I won't' I said, 'I'm not ill'. Well, we eventually compromised. My jeans didn't come off but I did eventually get into bed, though only when it got dark. They didn't really mind. They were very good.

I was hooked up to a variety of machinery and told that cardio-reversion was going to be done the following day but, during the night, my heart went back into sinus and the following day, to my great relief, I was given my freedom and let out. Before leaving I'd had a long chat with a heart specialist who told me that I had had Atrial Fibrillation, probably caused by too much caffeine, and that it would probably now be a feature in my life. 'One more thing' he said 'You'd better tell the Civil Aviation Authority about this'.

I did, and they very unhelpfully suspended my flying medical certificate. That was the first impact that AF had on my life. There were to be others.

After discharge from hospital I had, as a follow-up, the usual thyroid test and echo-cardiogram, all of which proved to be normal. Slowly, I reverted back to my usual way of life and resumed 'business as usual' apart from the flying, which I really missed. Months went by, and I started to think

that it had all been a bad dream. I began to rediscover my love of strong black coffee when suddenly, out of the blue, wham! AF again.

This time the episode did not last long, just a few hours, but I knew then that the original 'happening' had not been a one-off and that AF was probably here to stay.

In those far off days ablation was very much in its infancy in the UK and only done for flutter – to some extent it still is even today, as we shall see – so the solution put forward by medical opinion in the form of the local doctor offered nothing more than pills. True, there was available an intriguing variety of pills and as many as I could eat, but pills are something else I don't much care for. I decided this was not an option.

Months passed with a few minor episodes of AF, all of which reverted to sinus within a fairly short time but which nevertheless made me very conscious that 'I had a problem'. As these months passed I became more and more determined that the solution – for me – would be to beat this thing on my own terms. I began to realize that, to some extent and in some people, AF is life-style problem and so I determined to find out, as far as was possible, what might be triggering these episodes in me.

First, my coffee machine was consigned to history, though I subsequently bought another when I realized you can make thoroughly decent decaffeinated coffee which tastes just as good as the stuff with caffeine! I had always taken several grams of vitamin C a day but I now included a whole range of other vitamins and health supplements and made serious efforts to determine what part of my daily life might be causing my AF.

Eventually, through trial and error, I found that caffeine, emotional sadness, hard cheese, bananas and sleeping on my left side were the main triggers for me. Alcohol, to my delight and the relief of the world's wine growers, has never been a trigger but I know that it is for many. I only ever drink red wine in moderation and the occasional beer when playing my melodeon (though not at the same time) so it may be that spirits do not agree with me, but red wine and the odd beer certainly do.

Time passed and I formed a folk band with a banjo-playing friend, and then a delightful lady who sings and plays the guitar also joined the band. Dear reader, the course of true love ran true, and this lady has now been my wife for the past 6 years.

Happiness does I'm sure lessen the effects and frequency of AF but, to counter that, the taxman certainly does not so I continued to have the odd episode of AF as the months and years went by. And then, a dear old friend died.

This friend was rather old and had been the best friend of my own dear father, who had died when I was 13, so there was a great bond of fondness between us, reinforced by the fact that he did not himself have any family. By this time my wife and I had moved from Devon to South West Wales, where we now live, so as soon as we heard the sad news we drove the 200 miles to where he lived and started to make arrangements for his funeral.

By the time I arrived, I was in the grip of the worst AF episode I had ever had. My heart was fluttering, racing and banging like an old tin can, I had no discernable pulse, and I was as white as a sheet and feeling pretty low. There was no alternative but to carry on with the arrangements and attend the funeral but after that, in company with good friends and with a glass of red wine, I began to feel better and as I did so my heart reverted to sinus. But it was a terrible shock and what has since followed, and the subsequent operation to cure my AF, is all as a direct result of knowing that extreme sadness was always going to trigger AF no matter how well I looked after myself.

Months passed without any further serious episodes, but in my mind was the certainty that sooner or later this thing would rise up and strike me again. I'd heard of catheter ablation and had been told that it offered the best chance of a cure, so I made real efforts to see whether this could be done for me 'free' on our National Health Service. I say 'free' but of course although the NHS is free at the point of contact we do pay for it through our taxes, and in my lifetime I must have paid for the operation many times over.

Although kind and considerate and ready to offer a whole warehouse full of pills the NHS – bless them, they only get 90 thousand million pounds sterling a year in funding – simply could not offer me catheter RF ablation for AF. They might, just might, have been able to offer flutter ablation if I'd waited until I was dead, but what would be the point of that when I needed AF ablation and wanted to get on with my life now?

The next avenue to explore was to see if the operation could be done privately within the United Kingdom at reasonable cost and in a reasonable time scale. Nope! £15,000 and a long wait if you were lucky enough to find someone needing to practice the operation, in an environment where AF ablation is a pretty new science. First of all, £15,000 was simply off the board – I don't actually believe there's that much money in the world – and secondly, I'd prefer not to be somebody else's learning curve.

So, what to do? The usual well-known centers of medical excellence such as the USA, Canada, France and Germany were all very expensive or still learning how to respond to emails. It seemed I had reached an impasse and was doomed! And then, like a sunbeam bursting through clouds, I discovered India!

India, as many will know, is a land of gentle friendly intelligent people. It is a pragmatic land, an emerging world power and – more importantly – the world's largest democracy. A land of the future certainly, but not, in my mind, a world centre of excellence for medical procedures.

How wrong I was! A few simple clicks on my computer and the amazing medical facilities of India lay before my eyes - and there it was! At the Escorts Heart Institute and Research Centre (EHIRC) in New Delhi I could get RF catheter ablation for AF, including carto-mapping, for the all-inclusive price of £2,300.

I contacted the Taj Medical Group within the UK, who can facilitate arrangements for medical procedures in India, and within days I had made the decision to go to EHIRC and have the full works. Arrangements were soon made and within weeks of discovering the medical facilities of India I found myself at Heathrow Airport in London going through the interminable – *Take your belt off. Take your keys out. No, don't let your trousers fall down, shuffle through that archway* – but necessary security checks before boarding an overnight flight to New Delhi with the excellent Virgin Atlantic.

There can be few finer things than to arrive in India, bleary-eyed from an overnight flight, in the morning rush-hour! Well, perhaps a few but the first thing I saw on leaving the baggage reclaim, apart from a few welcoming flies and the lovely sunshine, was a smiling young Indian holding up a board upon which was written my name in very large letters. Yes, EHIRC had sent a chauffeured car, and the head of their hospitality department, to whisk me off to the hospital! Despite the traffic and the odd cow we arrived and, after a few formalities, I was shown to a spotless room with panoramic views of New Delhi - and a daunting array of medical machinery on the wall above the bed.

I had many visitors during my stay, and without any doubt, received VIP treatment from everybody. Tests started almost immediately, and I was wheeled down to various laboratories over the next two days for a variety of procedures which were designed to diagnose my condition exactly and determine the treatment required. My only real problem was with the enormous baggy white draw-string two-part smock everyone has to wear, which needs a masters in cunning if you are to avoid it falling down to

your ankles every few minutes. I never quite got the hang of it. They probably still talk about it.

The tests, apart from one, were all quite reasonable and very thorough. I was always wheeled to these tests by two or three impossibly young but excellently trained nurses, one to push, one to make sure I didn't fall out and probably one to make sure my smock stayed up. The hospital was very busy – they do over 500 catheter ablations per year plus every other form of heart surgery including pediatric – and was highly efficient and superbly well organized.

India, as you will know, is a land of Tigers and Elephants. The Tigers tend to snack off people so are avoided but Elephants are very popular. They come in all sizes, are usually grey and most of them have trunks. I say 'most' because some must be missing their trunks because that, dear reader, is what they put down your throat when they do the transesophageal echocardiogram - and they must be from fully-grown Elephants, too.

My surgeon was the brilliant Dr. Balbir Singh, principal consultant cardiologist working with the world famous heart surgeon Dr. Naresh Trehan and, all tests being OK, my operation was scheduled for the following day. Everything went well. The AF was induced, carto-mapped and ablated, and after 4 hours I was wheeled into catheter recovery for a very welcome cup of tea. The operation itself consists of feeding 4 catheters up through veins in your groin into your heart, which sounds scary but is in fact quite OK. The surgeon then induces the AF and maps the electrical conductivity of the heart to determine the areas to ablate, and then zaps these areas with RF energy.

The hospital was superbly equipped and the surgeons, doctors and nurses are clearly as good as any in the world. The food was excellent, with a choice of continental or Indian cuisine (I had fish curry every day. I'd go back just for that!) and the care and cleanliness is exceptional, the hospital priding itself on a 0.3% infection rate.

Following my ablation I had a 24-hour Holter monitoring and then, when that was complete and the results checked I was pronounced free to leave. I could have stayed on in India – the Taj Mahal is not far way – and the hospital would gladly have arranged things for me but my wife was at home in Wales so I was keen to return. Normally, when I find myself in a land of sunshine and about to board a plane to return to rain and grey skies, I have to be forced aboard and chained to my seat but this time the allure of my wife made me happy to skip aboard for the 8 hour flight to London and the inevitable rain. I had been in India altogether for 5 days, but it seemed rather longer.

As I write this it is now just three months since I returned from India. I was told by Dr. Balbir Singh that the heart can take this long to heal and settle down, but I have experienced no problems so far and I am confident, as is Dr. Balbir, that my AF really has been ablated. Time will tell, but as each day passes my confidence increases.

Did I make the right decision to go to India? Definitely. Five days in an excellent air-conditioned room with panoramic views, satellite TV, Internet facilities and all the tests and treatment for £2,300 sterling (less than 4,000 USD) was simply amazing. Would I recommend the medical facilities of India to anyone else who needs treatment that they cannot get or cannot afford in the affluent west? Certainly, without doubt. There are many world centers of excellence in India offering almost every medical procedure.

As far as one can enjoy these things, I did enjoy my trip to India. From the excellent Virgin Atlantic flight to the friendliness and competence of the hospital staff, from the delicious food to the friendships made, from the sunshine to the allure of a new and exciting land – yes, I did enjoy it. But I will never be able to look at an Elephant in quite the same way again and I will never, but never again, wear a huge and baggy white two-piece draw-string smock with a mind of its own!

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P.S. Happily, I continue to enjoy my afib-free life.

How Suffering and Curing Atrial Fibrillation Changed My Life

Michael Coleman

The two visits for my Executive Health Check, one in September 2002, and the next September 2003, could not have presented more surprising or contrasting advice on my heart function.

Having maintained a regular diet/exercise regime all my adult life, including competing in long "community" running events and ocean swims, I watched on with near smugness as my doctor tore off the cardiogram, knowingly surveyed the pattern and would pronounce, year after year "this Michael, is a heart that functions in the top 5% for your age, you have been blessed with a "Ferrari of an engine"!

In September of 2003 at the age of 42 all this veered wildly onto a totally unfamiliar road. After feeling uncharacteristically light-headed and fatigued following several exercise sessions, my vigilant gym manager suggested that I promptly see my doctor. The same doctor's cardiogram revealed that my heart was in atrial fibrillation…I needed to see a cardiologist fast!!

The early days with AF were a mixture of disbelief that my previously bullet proof heart function had gone awry, with general confidence that a cure would be quickly found, and life as usual, would return.

The "cure" presented to me by my cardiologist was to medicate the heart into finding it's former silky rhythm. I was given a 60% chance that the prescribed beta-blocker would fix the AF. When, after 3 weeks, this medication had no effect, I had an electro cardioversion, which held me in normal sinus rhythm for just 2 days. I was also told from this point that I needed to try other medications and that there could be some side effects.

Though every body is different, in my case I was hit hard by the drug protocol, and in hindsight should have listened much more carefully to my protesting body… instead I embarked on an increasingly desperate quest to find normal sinus rhythm, with drugs as my only "hope" for a cure. This quest saw me anxiously consuming increasingly high doses of Sotalol, Amiodarone, Tambocor, Quinidine, Metoprolol, Isoptin, and Rythmodan.

Daily life began to become more challenging, with the combination of an average 5 hrs/day in AF, as well as a constant run of side effects from the medications. Lethargy would descend over me, insomnia, headaches, weight loss, and most debilitating of all, depression, littered my life.

My former rigorous exercise regime was pared back to shuffling my local streets… wondering "why me"?

After 12 months (August 2004) I underwent a flutter ablation in Sydney. This, combined with a huge (450 mg) daily dose of Tambocor, kept me in NSR for about 1 month. The resumption of AF coincided with the sad passing of my dear Dad. I can't help think, in hindsight, that the "heartbreak" I felt at the time translated literally to my physiology.

When we are sick or suffering disease, every person has, in trying to rebalance their health, a threshold of questioning whether their path is correct. The turning point for me was sitting, half asleep in front of my family doctor, desperately seeking yet one more medication solution. "We can try something experimental, he offered. You can take 2 different anti-arrhythmic drugs, as well as a beta-blocker. This should cover ALL electrical paths, and stop the AF". I pondered this strategy, quietly desperate, "What's the worst case scenario doc?" I asked. "Heart block", he replied, "where you heart stops and you lose consciousness". I thanked him for his time and walked out of his surgery. Knowing that he was recommending I experiment out of desperation with even more drugs – effectively putting my hand up and saying. "Body I have no respect for your myriad of miraculous healing systems, and opt to become a western medicine junkie". I knew this was just a "band aid" approach, and vowed to start looking at more natural alternatives.

About this time, I discovered Hans Larsen's research, and was extremely impressed by his drive to assist others dealing with AF. I subscribed to his newsletter, made contact with nutrient specialist Dr Michael Lam in California, and commenced a new "hope inspiring" nutrient protocol, in concert with visits to an excellent Sydney-based naturopath, Catherine Pritchard.

Sadly, solving the AF riddle with nutrients alone was never possible in my case, for every time I reduced the drug dosage, my AF would "spike", and I never had the nerve to withstand 24/7 AF, while waiting to see if the nutrients alone would cure me.

In the background, my Sydney cardiologist, a caring guy with a big reputation, Dr David Whalley, was increasingly blunt about my best possibility of a cure. He was suggesting pulmonary vein ablation (with

about a 40% chance of a cure, [ie. no AF, no drugs, 6 months after procedure]).

It was Hans' research into global PVI success rates that convinced me to finally try and get off the medication merry go round, and have the ablation procedure– in France. My confidence was further buoyed, when Hans reported on his web site that he had travelled to France for a completely successful cure.

I booked my PVI and flights for my wife and 2 children, just days later, in May 2005. Every aspect of my dealing with the Hospital Haut Leveque, Bordeaux, was impressive. The French have constructed a formidably efficient, professional healing system.

During the 7 months waiting time, I admit trying desperately, to find an alternative cure, which would allow me to defer or avoid what I had convinced myself was "playing my last card". I was still telling friends as close as 2 weeks from departure for France, that I thought I was "stable" enough to delay the procedure. A positive aspect of my nutrient protocol was that I was so full of vitamins that my immune system had been failsafe, for 24 months I had no illness of any sort. Interestingly, the mounting stress of the journey, as a family, "into the French unknown", crashed into me just 1 week prior to departure, when I contracted a nasty respiratory virus spending the first 4 days in years in bed. I recall corresponding 2 days before leaving Australia, with Dr Pierre Jais (who replied patiently to a stream of my emails over 6 months) at the Bordeaux Hospital, and telling him of my concern for undergoing surgery, after being belted by a virus…"You should come, Mr. Coleman, we can wait until your chance of success is best".

In reality, the PVI procedure is now so regularly performed in Bordeaux, that significant risk of injury/mortality has practically been eliminated. The "last card" I had imagined, was a classic case of patient anxiety.

Prof Michel Haissaguerre had been "talked up" to legendary status by Hans Larsen and even my own Australian cardiologist, but meeting him and witnessing the total passion and confidence with which he operates, took my estimation to a new level. He is an exceptional electrophysiologist. I noticed very soon after my first meeting with Michel, that he moved at most times around the hospital with a small army of supporters, all seeming to hang on every word of his medical judgment and experience.

For my first procedure, December 12, 2005, I was surprised at the resources involved – 5 EPs, (including three professors of cardiology and 2 nurses). The procedure consisted of a PVI of all 4 veins. An ablation

line was performed at the roof of the left atrium connecting both superior pulmonary veins and terminating AF.

I was carefully monitored for several days in Bordeaux, which has some of the best post-operative care for this procedure, worldwide. Just as well, as in my case, one of the 4 veins had become conductive…. and this necessitated a second procedure 3 days after the first. I was naturally quite apprehensive about needing a second procedure so soon after the first, but Prof Michel soon allayed my fears with his absolute conviction that my history of numerous 24 hr+ episodes of AF, pre-determined that I would be a "difficult" case to cure.

The second procedure consisted of a second line performed at the left isthmus between the left inferior pulmonary vein and mitral annulus resulting in a complete bi-directional block. All in all, in Prof Haissaguerre's words, "The ablation equivalent of the surgical maze procedure…"

The care shown by all at Haut Leveque was exceptional. I felt like I was being treated as though I was "family" to Prof Haissaguerre and his team. I had my own young family with me (my beloved Jacqueline refused point blank to have it any other way), and an abiding memory of Prof Michel, is the way in which he reacted to meeting my 9-year-old son, Callum.

Cal was clearly overwhelmed by the sight of me returning from the first procedure, a little pale and lethargic. Prof Haissaguerre quickly assumed the role of 'surrogate dad', put a comforting arm around my son, and led him quietly to the telemetry station, to show and explain to him the new sinus rhythm of my heart. This man is a completely empathetic, dedicated practitioner!

The day after the second procedure, Prof Michel confidently informed my wife that I may well have small episodes of AF and extra "ectopic" beats for the next months as the scar tissue formed new electrical pathways, but … "he is cured". He said this with such confident emphasis that I remember feeling quietly elated that my suffering would soon be over.

Two other doctors deserve special mention, being Dr Pierre Jais, and Prof Prash Sanders. They were completely involved in thoroughly addressing my myriad of questions pre and post procedures, and struck me as both being "at the top of their game".

Haissaguerre's prediction of slight AF and ectopic beats was very accurate. I had several 15-min AF episodes during the ensuing 3 weeks. In addition, extra beats have occurred spasmodically right up until the last

few days. As any doctor will advise, "ectopic" heartbeats are quite normal.

However, it is now over 4.5 months since I have experienced an AF episode, and following an extremely slow medication withdrawal, I am practically "drug free" (1.25mg bisoprolol/day) I am also back in training for a 10km community fun run in 8 weeks time.

My life has changed irrevocably to being far more mindful of "living in the moment". Mainly, I have discovered this simple joy through the practice of daily relaxation meditation. I am a more compassionate, and grateful, human being than ever. I have never felt physically or mentally tougher in my entire life. I have a new depth of love and respect for my wife Jacqueline and children Kaitlin and Callum. We did it as a team!

The journey through AF has given me all of these insights. If I can help alleviate the torment of just one person's AF through this story, I will be content. I sincerely hope that my story provides further belief to those who need it.

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My life continues happily with normal sinus rhythm and I am so grateful.

Living with Vagal Lone AF

David Booth

History

My first episode of AF occurred in the middle of winter. I was then 50, active, in good health and working under some stress. After 3 more episodes and a visit to emergency, I became a patient of the heart clinic. Tests revealed no obvious cause and the cardiologist prescribed Sotalol. It was considered to be a prescription for life, a prospect that grated against values that dated back to childhood when my parents mistrusted use of any unnecessary medicines. Within a couple of months, I had abandoned the medication in the hope that the whole experience was an isolated one.

Athletic sports were a major part of my life as teenager. Since then, non-competitive physical activity has remained imbedded in daily life. The body worked and performed well and I believed that I was looking after its well-being. There was, however, a tendency to push myself in order to achieve various goals, both at work and of a personal nature. Many of these had as an underlying aim to prove my own existence.

Four years after the first episode, again at a time of stress in the middle of winter, four more episodes hit me. With the heart thumping wildly, I got to emergency where another cardiologist gave me the same prescription as before. I left with the impression that indeed the problem was serious and followed instructions by taking the medication. Spring did not bring me the usual revival of energy and enthusiasm. My family doctor was concerned about high blood pressure. In June, more episodes of AF occurred with two more visits to emergency. The dose of Sotalol was increased. I spent the summer devoid of energy. The cardiologist explained that according to her experience AF was usually just the tip of the iceberg and that the symptoms increased with age. It was at that moment that the need to understand became urgent. Soon afterwards, I found the www.afibbers.org site, which gave me the tools to take responsibility for my own condition.

During the autumn, several more episodes occurred and the level of anxiety increased to a level that made work as a university teacher virtually impossible. My family doctor took me off work but learning that the insurance did not recognise AF as a valid reason for sick leave only added to the anxiety. The episodes became more frequent and I came to believe that this half existence was to be my lot for the rest of my life. Medication was again increased and the feeling of vulnerability became

ever more present until I started to question the medication itself. In an attempt to find some solution, I stopped the medication. After a couple of weeks, some normality returned, and I started to regain a little energy and plan a return to work. The cardiologist accepted that the medication might be unsuitable and suggested a milder Beta-blocker. She also brought up the possibility of ablation but I was far from ready to accept such an intervention. I did try the new medication for a short while but regarded it with suspicion as the feeling of vulnerability returned.

The next series of episodes happened again in the middle of winter. By now, I was accustomed to the experience and the intensity of AF was much reduced. A further series occurred later in the spring, once again during a period of stress.

During this past year and a half, I have become more familiar with my own body. Some observations seem particularly important and it is these that I wish to share. Many of these observations are in agreement with those found in Hans Larsen's books.

Use of a journal

Although it may seem obsessive to the medical profession, writing a journal to keep track of episodes of AF has been beneficial. Not only does it help in identifying patterns but it also allows one to stand back from the experience.

Classification of AF

Initial episodes of fibrillation were generally intense and lasted several hours. Later, the intensity decreased and the duration became more variable, ranging from a few minutes to a whole day. Virtually all of my episodes of AF began just after a meal, getting into bed, while in bed or on getting up. The very occasional episode that did not fall into this pattern started soon after a séance of meditation. Although the classification of vagal AF is not generally recognised, the pattern in my case is very clear and undoubtedly important when deciding how to deal with the problem.

Symptoms

Apart from the discomfort of a crazy heart, other symptoms include a pressure and irritation in stomach, considerable belching, exhaustion, a salty taste in the mouth, and a need to urinate frequently. The most consistent symptom, however, is a tension in the region of the diaphragm, just under the solar plexus.

Triggers

Episodes of AF always occurred during periods of stress, often at work. After an initial episode, there were almost always a few more during the following days. An initial event made me more vulnerable, but the

background of stress always seemed to be present during these periods. Foods that irritated the gut or the stomach, spicy or salty dishes for example, appeared to initiate episodes. Watching the television news just before bed also increased my vulnerability, as did the obligation to be in a noisy or crowded place. In bed, I was more likely to have an episode while lying on my side, particularly the left side. When AF started in the middle of night, I had usually just woken up on my side with the impression that I had stopped breathing.

Strategies used to end an episode

Visits to emergency were, at first, the only way I knew of dealing with an prolonged episode, and indeed the official medical advise was to do just that. On the fourth visit, however, a doctor questioned the nurse as to why I had come in with just fibrillation. It was then that I realised that, despite the gloomy predictions of the cardiologist, this was something that could be dealt with. I have now come to use several ways of attempting to end an episode. The first "technique" is to stand with knees slightly bent and to shake the hands vigorously, if necessary for some minutes. This has worked for me many times. If not, I try relaxing in a warm bath: AF often calms and stops by itself. While in bed, the intensity of AF seems to be reduced by sitting up. If already in AF, I try sleeping in a reclining long chair rather than in bed. Free breathing, however, appears to be an important aspect of any attempt to stop AF. By free breathing I mean natural deep unforced breathing and it is particularly helpful to turn one's attention to a part of the body other than the abdomen area, the nose for example.

Strategies used to reduce risk

Probably the most important is an attempt to reduce stress, not by forcing anything, but by facing and dealing with it as soon as it arises. This, of course, is easier said than achieved, and sometimes requires considerable attention and honesty with oneself. For me, however, dealing with sources of stress has made me question many aspects of life, including my professional priorities and objectives. In general, however, it means being attentive to one's state of mind and responding to its needs. In my case, fighting against emotions may be one major source of stress. It may help to give oneself space to acknowledge them and allow them to be.

The second change I made to my daily life was to give myself whenever possible ample time to digest after meals. I now try to sit and read simply for relaxation after eating. This, apart from avoiding irritating foods and eating slowly, seems to be the most important way of avoiding episodes after meals.

My wife urges me to rediscover the pleasures of being. This may be rich advice indeed, for I wonder now if AF may be in some way a manifestation

of a stressed-out body. I do notice that, in spite of fatigue, my body seems more at peace after an episode of AF than before. Maybe the heart needs to dissipate pent up tension and chaotic oscillation is its only way. If so, the pleasures of being may help us find a more balanced frame of mind.

Other strategies include avoiding prolonged work at the computer, a reduction in daily work objectives, an acceptance of need to relax at frequent intervals and a recognition that the body is no longer as young and able as it was.

Diet

My diet has become simpler. Although vegetarian, apart from an occasional meal of seafood, for the past two decades, I feel the increasing need for the most basic of foods prepared in simple ways. Added salt and all processed additives have been eliminated even to the extent that the food may appear fad to another, but this is what my body seems to want. Refined sugar too has been eliminated, and just this one change seems to have decreased considerably my everyday blood pressure. Fresh fruit now tastes sweet while a sugared muffin, for example, is now almost inedible. I limit my intake of bread, which seems to irritate the stomach. The breakfast that seems to suit me best is one based on cooked quinoa with some fruit, a soy based yogurt and flax oil. Lunch is simple, often a thick soup with some source of protein. Supper is still the main meal, but more modest and less rushed. I drink little but water and soymilk, which helps calm the stomach. A very occasional beer is sometimes welcome, but even this can sometimes instil a sense of vulnerability. I now distrust restaurant meals, particularly those with sauces. Although I prefer to eat at home, when eating out I choose the simpler dishes.

I take no supplements other than a little fish oil. For many months during the winter, however, I had the almost insatiable urge to eat cooked dates. Whether or not this has anything to do with a bodily need, I do not know, but the urge diminished as spring arrived.

Sleep

I accept now that the body needs seven or eight hours of sleep each day. I no longer force the body to get up in an attempt to get more out of the day. It may be simply an acceptance of corporal limits. The fact that vulnerability to AF increases when the body is fatigued is reason enough to give oneself ample sleep. I suspect that many of my episodes occurred during periods of sleep deficiency.

T'ai Chi

This slow precise form of exercise is of great benefit; at least it seems so in my case. Not only have I recorded a drop of 12 points in systolic blood pressure during a single half-hour of T'ai Chi, but I have also been able to

terminate episodes of AF while exercising. In general, T'ai Chi does help to keep the body supple and relaxed, a condition that can only help minimise AF. It seems particularly important to keep the torso relaxed.

Meditation

Meditation has been an important part of me life for many years. Although simple meditation can be done for relaxation, on deepening the practice, one enters into the conflicting tensions of life. This can bring to the surface and thus amplify confusion, dread, depression and anxiety, all of which need to be faced for what they are. This level of meditation should be undertaken under the guidance of a competent master. Otherwise, it is very easy to slip into a practice of endless rumination or of a dreary stupor. What is of interest, however, is that meditation seems to change the functioning of the nervous system. In my case, episodes of AF often occur around periods of intense meditation, and in particular when the body tightens after a deep letting-go. Meditation can thus help us learn how we function, but working with this kind of practice is difficult and guidance is essential. Despite periods of difficulty, I am convinced that such practice can be deeply beneficial, although in the end meditation is of no use if undertaken with a particular objective in mind; doing so immediately puts a stick between the spokes.

Osteopathy

Treatment from a competent and sensitive osteopath has been of the utmost help. By feeling tension in the body and working with his hands, the osteopath is able to influence the nervous systems. On one occasion, I arrived for treatment with the heart already in AF. He was able to relieve the tension and stop the fibrillation. I now go for a monthly treatment in an attempt to limit the accumulation of tension. In my case, the sympathetic nervous system is generally overactive. Gradually, the upper body seems to be learning how to relax. Of interest however is the feeling after a treatment. For a couple of days, there is a general feeling of well-being and a desire for action. At the same time, the body feels unusually vulnerable to AF, especially during the first night. It thus appears important to stay particularly attentive and avoid excessive activity while the body readjusts itself. In this respect, I suspect that osteopathy and meditation can affect the body in similar ways. It is worth noting here, however, that there are many kinds of osteopathic manipulations. Not all are necessarily beneficial. With me the osteopath works, usually in a very gentle and sensitive manner, around the abdomen area, at the lower and upper ends of the spine, and around the top of the head. He is able to sense the state of tension and resistance in the body and thus ease it out of its usual defence.

Emotions

I have come to recognise the emotions that prevail during periods of frequent episodes. For me these are in the main a simmering anger or frustration with the "system" in which I work, often with a feeling of being up against a brick wall. I realise now that my values are not those of the institution, and this constantly puts me in a situation of tension. Within myself, the tension manifests as a tug of war between what I believe is essential and what I believe is expected of me. Coming to terms with this tension is, I suspect, an important step. To be able to step back and see this dynamic as a construction rather than a reality does take the sting out of the tension. Gradually it may be possible to enter into the simmering emotion and allow it dissipate before any accumulation of tension. Some might see this as an attempt to give more space to the heart. It is of interest that on the two occasions that I broke down into tears through despair during an episode of intense AF, the heart regained its normal rhythm within minutes.

Tension in the abdomen

Tension just below the solar plexus in the region of the diaphragm is the most persistent and frequent symptom during periods of AF. Whenever the heart is in fibrillation, the diaphragm muscles feel tight and taut. Breathing lacks its usual fluidity. Well before the onset of an episode, one of the very early signs is a conscious feeling of the pulse just below the solar plexus. This is an indication of the need to stop and relax and increasingly it is possible to avoid an episode before any clear symptoms in the heart rhythm. I now suspect that muscle system of the diaphragm may play an important part in the process.

Conclusion

My understanding of what happens is based on a mechanical viewpoint. This may be naive and simplistic but the model gives us a means to link some of the observations thus far. The heart is, in mechanical terms, a complicated forced oscillator, sitting just above the diaphragm and held in place by elastic suspenders. Some mechanical oscillators can go into chaotic movement as the elasticity is changed. The fact that AF symptoms change with orientation of the body does suggest that gravity affects the dynamic. I wonder therefore if tension in the muscular system simply limits the supporting elasticity and constricts the usual heart movement thus driving it into fibrillation. This does not reject the role of the autonomic nervous systems and indeed the suggestion that variations in the balance between the sympathetic and parasympathetic branches play a role in the onset of AF may be supported by what I experience after an osteopathy treatment or a period of deep meditation. Nevertheless, whether the process is a mechanical interaction or an adjustment in the nervous system, being mindful of tension in the upper abdomen and diaphragm region does appear to minimise and weaken episodes of AF.

With this limited understanding of the workings of my own body, I try therefore in whatever way possible to allow the upper body to relax. All the strategies that seem to work for me, whether to reduce the risk of an episode or to weaken and stop the fibrillation, have this effect. I strongly suspect that when the diaphragm is relaxed and supple, risk of AF is considerably reduced. Even if a relaxed diaphragm is but a sign of something underneath such as balanced nervous system, tension in the diaphragm remains a clear warning indicator.

It would be tempting to claim that nothing is wrong with the heart and that it is all in the mind. There is obviously a weakness and fibrillation is its manifestation. But perhaps, AF in some cases may be a symptom of something much more general and should therefore be welcomed as an invitation to learn. Perhaps the cardiologist was right in saying that it is just the tip of the iceberg. This iceberg, I now suspect however, is not just physiological but encompasses the whole workings of the human being. It is my hope that by taking a holistic viewpoint, I may be able to learn and eventually find a way of allowing the body and all its being function in relative harmony, even in times of difficulty. I tend to take things to heart but do not allow the heart to express itself. Maybe my fibrillation is a call from the heart. Maybe it is no wonder that the heart is considered the centre of emotion.

Journal Summaries

Incidence & Management

Prevalence and incidence of AF

ROTTERDAM, THE NETHERLANDS. It is becoming increasingly clear that atrial fibrillation is reaching epidemic proportions and that the incidence (new cases per 1000 person-years) and prevalence (percent of a given population having the disorder at any given point in time) of the condition continue to rise. A team of Dutch and British researchers has just reported the results of a 7-year study involving 6400 inhabitants (aged 55 years or older in 1990) of a suburb of Rotterdam. At the start of the study 5.5% of the participants had been diagnosed with afib for an average prevalence among men of 6.0% and a prevalence of 5.1% among women. The prevalence increased significantly with age, with the prevalence being only 0.7% in the 55-60 year age group versus 17.8% in the over 85 year age group. By January 2000, the overall prevalence had increased to 8.3%.

The incidence (new cases) over an average of 7 years was 9.9/1000 person-years or about 1% a year. The incidence was highly dependent on age with the group aged 55-60 having an incidence of 0.1% a year and the age group 80-85 having an incidence of 2.1% a year. The incidence was higher in men than in women across all age groups. The results of the study also showed that a 55-year-old man has a 25% chance of developing afib during his remaining life. The average lifetime risk for a 55-year-old woman was found to be 23%. Lifetime risk remained pretty well constant until age 75 when it began to decline. This means that about a quarter of the population between the ages of 55 and 75 years can expect to develop afib at some point in their lives – a sobering thought indeed!

Heeringa, J, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European Heart Journal, *Vol. 27, 2006, pp. 949-53*

Boriani, G, et al. The epidemiological burden of atrial fibrillation: a challenge for clinicians and health care systems. European Heart Journal, *Vol. 27, 2006, pp. 893-94 (editorial)*

Editor's comment: This study, as is unfortunately often the case, did not distinguish between lone atrial fibrillation and atrial fibrillation associated with heart disease or other conditions. However, reviewing the baseline data it would appear that about 50% of the study participants probably did develop lone afib. It is also highly likely that both the incidence and

prevalence figures are understated since it is now known that a substantial proportion of afibbers have asymptomatic episodes which may not have been detected either by the patient or through the 3 routine follow-ups where 10-second ECGs were used to check for afib.

AF prevalence higher than expected

ROCHESTER, MINNESOTA. A 2001 study by Kaiser Permanente researchers estimated the number of afibbers in the United States at 2.3 million rising to 5.6 million in 2050. Mayo Clinic researchers now report that these estimates are likely to be low by a factor of two to three. The Mayo study determined the incidence (first AF episode documented by an electrocardiogram) of atrial fibrillation in Olmsted County, MN. They found that the number of new afib cases in 1980 was 4.09 per 1000 person-years for men and 2.36 per 1000 person-years for women. By the year 2000, the incidence had increased to 4.89 per 1000 person-years for men and 2.80 per 1000 person-years for women. This corresponds to an overall increase of 12.6% over 21 years. Applying their data to the entire US population, the researchers estimate that 5.1 million Americans were suffering from AF in 2000. The prevalence in 2006 would be about 6 million and by 2050 it would be 15.9 million assuming the growth rate observed over the period 1980-2000 continues.

The Mayo researchers point out that the prevalence of obesity (BMI of 30 or more) increased from 10% in 1980 to 25% in 2000 and suggest that about 60% of the observed increase in AF cases could be due to the increase in obesity.

Miyasaka, Y, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation, *Vol. 114, July 11, 2006, pp. 119-25*

Editor's comment: It is quite possible that even the Mayo Clinic numbers for afib incidence and prevalence are low. Less than 20% of Olmsted County residents had an ECG in any one year and some presumably never had one. Whatever the real prevalence is, it is obviously high and growing. It is to be hoped that this new reminder of the seriousness of the AF epidemic will result in more research being directed toward finding the cause(s).

Mechanistic Insights

Inflammation and atrial fibrillation
IRMINGHAM, UNITED KINGDOM. British researchers present a thorough review of the current knowledge regarding an association between systemic inflammation and atrial fibrillation. Please note that the review does not distinguish between lone AF and atrial fibrillation with underlying heart disease. Thus the conclusions presented may or may not apply to lone afib.

The researchers point out that it is generally accepted that afib results in both electrical and structural remodeling of the atria. The main features of the electrical remodeling are shortening of the atrial refractory period (the rest period following a contraction of the heart muscle. The cell [myocyte] does not respond to stimulation during this period), prolongation of atrial conductivity, and the loss of rate adaptation. Another feature of the electrical remodeling is the accumulation of calcium within atrial myocytes leading to a further shortening of the atrial refractory period. The main features of the mechanical remodeling are enlargement of the left atrium and increasing atrial fibrosis (deposition of connective tissue between individual myocytes). These electrical and structural changes increase the likelihood of further afib episodes (afib begets afib).

There is now also increasing evidence that atrial fibrillation is linked to a systemic inflammation. Atrial biopsies have demonstrated the presence of inflamed tissue in both lone and non-lone afibbers. Measurements of blood levels of the inflammatory marker C-reactive protein (hs-CRP) have shown that levels tend to be higher among people with afib than among normal controls. There is also evidence that levels are higher among persistent afibbers than among paroxysmal afibbers, and finally, studies have shown that high hs-CRP levels are associated with an increased risk of developing new onset AF.

Several drugs and supplements have anti-inflammatory properties and have been found to reduce the risk of developing afib and/or reduce the number of episodes. Four studies have shown that statin drugs may have a role in the prevention of afib in humans, and animal studies have shown that statins may also reduce the frequency of episodes. Methyl prednisolone, a steroid anti-inflammatory drug, has been found to reduce recurrence of afib episodes when taken together with propafenone. There

is evidence that both ACE inhibitors and angiotensin-receptor blockers (ARBs) have significant anti-inflammatory properties and may help prevent both the development and recurrence of AF – at least in patients with hypertension or heart disease. Fish oils also have significant anti-inflammatory properties and may be beneficial in preventing ventricular arrhythmias and AF occurring after bypass surgery. However, there is no convincing evidence that fish oils help prevent lone AF. Vitamin C has also been found to reduce the incidence of post-surgery afib and may help reduce the risk of early recurrence after cardioversion.
The researchers conclude that there is ample evidence of a link between inflammation and afib, and that anti-inflammatory drugs or supplements may play a role in preventing atrial fibrillation and its recurrence.
Boos, CJ, et al. Is atrial fibrillation an inflammatory disorder? European Heart Journal*, Vol. 27, 2006, pp. 136-149*

Editor's comment: As is, unfortunately, often the case in articles dealing with AF, no attempt was made here to distinguish between lone afib and afib with underlying heart disease. This is perhaps understandable since lone afibbers are a distinct minority (perhaps 20% of all afibbers). Nevertheless, recent work by Patrick Chambers, MD (*The AFIB Report*, February 2006) points to the very real possibility that lone AF may be a condition distinctly different from AF related to heart disease. Thus, the findings of the review may be only partly applicable to lone atrial fibrillation.

More evidence of asymptomatic AF episodes

HAMBURG, GERMANY. There is increasing recognition that even a seemingly successful pulmonary vein isolation (PVI) may not keep the patient in continuous normal sinus rhythm (NSR) when asymptomatic (silent) AF episodes are included in the evaluation of success.

German researchers recently reported on a study of 80 highly symptomatic, paroxysmal afibbers who had undergone a first-time PVI (segmental ostial ablation). Only 10% of the afibbers had coronary artery disease. After a seemingly successful ablation involving complete entrance and exit block of all pulmonary veins and bidirectional right atrial isthmus block (flutter ablation), the patients were provided with a transtelephonic ECG recorder for use during the 6 months following the ablation. They were instructed to transmit a 1-minute recording once a day as well as recordings whenever they felt symptoms that could be afib. They were also instructed to specify their symptoms by telephone.

A total of 6835 transtelephonic recordings were gathered and analyzed over the 6-month period. NSR was observed in 79.5% of the recordings with the remaining showing afib. Only 28% of participants showed

continuous NSR during the entire 6-month study period. Seventy-two per cent of participants experienced an episode during the first month; however, about half of them were afib-free after 3 months. Thus, the total number of patients in NSR after 3 months was 52 or 65%. After 6 months, the success rate had declined to 61% and 23% of the patients underwent a second ablation.

Ninety per cent of patients who were in NSR reported being so, while 10% reported symptoms, predominantly palpitation (73%), tachycardia (13%), breathing difficulties (10%), and chest pain (4%). Conversely, when patients actually were in afib (as per recordings) only 46% of them reported symptoms, while the remaining 54% reported no symptoms. The most commonly reported symptoms were palpitation (60%), tachycardia (31%), breathing difficulties (5%), and chest pain (3%). The percentage of asymptomatic episodes increased from the first month after PVI (43.5%) to the 2nd to 6th month (57.5%). This confirms earlier reports that the preponderance of asymptomatic episodes tends to increase over time.
The researchers conclude that success of a PVI cannot be accurately judged by just considering patients with symptoms since more than half of all episodes are likely to be entirely symptomless (asymptomatic). This clearly has significant implications as far as anticoagulation and drug treatment is concerned.
Klemm, HU, et al. Correlation of symptoms to ECG diagnosis following atrial fibrillation ablation. Journal of Cardiovascular Electrophysiology, *Vol. 17, February 2006, pp. 146-50*

Inflammation and atrial fibrillation

THRACE, GREECE. The association between systemic inflammation and lone atrial fibrillation (LAF) has fascinated researchers ever since 1997 when Dr. Andrea Frustaci and colleagues at the Catholic University of Rome discovered that lone afibbers tend to show evidence of current or past inflammation in their heart tissue. Later research confirmed an association between elevated levels of high-sensitivity C-reative protein (hs-CRP), a marker of systemic inflammation, and the presence of LAF. Paroxysmal afibbers were found to have higher hs-CRP levels than controls, and persistent and permanent afibbers were found to have higher levels than paroxysmal afibbers.

Researchers at the University of Thrace now report that hs-CRP levels measured during a first LAF episode are significantly higher than those of controls and that a higher CRP level during the first episode predicts the risk of recurrence. Their study included 125 patients with a first, documented paroxysmal episode of LAF who had blood samples drawn for hs-CRP analysis while in afib. Their CRP values were compared to those of matched controls who had never been diagnosed with AF. The average (median) value for the afibbers was 0.23 mg/dL (2.3 mg/L), while the

median for controls was 0.087 mg/dL (0.9 mg/L). Sixty per cent of the 125 afibbers whose first episode was documented had recurrences during a mean follow-up of 2 years. Patients with CRP levels in the top quartile (0.23 mg/dL) were 15% more likely to have a recurrence than were patients in the bottom quartile (median of 0.1 mg/dL).

The researchers also observed that the hs-CRP levels of afibbers were significantly lower (median of 0.14 mg/dL) during sinus rhythm than during an episode (median of 0.28 mg/dL). The researchers conclude that hs-CRP may be a marker for inflammatory states that may promote the initiation of lone atrial fibrillation.
Hatzinikolaou-Kotsakou, E, et al. Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. American Journal of Cardiology, *Vol. 97, 2006, pp. 659-61*

Editor's comment: There seems to be little doubt that inflammation and LAF are somehow connected. What is much less clear is the mechanism by which they are linked. The University of Thrace researchers and, as far as I know, all other researchers (myself included) who have given the matter some thought believe that inflammation is a causative factor in the initiation and recurrence of afib. The possibility that the association may be the opposite of what seems intuitively right, in other words, that fibrillation may result in inflammation has not been given much credence. However, this may now change with the discovery by Martin Rotter and colleagues in Bordeaux who recently reported that hs-CRP levels decrease markedly after a successful pulmonary vein isolation procedure. They concluded that restoration of sinus rhythm results in a significant decrease in inflammation. Which interpretation is correct? More research is required to determine this, but it is certainly not beyond the realm of possibilities that atrial fibrillation may result in inflammation rather than inflammation causing afib.

Successful ablation reduces inflammation

BORDEAUX, FRANCE. Several studies have shown that afibbers with persistent or permanent afib tend to have higher C-reactive protein (CRP) levels than do paroxysmal afibbers and those in sinus rhythm. What is not known is whether restoring sinus rhythm through radiofrequency ablation will reduce CRP levels to normal. Martin Rotter, MD and colleagues at the Hopital Cardiologique du Haut-Leveque have now answered this question.

Their clinical trial included 50 patients aged 43 to 63 years (49 male and 1 female). Five of the patients had long-lasting persistent afib (episode duration of 3-10 months), while the remaining 45 were in permanent afib. The patients all underwent a single pulmonary vein isolation (PVI)

procedure with additional lesion lines as required to restore sinus rhythm. The patients were examined 1 and 3 months after their ablation and remained on their pre-ablation medications throughout the trial period. At 3 months, 66% (33 patients) were still in sinus rhythm, while 12 had paroxysmal afib, and 5 had atrial tachycardia. While the CRP levels among the successful and unsuccessful ablatees were similar prior to the ablation (2.82 mg/L or 0.28 mg/dL vs 2.46 mg/L or 0.25 mg/dL), there was a significant decline in the level among patients still in sinus rhythm at the 3-month checkup. Among these patients the CRP level had declined from 2.82 mg/L to 1.37 mg/L. In comparison, the average CRP level in the unsuccessful group did not change significantly (2.46 mg/L vs 2.58 mg/L).

The researchers also noted a significant decrease in left atrial size (parasternal diameter) from 45.8 mm to 42.6 mm in the successfully treated group. No such change was observed in the unsuccessful group (45.2 mm vs 45.4 mm). The study clearly demonstrates that it is not radiofrequency ablation as such that reduces atrial size and inflammation, but rather the restoration of sinus rhythm. The Bordeaux researchers conclude that restoration of sinus rhythm by a PVI results in reverse remodeling of the left atrium and a significant decrease in inflammation.

Rotter, M, et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. Journal of the American College of Cardiology, *Vol. 47, No. 6, March 21, 2006, pp. 1231-33 (letter to the editor)*

Editor's comment: It is also evident from the results of this trial that being out of sinus rhythm causes inflammation (high CRP levels) rather than the other way around. This would explain why CRP levels increase from paroxysmal to persistent to permanent afib.

Lone atrial fibrillation and C-reactive protein

BOSTON, MASSACHUSETTS. There is considerable evidence of an association between inflammation and atrial fibrillation. Biopsies have found inflammatory infiltrates in patients with AF and several studies have found that AF patients tend to have higher blood levels of inflammatory markers such as C-reactive protein (CRP), prothrombin fragments and interleukin-6. Unfortunately, most studies involving atrial fibrillation do not distinguish between AF with and without underlying cardiovascular disease, so it is not at all clear whether the inflammation connection applies to lone atrial fibrillation, that is, AF without underlying heart disease.

A group of researchers at the Massachusetts General Hospital recently released the results of a study designed to determine if systemic

inflammation (as measured by CRP level) is associated with AF *per se*, or rather with an underlying cardiovascular disease. The study involved 121 lone afibbers (no history of coronary artery disease, rheumatic heart disease, cardiomyopathy, significant valvular disease, hyperthyroidism, or hypertension), 52 patients with none of the above conditions except hypertension, and 75 healthy controls without heart disease, hypertension and AF. The mean age of the lone afibbers at enrolment was 54.3 years and the mean age at diagnosis was 44.8 years. The mean age of the AF + hypertension participants at enrolment was 60.2 years and the mean age at diagnosis was 50.6 years. Most study participants (83%) were men, and most lone afibbers (91.7%) and AF + hypertension patients (84.6%) had paroxysmal afib. Just over 56% of the lone afibbers had experienced more than 100 episodes. It is interesting that 34% of the lone afibbers and 37% of the AF + hypertension patients had a first-degree relative with AF.

All study participants underwent a detailed medical examination and had an electrocardiogram and an echocardiogram at enrolment. They also provided a blood sample for CRP analysis. The researchers observed no statistically significant difference in CRP levels between lone afibbers and controls (1.34 vs 1.21 mg/L); however, they did note a significant difference between AF + hypertension patients and controls (1.90 vs 1.21 mg/L), but suggest that this is primarily due to a greater proportion of overweight and obese individuals in the hypertensive group. They found no difference in CRP levels between the 20% of afibbers taking statin drugs and those not taking them. They also found no significant difference in CRP level among lone afibbers who were in sinus rhythm at time of blood sampling versus those in afib (1.37 vs 1.38 mg/L).

Finally, they observed no significant difference in CRP values between paroxysmal and permanent afibbers. They did, however, observe a strong correlation between a high body mass index and an elevated CRP level. The researchers conclude that atrial fibrillation on its own (without underlying heart disease, hypertension or obesity) is not associated with evidence of systemic inflammation.
Ellinor, PT, et al. C-reactive protein in lone atrial fibrillation. American Journal of Cardiology, *Vol. 97, May 1, 2006, pp. 1346-50*

Editor's comment: This study confirms my own intuitive feeling that systemic inflammation (high CRP levels) may not be as important in true lone atrial fibrillation as previously thought. It also strongly underlines the importance of not automatically assuming that data obtained from studies of AF patients in general are necessarily applicable to lone afibbers. The study is also of considerable interest in that it confirms many of the values obtained in our early LAF surveys. For example, the percentage of women in the sample of lone afibbers was 17% vs 21% in

our database of 625 lone afibbers. The average age at diagnosis was 45 years vs 47 years in our database; the average blood pressure was 122/75 vs 124/76 in our LAF Survey V. This is a comforting confirmation that our surveys do indeed reflect the general population of lone afibbers.

Fibrinogen level linked to afib

COPENHAGEN, DENMARK. An elevated level of the blood coagulation factor fibrinogen has been linked to inflammation and in increased risk of heart disease, stroke, and periodontal (gum) disease. Danish researchers now report an association between high fibrinogen levels and an increased risk of developing atrial fibrillation. Their study involved 8870 men and women free of cardiovascular disease who were enrolled in the Copenhagen City Heart Study. During an average 7.5 years of follow-up, 286 of the participants developed AF (4.3 cases per 1000 person-years).

The researchers observed that men with a plasma fibrinogen level above 353 grams/L had twice the risk of developing AF than did those with a level below 243 grams/L. Among women, those with a fibrinogen level above 360 grams/L had a 2.14 times higher risk of AF than did those with a level below 250 grams/L. There was also a clear correlation between a low level of serum albumin in women and an increased risk of AF. No such correlation was observed for the men.

Both an elevated level of fibrinogen and a low level of albumin are markers of inflammation. The Danish researchers conclude that their findings support the hypothesis that inflammation contributes to the etiology of atrial fibrillation.
Mukamal, KJ, et al. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). American Journal of Cardiology*, Vol. 98, July 1, 2006, pp. 75-81*

Editor's comment: High fibrinogen levels are also an important risk factor for stroke. An increased water intake and supplementation with fish oils and niacin have been found to lower fibrinogen levels.

AF and the renin-angiotensin system

BOSTON, MASSACHUSETTS. Evidence is mounting to the effect that the renin-angiotensin system (RAS) also known as the renin-angiotensin-aldosterone system (RAAS) is involved in the initiation and recurrence of afib, at least in afibbers with hypertension or congestive heart failure (CHF). The RAS is the body's main system for dealing with a decrease in blood pressure that is too great to be dealt with by the automatic nervous system alone. It works as follows:

The low blood pressure is first sensed by the kidneys which proceed to secrete a small peptide called renin. Renin is transported to the liver where it helps to produce angiotensin I from a large protein called angiotensinogen. Angiotensin I, in turn, is carried by the blood to the lungs where it is converted into angiotensin II. Angiotensin II (inhibited by ACE inhibitors) is the most potent vasoconstrictor in the body. It causes the blood vessels to constrict and potentiates the sympathetic nervous system resulting in an increase in blood pressure.

Recent research has shown that structural and electrophysiologic changes in atrial tissue result in an arrhythmogenic substrate susceptible to induction and maintenance of afib. The electrophysiologic changes relate mainly to a shortening of the atrial effective refractory period (AERP) – the rest period following a contraction of heart muscle; the cell does not respond to stimulation during this period. The structural changes involve fibrosis (the formation of scar-like [fibrous] tissue) which, in turn, is associated with excessive collagen production. Animal and human experiments have shown that angiotensin-converting enzyme and angiotensin II may be involved in fibrosis and that the RAS is also involved in the shortening of AERP.

Researchers at the University of Massachusetts Medical School have just published a review of the current knowledge of the effect of the RAS on afib and the possible role of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) in the prevention of AF. They conclude that ACE inhibitors such as trandolapril (Mavik) and enalapril (Vasotec) help to prevent the development of afib in patients with CHF and left ventricular dysfunction. Similar observations have been made in studies involving the ARBs valsartan (Diovan) and candesartan (Atacand). There is also evidence that ACE inhibitors can help prevent the development and recurrence of afib in patients with hypertension.

Finally, there is some evidence that inhibition of the RAS (with ACE inhibitors or ARBs) can help in maintaining sinus rhythm after cardioversion. It is not yet known whether RAS inhibition may be useful in lone atrial fibrillation, but the Massachusetts researchers tend to believe that the major effect will be found among patients with left ventricular hypertrophy, left ventricular dysfunction, heart failure, or hypertension.
Patlolla, V, et al. The renin-angiotensin system: A therapeutic target in atrial fibrillation. PACE, *Vol. 29, September 2006, pp. 1006-12*

Risk Factors & Triggers

Atrial fibrillation: The genetic component
REYKJAVIK, ICELAND. Iceland is unique in the fact that it has a genealogy database containing records for all 284,000 living Icelanders and a large proportion of their ancestors as far back as 930 AD. NOTE: According to studies based on Y-chromosome and mitochondrial polymorphism, it appears that 75% of all male Icelanders originally came from Norway, while 66% of all female Icelanders are of Celtic origin – seems that the Vikings went far afield for their wives!

A team of researchers from the University Hospital in Reykjavik and the National Institutes of Health in the US has just completed a study using the genealogy database and hospital records for 5269 patients admitted with atrial fibrillation during the period 1987-2003. The aim of the study was to determine the inherited risk of developing AF.

The researchers conclude that Icelanders with a first-degree relative with afib have a 77% (RR=1.77) greater risk of developing afib than do members of the general population. The risk declines the further the afflicted family member is removed. Thus, an Icelander with a third-degree relative diagnosed with afib has an 18% increase in risk. The heritability factor was particularly pronounced in afibbers who were diagnosed prior to the age of 60 years. Their immediate offspring were almost 5 times (RR=4.67) more likely to develop AF than were matched members of the general population. The researchers speculate that this may indicate that a genetic connection is much more common among lone afibbers than among afibbers with heart disease.
Arnar, David O, et al. Familial aggregation of atrial fibrillation in Iceland. European Heart Journal, *Vol. 27, March 2006, pp. 708-12*

Editor's comment: One of the early LAF surveys found that 43% of the 100 lone afibbers responding had a close relative who also suffered from atrial fibrillation. Either the mother or the father was "the carrier" for 23% of the 100 respondents.

Fish consumption and atrial fibrillation
ROTTERDAM, THE NETHERLANDS. There is substantial evidence that a high consumption of oily fish or more specifically, long-chain omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is associated with a reduced risk of sudden cardiac death and ventricular

fibrillation. This fact prompted Dutch researchers to investigate if a high intake of fish would decrease the risk of developing atrial fibrillation.

Their study involved 5184 men and women aged 55 years or older who were afib-free at baseline. The participants completed a validated food frequency questionnaire during an interview with a trained dietician and were then followed for an average period of 6.4 years. During this period, 312 participants (6%) were diagnosed with atrial fibrillation. The researchers found no correlation between the consumption of fish and the risk of developing afib. They also found no correlation between the (calculated) intake of EPA and DHA and the risk of developing afib. The calculated daily intake of EPA plus DHA ranged from an average of 20 mg to an average of 330 mg with the maximum being 570 mg/day. Only 0.5% of participants were taking fish oils supplements. The researchers conclude that their findings do not support the hypothesis that long-chain omega-3 fatty acids (fish oils) have a general antiarrhythmic effect.
Brouwer, IA, et al. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. American Heart Journal, *Vol. 151, April 2006, pp. 857-62*

Editor's comment: This study confirms the findings of a previous Danish study but contradicts the findings of an American study, which observed an inverse association between the intake of tuna and other broiled and baked fish and the occurrence of atrial fibrillation.

The Dutch study raises a couple of interesting points.

- Is fish a good source of EPA and DHA? The answer, unfortunately, is probably not. There is substantial evidence that most fish (except wild Pacific salmon) is contaminated with mercury. A landmark study at Harvard Medical School found that there is a direct relationship between fish consumption and mercury levels in humans with an average consumption of ¾ lb (357 grams) of fish per week corresponding to a mercury level of 0.75 micrograms/gram (in toenail clippings). In contrast, a consumption of 1/3 lb (145 grams) per week was associated with a mercury level of only 0.29 micrograms/gram.[1-3] Thus, it is clear that nowadays an increased fish consumption is associated with an increased intake of mercury. Could the beneficial effects of EPA + DHA from fish be cancelled by the detrimental effects of mercury from the same fish? I am not aware of any research addressing this very key question.

- Were the amounts of EPA + DHA consumed by the participants in the Dutch study too low to be likely to have an

> effect? Hard to know, but three afibbers who eliminated afib through major dietary changes had average intakes of 2000 mg of EPA and 2200 mg of DHA for a total of 4200 mg/day of long-chain omega-3 fatty acids.[4] This amount is almost 30 times higher than the average amount (146 mg/day) consumed by the participants of the Rotterdam study. So, the study does not, in any way, prove or disprove whether therapeutic amounts of EPA + DHA would be effective in reversing or preventing afib.

Fish oils have many beneficial properties and are an essential part of a natural stroke prevention program. The minimum recommended daily intake is 650 mg/day. It is vitally important, however, that fish oil supplements be of the highest quality. Only fresh, molecular-distilled (pharmaceutical grade) products should be consumed.

Cardioversion

Cardioversion success and CRP level

ROCHESTER, MINNESOTA. Electrical cardioversion is a common procedure for converting atrial flutter and persistent afib to normal sinus rhythm (NSR). Persistent afib is defined as afib lasting longer than 7 days without converting spontaneously to NSR. Unfortunately, in as much as two thirds of cases the conversion does not hold and afib or flutter recurs within one month of cardioversion.

Researchers at the Mayo Clinic now report that a high blood level of C-reactive protein (CRP), a marker of systemic inflammation, prior to cardioversion is associated with a greater probability of afib recurrence within one month. The researchers studied 17 patients with atrial flutter and 50 patients with persistent afib. They measured CRP level just prior to cardioversion and observed that the average level in patients who remained in sinus rhythm after cardioversion (6.0 mg/L) was significantly lower than the level (10.7 mg/L) in patients who reverted to afib or flutter within one month after cardioversion. They conclude that high CRP levels prior to conversion double the risk that the cardioversion will not result in maintenance of NSR beyond the first month (after adjusting for other relevant factors such as age, gender, and medications used prior to cardioversion). About two thirds of the patients cardioverted had no recurrence within the first month. The researchers conclude that anti-inflammatory medications may help retain NSR after cardioversion and that measuring CRP prior to cardioversion may provide valuable information as to the likelihood of the cardioversion being successful beyond the first month.

Malouf, JF, et al. High sensitivity C-reactive protein: a novel predictor for recurrence of atrial fibrillation after successful cardioversion. Journal of the American College of Cardiology, *Vol. 46, October 4, 2005, pp. 1284-87*

Editor's comment: There is usually a 6-week waiting period between establishing the need for cardioversion and actually carrying out the procedure. During this period warfarin is administered to prevent blood clotting and a potential ischemic stroke immediately following the procedure. It would seem prudent to use this 6-week period to reduce the CRP level using such natural anti-inflammatories as Moducare or beta-sitosterol. There is also evidence that a low level of potassium is associated with poorer outcome of cardioversion, so supplementing fairly

heavily with potassium and magnesium prior to the procedure may also be beneficial.

Effectiveness of electrical cardioversion

ROCHESTER, MINNESOTA. Patients with persistent atrial flutter or fibrillation often undergo direct-current cardioversion (DCCV) in an attempt to bring the heart back into normal sinus rhythm (NSR). Dr. Paul Friedman and colleagues at the Mayo Clinic have just released the results of a study aimed at determining just how effective DCCV really is. The study included 351 patients with atrial fibrillation (179 with a first episode) and 126 patients with atrial flutter (78 with a first episode). The patients were all over the age of 60 years and most had hypertension (68%), while 49% had moderate to severe atrial enlargement. Most were on one or more medications including 29% on digoxin, 92% on warfarin, and 53% on ACE inhibitors or angiotensin-converting enzyme inhibitors.

The study participants underwent standard DCCV and were then followed-up for a year. At the one-year follow-up 63% of the patients who had been cardioverted after a first atrial flutter episode remained in NSR. However, only 33% of flutter patients with recurrent episodes remained in NSR.

The results for afibbers were even worse. Only 30% of patients in the new-onset afib group and 35% in the recurrent group were still in NSR after a year. It is interesting that not all atrial flutter patients relapsed into atrial flutter. In patients with recurrent atrial flutter, 39% relapsed into atrial fibrillation. AF patients, on the other hand, almost always (92-95% of cases) relapsed back into atrial fibrillation rather than into atrial flutter.
Elesber, AA, et al. Relapse and mortality following cardioversion of new-onset vs. recurrent atrial fibrillation and atrial flutter in the elderly. European Heart Journal, *Vol. 27, April 2006, pp. 854-60*

Editor's comment: Electrical cardioversion is clearly not very effective for the general afib population and there is no evidence that it is more effective for lone afibbers. However, there is some evidence that effectiveness increases if used together with antiarrhythmic drugs.

Success rate for cardioversion

MIDDLESBROUGH, UNITED KINGDOM. It is unfortunate, but by now a well-established fact, that direct current cardioversion (DCC) is not very effective in keeping persistent and permanent afibbers in normal sinus rhythm (NSR). A group of cardiologists at the James Cook University Hospital now report that pre- and post-treatment with amiodarone greatly improves the chances of staying in NSR after DCC. Their clinical trial included 91 patients with persistent or permanent afib scheduled for DCC

after 6 weeks of warfarin therapy. During the 6-week waiting period 20 patients were randomized to receive amiodarone (200 mg 3 times daily for the first week, 200 mg 2 times daily for the second week, and then 200 mg daily for the remainder of the trial period); 28 patients received sotalol (160 mg twice a day, or 80 mg twice a day if intolerant of the higher dose) and the remaining 29 patients received no antiarrhythmic drug. All patients were given beta-blockers (usually atenolol) or digoxin as required for rate control and all remained on the drug regimen in effect pre-DCC for the entire 6-month observation period. During the 6-week waiting period 7 patients in the amiodarone group and 7 in the sotalol group converted spontaneously to NSR and were not given DCC. None of the patients not receiving antiarrhythmics converted on their own.

The immediate success rate of cardioversion (patients in NSR at time of discharge from the hospital) was 92% for those in the sotalol group, 81% in the amiodarone group, and 74% in the no-antiarrhythmic group. Unfortunately, the effects of the cardioversion did not last. Six weeks after DCC only 53% of those in the sotalol group, 67% in the amiodarone group, and 42% in the no-antiarrhythmic group were still in NSR. Corresponding numbers at the end of the trial (6 months after DCC) were 39%, 63%, and 16%. The researchers conclude that amiodarone (200 mg a day) is more effective than sotalol (160 mg twice a day) in maintaining NSR after cardioversion. Adverse effects were observed in 4% of the patients assigned to amiodarone and in 11% assigned to sotalol.

Vijayalakshmi, K, et al. A randomized trial of prophylactic antiarrhythmic agents (amiodarone and sotalol) in patients with atrial fibrillation for whom direct current cardioversion is planned. American Heart Journal, *Vol. 151, April 2006, pp. 863-68*

Editor's comment: It is very clear from this clinical trial that DCC on its own (without concomitant use of antiarrhythmics) is ineffective in maintaining NSR in persistent and permanent afibbers. Only 16% of converted patients in the no-antiarrhythmic group were still in NSR 6 months after DCC. Thus, the message to take away from this trial is that DCC without concomitant antiarrhythmic therapy is rarely worthwhile.

Earlier cardioversion possible

CLEVELAND, OHIO. It is generally accepted practice that electrical cardioversion must be performed either within the first 48 hours after the onset of an AF episode, or after 3 weeks of anticoagulation with warfarin (Coumadin). Electrical cardioversion is usually followed with a 4-week course of anticoagulation to further reduce the risk of a stroke caused by blood clots (thrombi) released from the left atrium (particularly the left atrial appendage) after the return to regular sinus rhythm. A team of

American, Australian and German researchers now report that electrical cardioversion can be performed safely without the 3-week pretreatment with warfarin if a transesophageal echocardiogram (TEE) taken immediately prior to cardioversion shows no signs of thrombi in the left atrium.

The clinical trial involved 525 patients assigned to TEE prior to cardioversion and 509 patients assigned to the conventional 3-week course of warfarin. The average age of the patients was 65 years and most of them had one or more comorbid conditions such as hypertension, or congestive heart failure. All patients had been in AF for at least 48 hours prior to enrolment and 82% were taking one or more antiarrhythmic drugs. The patients in the TEE group underwent TEE, anticoagulation with unfractionated heparin, and cardioversion within 3 days of enrolment, while patients in the conventional group underwent electrical cardioversion between 20 and 40 days after enrolment.

The immediate conversion rate (to normal sinus rhythm) was 82% in the TEE group and 78.4% in the conventional group. The TEE indicated the presence of thrombi in 62 patients and cardioversion was postponed for this group. After 6 months 62.5% of patients in the TEE group who had undergone cardioversion were still in sinus rhythm as compared to 53.9% in the conventional group. The incidence of ischemic (embolic) stroke and TIA (transient ischemic attack) was 1.9% in the TEE-guided group and 0.8% in the conventional group; however, this difference was not statistically significant. The rate of serious bleeding events was significantly higher in the conventional group (7.5%) than in the TEE-guided group (4.4%). Death from cardiovascular causes over the 6-month follow-up period was similar in the two groups at 2% and most were classified as sudden cardiac death not involving stroke or bleeding.

The researchers conclude that TEE-guided electrical cardioversion is a clinically effective alternative to the conventional anticoagulation strategy followed by cardioversion. They point out that the TEE-guided approach may be particularly useful in highly symptomatic, new onset AF and for patients at high risk for bleeding and stroke.

Klein, AL, et al. Efficacy of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation at 6 months: a randomized controlled trial. American Heart Journal, *Vol. 151, February 2006, pp. 380-89*

Prevention & Treatment with Antiarrhythmics

Digoxin and paroxetine do not mix

HIROSAKI, JAPAN. Japanese physicians report a case of a 68-year-old woman who developed severe digoxin (digitalis) intoxication after starting on paroxetine (Paxil) for depression, insomnia, and difficulty concentrating. The patients had suffered from atrial fibrillation for 2 years and, during this time, had been treated with 0.25 mg digoxin and 1 mg warfarin daily. Two days after beginning on 20 mg/day of paroxetine she experienced nausea, vomiting, and dizziness. Delirium with visual hallucinations followed on day 4 and by day 8 she could no longer eat or walk. On day 9 the doctors suspected digitalis intoxication (serum digitalis concentration was 5.2 ng/mL compared to the normal range of 0.5-2.0 ng/mL). An ECG showed numerous PVCs and complete A-V block. On day 10 all medications were withdrawn resulting in the patient going into bradycardia as a rebound effect of discontinuing digoxin. On day 19 digoxin and warfarin (but not paroxetine) were restarted. The patient remained depressed, developed pneumonia, and died in hospital 3 months later.

The physicians speculate that paroxetine and digoxin are metabolized via the same pathway and that the competition leads to digitalis intoxication. They suggest that citalopram (Celexa) or venlafaxine (Effexor) may be better choices for an antidepressant to be co-administered with digoxin.
Yasui-Furukori, N and Kaneko, S. Digitalis intoxication induced by paroxetine co-administration. The Lancet, *Vol. 367, March 4, 2006, p. 788*

Editor's comment: A lone afibber should NEVER ever accept a prescription for digoxin. There is absolutely no evidence that it is beneficial and substantial evidence that it is likely to materially worsen lone AF.

Promising trials of dronedarone

FRANKFURT, GERMANY. Amiodarone (Cordarone) is probably the most effective antiarrhythmic drug on the market today and is widely used in the management of atrial fibrillation, especially in Europe. Unfortunately, the drug has many serious adverse effects and its long-term use can lead

to pulmonary congestion, liver toxicity, severe thyroid problems, ventricular tachycardia, dermatitis, and visual disturbances. About 75% of patients taking amiodarone experience one or more adverse effects. Amiodarone also has a very long half-life (2-3 months) which means that any adverse effects can linger for a long time. Nevertheless, amiodarone is very effective in preventing the recurrence of atrial fibrillation, so a great deal of research has been directed toward finding a substitute which would maintain the benefits of amiodarone but avoid the adverse effects.

Early research pointed to the iodine part of the amiodarone molecule as being the culprit in most of its adverse reactions. This led to the development of dronedarone – a molecule similar in structure to amiodarone, but without the iodine moiety. Dronedarone also contains a methane sulfonyl group, which shortens the drug's half-life and decreases tissue accumulation. All in all, it is clear that dronedarone is a much safer drug than amiodarone, but is it as effective?

Preliminary studies showed that dronedarone is as effective as amiodarone in blocking Na^+, K^+, Ca^{2+} and slow L-type calcium channels and, as a result, is effective in prolonging action potential duration. Dronedarone also exhibits beta-blocking activities similar to those of amiodarone, but has no significant effect on plasma levels of thyroid hormones (T3, T4 and reverse T3).

The DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion) clinical trial evaluated the effectiveness of dronedarone (400 mg twice a day) in maintaining sinus rhythm in 200 persistent afibbers who had undergone electrical cardioversion. The median time to recurrence of AF was 5 days in the placebo group and 60 days in the dronedarone group. There was no evidence of thyroid, ocular or pulmonary toxicity over the 6-month trial period, but about 3.9% of study participants did experience diarrhea, nausea or vomiting during the trial.

Two other clinical trials of dronedarone are now nearing completion. EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) involves 612 patients at 65 centers in 12 European countries. ADONIS (American-Australian-African Trial with Dronedarone in Atrial Fibrillation/Flutter Patients for the Maintenance of Sinus Rhythm) involves 625 patients recruited from 101 centers in the USA, Canada, Australia, South Africa and Argentina. Both trials are placebo-controlled, multicenter, multinational, double-blind, parallel-group trials using 400 mg of dronedarone twice daily or a placebo to prevent recurrence of AF. Publication of final results is eagerly awaited.

Wegener, FT, et al. Dronedarone: an emerging agent with rhythm- and rate-controlling effects. **Journal of Cardiovascular Electrophysiology**, *Vol. 17, Suppl. 2, September 2006, pp. S17-S20*

Azimilide not effective for AF prevention

VANCOUVER, CANADA. A group of researchers at the University of British Columbia (St. Paul's Hospital) has evaluated the efficacy of the experimental antiarrhythmic azimilide in maintaining sinus rhythm in a group of patients with paroxysmal AF and heart disease (congestive heart failure, coronary artery disease, or structural heart disease). The patients were randomized to receive a placebo (215 patients) or 125 mg of azimilide (216 patients) twice a day for 26 weeks after a recorded afib episode. The median time to afib recurrence was 10 days in patients with congestive heart failure or coronary heart disease irrespective of whether they were taking azimilide or the placebo. Overall, the median time to afib recurrence was 9 days in the azimilide group and 8 days in the placebo group – not a significant difference. The researchers conclude that azimilide does not have a significant benefit, compared with placebo, in delaying afib recurrence in patients who were in sinus rhythm when starting the drug.

Kerr, CR, et al. Efficacy of azimilide for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation in the presence and absence of structural heart disease. American Journal of Cardiology, *Vol. 98, July 15, 2006, pp. 215-18*

New afib drug on the horizon

ATI-2042 is an analogue of amiodarone with a much shorter half-life (7 hours vs. 50 days). Because it is rapidly metabolized and excreted, it is expected to have less severe side effects than those observed with amiodarone and yet be equally effective. British researchers recently put the drug to a preliminary test involving 6 female afibbers. The participants underwent six 2-week test periods during which they received ATI-2042 daily in dosages ranging from 200 mg twice a day to 800 mg twice a day. The average afib burden (% of day spent in afib) prior to the trial varied from 5 to 45% with a mean of 20%. With 200 mg of ATI-2042 taken twice daily the burden decreased to an average of 5.1% and with 800 mg twice daily it reduced to 1.7%. The researchers conclude that ATI-2042 is highly efficient in reducing afib burden and are now planning large-scale phase 2 trials.

PACE, Vol. 29, Suppl 1, April 2006, Abstract #124, p. S62

Prevention & Treatment with Other Drugs

Statin drug may help prevent AF

MYTILINI, GREECE. There is considerable evidence that a systemic inflammation may be involved in atrial fibrillation. There is also evidence that high blood levels of the inflammation marker C-reactive protein (CRP) are associated with an increased risk of developing afib and experiencing recurring episodes. C-reactive protein levels can be effectively reduced with statin drugs (and many natural compounds), and there is some indication that doing so may reduce the risk of recurrent afib episodes after a successful cardioversion. Now Greek researchers report that the cholesterol-lowering drug atorvastatin (Lipitor) is effective in reducing the number of episodes in paroxysmal afibbers. Their study involved 80 patients who had documented asymptomatic afib episodes on a 48-hour Holter monitoring prior to beginning treatment. The patients (55 men and 25 women) were between the ages of 29 and 85 years (median 52 years). Their baseline CRP level ranged from 0.8 to 13 mg/L (0.08 – 1.3 mg/dL) with a median of 5.9 mg/L (0.6 mg/dL). NOTE: The normal range is considered to be 0 – 5 mg/L. Half the patients were assigned to receive a placebo, while the other half received 20 mg/day of atorvastatin (increased to a maximum of 40 mg/day if a 20% reduction of CRP was not achieved by 6 weeks) for the duration of the 4-6 month study period. Holter monitors were used at the beginning and end of the study to ascertain the number and duration of episodes experienced over a 48-hour period.

The researchers, not too surprisingly, found that members of the atorvastatin group experienced a significant drop in total and low-density cholesterol. They also observed that average CRP levels in the atorvastatin group dropped from 5.8 mg/L to 2.8 mg/L over the study period. The average number of afib episodes (all asymptomatic) decreased from 9 in the baseline 48-hour monitoring to 0 in the end-of-study monitoring in the atorvastatin group, while it declined from 13 to 12 in the placebo group. The researchers conclude that atorvastatin may be useful in reducing CRP levels and the frequency of afib episodes in afibbers with the paroxysmal variety.

Dernellis, J and M. Panaretou. Effect of C-reactive protein reduction on paroxysmal atrial fibrillation. American Heart Journal, *Vol. 150, November 2005, pp. 1064-69*

Editor's comment: Although intriguing, I am not certain just how much hope these findings hold for the average paroxysmal afibber. The group involved in the study was somewhat unusual in that its members had mild or no symptoms during daily life and did not report any symptoms during the two monitoring sessions. They also tended to have elevated CRP levels, which does not seem to be common among the lone afibbers I have surveyed (my own level during my worst period of afib was less than 0.3 mg/L). So would atorvastatin or CRP-lowering as such help an afibber with highly symptomatic episodes? I don't know, but I am somewhat skeptical that the claims made by the Greek researchers would apply to the majority of afibbers. However, having a high CRP level is detrimental in many ways so reducing it can certainly do no harm. Successful reduction can be achieved by supplementing with beta-sitosterol, Moducare, Zyflamend or boswellia. Statin drugs will also do the trick, but should always be taken accompanied by at least 100 mg/day of coenzyme Q10.

Ablation - Procedures

RF ablation – One method does not fit all

TREVISO, ITALY. There are currently four common protocols for the performance of a radiofrequency ablation:

- **Segmental pulmonary vein isolation (SPVI or Haissaguerre procedure) –** In this procedure electrophysiological mapping (using a multipolar Lasso catheter) is used to locate the pathways taken by aberrant impulses from the pulmonary veins and these pathways are then eliminated by ablation around the veins approximately 5 to 10 mm from the ostium of the veins.

- **Circumferential anatomical pulmonary vein isolation (CAPVI or Pappone procedure) –** In this procedure anatomical mapping (CARTO) is used to establish the exact location of the pulmonary veins. Two rings of lesions are then created in the left atrium - one completely encircling the left pulmonary veins and another completely encircling the right pulmonary veins; the two rings are usually joined by a linear lesion on the roof of the atrium.

- **Pulmonary vein antrum isolation (PVAI or Natale procedure) –** This procedure is a variant of the Haissaguerre procedure. It involves locating aberrant pathways through electrophysiological mapping (using a multipolar Lasso catheter) and ablating these pathways guided by an ultrasound (ICE) catheter. The ablation is performed as close as possible to the outside edge (antrum) of the junction between the pulmonary veins and the atrial wall. All four pulmonary veins as well as the superior vena cava (if indicated) are isolated during the procedure.

- **Substrate ablation** – This procedure was pioneered by Dr. Koonlawee Nademanee and involves locating (with CARTO mapping) sites with complex fractionated electrograms recorded during atrial fibrillation and then ablating them. An electrogram is a picture of the electrical activity of the heart as sensed from within the heart as opposed to an ECG which senses the activity from outside the heart. Fractionated

electrograms are characterized by abnormalities in the baseline or a very short cycle length.

Some EPs use combinations of these procedures and some routinely perform a right atrial flutter ablation (ablation of the isthmus connecting the tricuspid annulus and the inferior vena cava) as part of the overall procedure.

Roberto Mantovan and colleagues now report the results of a clinical trial to determine the success rates of the Pappone method in comparison with the Pappone method followed by segmental PVI as per Haissaguerre. The trial involved 60 afibbers (39 paroxysmal, 13 persistent, and 8 permanent) who were randomly assigned to undergo only circumferential anatomical PVI (Pappone protocol) or circumferential PVI followed by segmental PVI as per Haissaguerre. The difference of course being that in the Pappone method the ablation lesions are placed based on anatomical features of the heart, while in the Haissaguerre method they are placed based on actual electrophysiological measurements of electrical potentials in the heart.

The total procedure time, fluoroscopy time, and the time RF energy was actually applied were similar in the two groups – 227, 50 and 43 minutes versus 232, 55, and 42 minutes respectively. The patients were followed for an average of 15 months at which time 57% of the Pappone group were in normal sinus rhythm as compared to 83% in the group who had undergone the Pappone protocol followed by an EP study (with a Lasso catheter) to locate and ablate conductive pathways missed during the circumferential ablation. Four patients from each group (13%) underwent a repeat procedure. The researchers conclude that an ablation approach combining circumferential anatomical ablation with a subsequent electrophysiological approach is superior to the circumferential approach on its own.

Mantovan, R, et al. Comparison between anatomical and integrated approaches to atrial fibrillation ablation: adjunctive role of electrical pulmonary vein disconnection. **Journal of Cardiovascular Electrophysiology**, *Vol. 16, December 2005, pp. 1293-97*

Irrigated ablation catheter superior

A team of American and Italian researchers has compared the safety and efficiency of the standard 8 mm radiofrequency ablation catheter and an open-tip, irrigated (with saline solution) catheter (*Celsius ThermoCool* diagnostic ablation catheter) in the performance of pulmonary vein isolation (PVI). Sixty-two afib patients were involved in the trial and complete isolation was achieved in all of them regardless of catheter used. However, radiation exposure (average fluoroscopy time) was significantly lower in the *ThermoCool* group (26 vs 39 minutes) and procedure time (total time catheters are present in left atrium) was also considerably lower in the *ThermoCool* group (60 vs 86 minutes). The team concludes that open-tip, irrigated catheters can safely be used for PVI procedures and that their use minimizes radiation exposure and procedure time.

PACE, Vol. 29, Suppl. 1, April 2006, Abstract #7, p. S4

CARTO mapping integrated with CT scan

LONDON, UNITED KINGDOM. Although the use of electroanatomic mapping techniques (CARTO) has greatly improved the EP's ability to visualize the structure of the heart, it still provides a pretty crude picture. Efforts have been underway for a while to integrate more detailed pictures of the heart with the CARTO image. Now researchers at St. Bartholomew's Hospital report on their experience with integration of a CT scan of the heart with the standard CARTO image. Their study group involved 30 patients (average age 59 years, 25 male) 12 of whom had paroxysmal and 18 of whom had persistent AF. The patients all had a multi-slice (8 slices) helical CT scan prior to their ablation. The scan was then aligned to the CARTO image using the pulmonary veins as landmarks. The integration (registration) was performed using the *Cartomerge* software and was found to be accurate to within 2.3 mm. The registration accuracy was not affected by whether the patients were in sinus rhythm or afib at the time the CT scan was taken. The integrated map was used to guide the encirclement of the pulmonary veins and achieved this successfully in 97% of cases. However, 15 (50%) of the patients required cardioversion at the end of the procedure since normal sinus rhythm had not been achieved as a result of the ablation. The authors provide no data with which to judge the long-term success of the procedure.

Kistler, PM, et al. Validation of three-dimensional cardiac image integration: Use of integrated CT image into electroanatomic mapping system to perform catheter ablation of atrial fibrillation. Journal of Cardiovascular Electrophysiology, *Vol. 17, April 2006, pp. 341-48*

Editor's comment: Researchers at Johns Hopkins University School of Medicine have carried out similar experiments using integration of the CARTO image with CT scans and MRIs. They were able to achieve complete isolation of 32% of the pulmonary veins encircled, but had to complete the procedure using the old standby, the Haissaguerre method. At the 6-month follow-up, 80% of paroxysmal patients, 50% of persistent afibbers, and 0% of permanent afibbers exposed to the protocol were still in normal sinus rhythm.[1] This is not an overwhelmingly impressive result.

Although the successful integration of CT scans and MRIs with the CARTO system is no doubt a technological triumph, it does not, so far at least, seem to have improved the success rate for the electroanatomical (Pappone) approach. The segmental and antrum isolation procedures developed by Prof. Haissaguerre and Dr. Natale are still the "gold standards", at least when performed by a highly skilled and experienced EP.

[1] Dong, J, et al. Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR/CT images to guide catheter ablation of atrial fibrillation. Journal of Cardiovascular Electrophysiology*, Vol. 17, May 2006, pp. 459-66*

Haissaguerre vs Pappone method

Cardiologists at the German Heart Center in Munich have compared the outcome of ablations performed according to the Haissaguerre protocol (segmental pulmonary vein isolation or PVI) and the Pappone protocol (circumferential pulmonary vein ablation or CPVA). One hundred consecutive afib patients with a mean age of 58 years were randomized to undergo PVI (guided by electrophysiological measurements) or CPVA (guided by anatomical imaging). If afib recurred within a 12-month period following the initial procedure, a repeat procedure was performed using the same protocol as used in the initial one. Repeat ablations were required in 12 of the 50 PVI patients (24%) and in 22 of the 50 CPVA patients (44%). After repeat ablation 10 out of 12 patients in the PVI group (83%) were in stable sinus rhythm as compared to only 6 out of 22 (27%) in the CPVA group. The majority (92%) of patients in the PVI group needed their repeat ablation because of recurrence of atrial fibrillation (AF). In the CPVA group, however, only 41% were re-ablated solely for AF, while the remaining 59% developed left atrial flutter as a result of the first procedure and had to undergo ablation for that as well.

PACE, Vol. 29, Suppl. 1, April 2006, Abstract #8, p. S4

New RF ablation approach in persistent and permanent afib

ROME, ITALY. It is now clear that performing a successful ablation in afibbers with persistent (episodes longer than 7 days, but amenable to cardioversion) and permanent afib is far more difficult than doing so in afibbers with paroxysmal (intermittent, self-terminating) episodes. The problem is that, while the source of paroxysmal afib initiation is largely in the pulmonary veins, the origin of persistent and permanent afib can be in several other areas of both the left and right atrium. Thus, while just isolating the pulmonary veins using the Haissaguerre (electrophysiological mapping), Natale (electrophysiological mapping), or Pappone (electroanatomical mapping) method will often suffice for paroxysmal afib, it is much less likely to be successful for the persistent and permanent varieties. The problem with sources other than the pulmonary veins is particularly serious in the case of the Pappone method, which is based on ablating fixed anatomical features located via CARTO mapping rather than on ablating specific, abnormal electrical potentials located through electrophysiological mapping.

A team of Italian electrophysiologists now reports that ablating certain specific anatomical features in the left atrium combined with ablation of other features in the right atrium is more likely to restore normal sinus rhythm in persistent and permanent afibbers than is left atrial ablation alone. Their clinical trial involved 52 men and 28 women between the ages of 50 and 68 years. Forty-three of the patients had persistent afib, while the remaining 37 had permanent afib. All patients had failed at least three antiarrhythmic drugs and 84% had structural heart disease. Most of the patients (53%) were on amiodarone before, during, and 6 months after the procedure; the rest of the patients were on sotalol (21%), flecainide or propafenone.

The patients were divided into two groups. Group I underwent just left atrial ablation (circumferential pulmonary vein isolation plus a line from the lesion encircling the left inferior pulmonary vein to the mitral annulus). Group II underwent left atrial ablation plus several specific ablations in the right atrium including the electrical disconnection of the superior vena cava from the right atrium. Total average procedure time for group I was 2 hours and 44 minutes compared to 3 hours and 48 minutes for group II. All patients were in afib at the beginning of the procedure, but afib was terminated in 85% of group II patients and in 24% of group I patients at the end of the procedure.

The study participants were followed for a total of 14 months after the procedure and remained on antiarrhythmic drugs for the first 6 months after the procedure. Success rates at the end of the follow-up period were as follows:

	Group I Left atrium ablation	Group II Left & right atrium ablat.
Persistent afibbers		
Afib-free without antiarrhythmics	21%	47%
Afib-free with antiarrhythmics	46%	42%
Still in afib	33%	11%
Permanent afibbers		
Afib-free without antiarrhythmics	12%	35%
Afib-free with antiarrhythmics	41%	45%
Still in afib	47%	20%

Thus, the overall complete success rate (no drugs) was 17% for left atrium ablation only and 41% for biatrial ablation.
Calo, L, et al. Left atrial ablation versus biatrial ablation for persistent and permanent atrial fibrillation. **Journal of the American College of Cardiology**, *Vol. 47, June 20, 2006, pp. 2504-12*

Editor's comment: The complete success rate (no antiarrhythmics) for this new "improved" ablation procedure was only 41% and a dismal 17% for the standard left atrium ablation. This clearly shows (again) that the Pappone method (circumferential anatomical pulmonary vein isolation) using the CARTO mapping system is vastly inferior to the Haissaguerre and Natale methods, especially when it comes to persistent and permanent afib. The Haissaguerre team in Bordeaux recently reported a complete success rate of 87% (95% after a follow-up ablation) in a group of persistent and permanent afibbers using extensive electrophysiologically guided mapping and ablation.[1-3] The superiority of the Haissaguerre method would probably apply to any afibbers who have ever experienced episodes lasting 24 hours or longer.
[1] Haissaguerre, M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: Critical structures for termination. *Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1125-37*
[2] Haissaguerre, M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: Clinical outcome and mechanisms of subsequent arrhythmias. Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1138-47
[3] Tse, Hung-Fat and Lau, Chu-Pak. Catheter ablation for persistent atrial fibrillation: Are we ready for "prime time"? Journal of Cardiovascular Electrophysiology, Vol. 16, November 2005, pp. 1148-49

Ablation by robot

Dr. Carlo Pappone and his group at the San Raffaele Hospital in Milan report on the first trial of robot-assisted ablation. Their trial involved 40 afibbers who underwent circumferential pulmonary vein ablation (CPVA) using a combination of the CARTO anatomical mapping system and a remotely-controlled, magnetic ablation catheter (4 mm tip). The procedure successfully achieved the end result of pulmonary vein isolation in 38 of the 40 patients. A very steep learning curve was experienced. The total average procedure time was 193 minutes for the first 12 patients dropping to 148 minutes for the next 18. The researchers conclude that remote magnetic navigation for AF ablation is safe and feasible with a short learning curve and is especially well-suited for less experienced EPs.

PACE, Vol. 29, Suppl 1, April 2006, Abstract #38, p. S20

Comparison of Haissaguerre and Pappone methods

COPENHAGEN, DENMARK. The two main radiofrequency ablation procedures used today are the segmental pulmonary vein isolation procedure developed by Prof. Haissaguerre in Bordeaux and the circumferential anatomical pulmonary vein isolation procedure developed by Dr. Pappone in Milan. The pulmonary vein antrum isolation procedure was developed by Dr. Natale in Cleveland and is essentially a variant of the Haissaguerre procedure.

The Haissaguerre and Natale methods use electrophysiological mapping (Lasso catheter) to determine the location of the pulmonary veins, while the Pappone method uses anatomical mapping (CARTO). The Haissaguerre/Natale methods are generally considered more technically challenging since they involve electrical isolation of each of the four pulmonary veins in close proximity to their junction with the left atrium. The Pappone method, on the other hand, requires only the "burning" of two large circles in the atrium – one encircling the left pulmonary veins and one encircling the right veins.

Researchers at the Copenhagen University Hospital now report on their comparison of the Haissaguerre and Pappone methods. The study involved 100 consecutive patients (51 paroxysmal, 49 persistent) who underwent RF ablation during the period November 2002 to November 2004. All procedures were performed by the same operator who had performed more than 200 afib ablations at the beginning of the study.

The success rate of the procedures (3 months post-ablation ignoring episodes during first 30 days) was 16% (22% for Pappone method and

11% for Haissaguerre method) without antiarrhythmics, with the remaining 84% experiencing symptomatic afib or left atrial tachycardia during the three months following the procedure. Seventy-four patients (74%) had a second ablation with success rates of 44% and 28% respectively for the Pappone and Haissaguerre methods. After 12 months the percentage of ablatees being free of symptomatic afib (without the use of antiarrhythmics) was 57% for the Pappone method and 31% for the Haissaguerre method. The success rate among persistent afibbers was significantly poorer than among paroxysmal ones (52% for Pappone method and 15% for Haissaguerre method). Four patients (4%) experienced a systemic embolic event during the 173 procedures, all occurring within 2 days post-ablation. Although 5 patients experienced breathing difficulties after the procedure, no systemic evaluation for PV stenosis was performed.

The authors of the study conclude that the circumferential anatomical pulmonary vein isolation procedure (Pappone) is superior to the segmental approach (Haissaguerre), especially for persistent AF.
Nilsson, B, et al. Recurrence of pulmonary vein conduction and atrial fibrillation after pulmonary vein isolation for atrial fibrillation: A randomized trial of the ostial versus the extraostial ablation strategy. American Heart Journal, *Vol. 152, No. 3, September 2006, pp. 537-44*

Editor's comment: The overall success rate (no antiarrhythmics) after a 74% repeat ablation rate was only 45% clearly indicating the inexperience of the EP performing the procedures. For example, the right inferior vein was only completely isolated in 24% of patients undergoing the Haissaguerre procedure. The conclusion that the Pappone method is superior to the Haissaguerre method is not surprising since the Pappone method requires considerably less skill and experience than does the Haissaguerre method and therefore would be expected to produce better results in inexperienced hands. In comparison, the success rates obtained in Bordeaux and Cleveland now exceed 90% for paroxysmal and 85% for persistent and permanent afib. Of course, the lead EPs at both institutions have, by now, performed well over 3,000 procedures each. Experience and innate skill make all the difference!

Improved circumferential ablation technique

BALTIMORE, MARYLAND. The circumferential anatomical pulmonary vein isolation procedure (Pappone method) is based on the use of anatomical mapping (CARTO) to establish the exact location of the pulmonary veins. Two rings are then created in the left atrium – one completely encircling the left pulmonary veins and another completely encircling the right pulmonary veins; the two rings are usually joined by a linear lesion. The Pappone method differs from the Haissaguerre and Natale methods in

that it does not use electrophysiological measurements (with a Lasso catheter) to guide the ablation and confirm complete isolation of the veins.

Now researchers at Johns Hopkins University School of Medicine report that they have developed and tested a new ablation protocol, which combines circumferential anatomical PVI with electrophysiological measurement to ensure complete isolation. The study involved 64 consecutive afib patients aged between 49 and 69 years. Seventy-three percent were male and the majority (45%) had paroxysmal afib with the remaining having either persistent (29%) or permanent (25%) afib. The patients underwent the standard Pappone procedure after which the Lasso catheter was used to determine if complete isolation had been achieved; if not, further circumferential lesions were made in order to achieve isolation. After the initial circumferential lesions, isolation was observed in 12 – 29% of all veins. This increased to 84 – 90% after continued ablation. The most common reason for the inability to achieve complete isolation was fear of burning through to the esophagus.

After a follow-up of 12 to 14 months 45% of ablatees were free of symptomatic afib with no antiarrhythmic drugs, while another 5% reported marked improvement. Seventeen (26%) of the 64 patients underwent one or more repeat ablations bringing the overall success rate (without antiarrhythmics) to 62% with another 9% demonstrating significant improvement. Forty (62%) of the 64 patients had recurrence of afib within the first 3 months following the ablation (92% during the first month). None of the patients experienced a first recurrence more than 12 months post-ablation. Overall, 72% of patients not experiencing an afib episode during the first 3 months went on to achieve complete long-term success as compared to only 27% achieving long-term success in the group having episodes during the first 3 months post-ablation.

The complication rate was 6% with the most serious one being tamponade (piercing of the heart wall). Total average procedure time was 216 minutes and fluoroscopy time was 72 minutes. The Johns Hopkins researchers conclude that the use of the Lasso catheter to ensure complete pulmonary vein isolation improves the outcome of circumferential anatomical PVI.
Cheema, A, et al. Long-term safety and efficacy of circumferential ablation with pulmonary vein isolation. Journal of Cardiovascular Electrophysiology, *Vol. 17, October 2006, pp. 1080-85*

Editor's comment: The success rates achieved with this new, "improved" approach is clearly not impressive with overall success rates (after repeat ablations) of 65% for paroxysmal, 52% for persistent, and 68% for permanent. The average procedure and fluoroscopy times were also

quite long compared to the average times reported from Bordeaux and Cleveland. Finally, the complication rate of 6% is excessive.

Is flutter ablation necessary with PVI?

Many afibbers also suffer from right atrial flutter and it is now common practice in several ablation centers to perform an ablation in the right atrium (cavotricuspid isthmus ablation) to prevent atrial flutter whether or not the afibber has actually ever experienced a flutter episode. Researchers at the University Hospital in Geneva, Switzerland now question this approach. In a study involving 176 afibbers (127 paroxysmal) who underwent a standard PVI, the researchers decided to limit the performance of a flutter ablation to patients who had experienced a documented episode of sustained typical atrial flutter before or during the PVI. Thus, 69 patients underwent the flutter ablation, while 107 did not. During a follow-up of 18 months, 2 patients in the group ablated for flutter had a recurrence and 2 patients among the 107 who did not have the flutter ablation also developed flutter. The researchers conclude that the atrial flutter ablation should be reserved for those with a previous episode since the post-PVI incidence rate among afibbers with no previous atrial flutter episodes is only 2%.

PACE, Vol. 29, Suppl 1, April 2006, Abstract #11, p. S6

Laser technology enters PVI arena

An international team of electrophysiologists from centers in the United States, Italy, the Czech Republic, and Germany reports the first human trial of a novel endoscopic laser balloon ablation system designed to cure atrial fibrillation (AF). The trial involved 20 patients with symptomatic paroxysmal afib. The average age of the patients was 54 years (range of 29-73 years) and they had suffered from afib for an average of 6 years (1.5 to 24 years). A circumferential mapping catheter and the laser balloon system were placed at each pulmonary vein opening (ostia) in turn and laser energy applied to create the necessary lesions to isolate the veins. Successful isolation was achieved in 86% of veins targeted. Seventy-five per cent of treated patients were free from symptomatic afib after 6 months of follow-up. No stenosis was observed. The electrophysiologists conclude that light-energy (laser) ablation is a viable option for PVIs.

PACE, Vol. 29, Suppl 1, April 2006, Abstract #14, p. S7

Ablation - Complications

Stenosis in anatomic PV ablation

BALTIMORE, MARYLAND. Stenosis (significant narrowing of the diameter) of the pulmonary veins is a potential, serious adverse effect associated with pulmonary vein isolation (PVI) using radiofrequency ablation. It was fairly common in the early days of ablation since ablation lesions were often placed in the veins themselves or very close to the edge (ostia) where the veins open into the wall of the left atrium. With better mapping techniques the incidence of stenosis has declined, but is still of concern. The circumferential pulmonary vein ablation protocol (Pappone method) was expected to further reduce the possibility of stenosis by ensuring that ablations lesions (two lesions encircling the left and right pulmonary veins respectively) were placed well away from the ostia.

Electrophysiologists at Johns Hopkins University School of Medicine now report the first study aimed at determining the actual incidence of stenosis in PVIs performed using the Pappone procedure (anatomic PV ablation). The study involved 41 consecutive patients who underwent anatomic PV ablations. Eighty per cent of the study participants had lone atrial fibrillation. Twelve patients had paroxysmal afib, 12 had the persistent variety, and 17 had permanent afib. The average age of the patients was 56 years and 18 were women. All patients underwent gadolinium-enhanced magnetic resonance imaging (MRI) immediately prior to and 8-10 weeks after their PVI. Twenty-five of the ablated patients (61%) had a successful ablation and were in normal sinus rhythm without the use of antiarrhythmics after 6 months of follow-up.

A comparison of MR images before and after the ablation showed that detectable stenosis (diameter narrowing of 3 mm or more) was present in 73% of all patients. Most (59%) had only mild stenosis (less than 50% narrowing), but 12% had moderate stenosis (50-70% narrowing), and one patient (2.4%) had severe stenosis (greater than 70% narrowing). The major variables associated with an increased risk of stenosis was the encirclement of individual veins rather than both left and both right veins within one circular lesion each and a larger initial vein diameter.

None of the patients required treatment for stenosis, but the authors of the study point out that stenosis tends to progress with time so it is possible that treatment may be required in the future. The researchers express surprise over the relatively high proportion of stenosis, but point out that electroanatomical mapping is not perfect in that it, among other

factors, depends on the patient being absolutely still during the mapping procedure. They also suggest that mild stenosis may be due to a shrinking of the atrium (remodeling) after reestablishment of normal sinus rhythm, rather than a result of ablation lesions being placed too close to the veins.
Dong, J, et al. Incidence and predictors of pulmonary vein stenosis following catheter ablation of atrial fibrillation using the anatomic pulmonary vein ablation approach. Journal of Cardiovascular Electrophysiology, *Vol. 16, August 2005, pp. 845-52*

Editor's comment: The surprising finding that pulmonary vein stenosis is a significant problem in anatomically guided pulmonary vein ablation emphasizes the importance of a 3-month follow-up MRI or CT scan to check for pulmonary vein narrowing.

Inflammation and early recurrence of post-ablation AF

There is some speculation that inflammation and edema caused by a pulmonary vein isolation (PVI) procedure may precipitate early recurrence of afib. Researchers at the Cleveland Clinic now report that treatment with a powerful anti-inflammatory (60 mg prednisone on day of procedure followed by methylprednisolone for 6 days) has no effect on the early recurrence of afib after an ablation. The only variable showing a significant association with early recurrence was left atrial size with a larger size predicting an increased risk of recurrence.
PACE, Vol. 29, Suppl 1, April 2006, Abstract #38, p. S20

Exploration of left atrial flutter

GENEVA, SWITZERLAND. The development of left atrial flutter after an otherwise successful radiofrequency (RF) ablation is a fairly common occurrence. In some cases the flutter resolves on its own within 3 months or so, but in other cases another ablation is necessary to cure it. Researchers at the Hopital Cantonal de Geneve now report that the majority of these flutters can be easily located and eliminated with one well-placed, 30-second "burn" (application of radiofrequency energy).

Their study involved 207 afibbers who had undergone a successful RF ablation to eliminate their AF (151 paroxysmal and 56 persistent). Sixteen (8%) of the patients developed left atrial flutter after the procedure. One case resolved spontaneously, but the other 15 required an additional ablation to correct the problem. The patients were all men with an average age of 56 years; 9 had paroxysmal afib and 6 had persistent afib prior to their ablation; 4 had underlying structural heart

disease. A careful ECG study combined with the location of fractionated electrograms showed that 11 of the 15 atrial flutters originated in discrete, narrow, and unique zones of marked slow conduction at or in the vicinity of previously ablated PV ostial sites. The offending zones were ablated and the left atrial flutter eliminated within 30 seconds with a single RF application. The Swiss researchers conclude that most left atrial flutter sources are located within a very small area and can be eliminated quite easily. They provide detailed instructions as how to locate the offending areas.

Shah, D, et al. Narrow, slow-conducting isthmus dependent left atrial reentry developing after ablation for atrial fibrillation: ECG characterization and elimination by focal RF ablation. Journal of Cardiovascular Electrophysiology, *Vol. 17, May 2006, pp. 508-15*

Merino, JL. Slow conduction and flutter following atrial fibrillation ablation: proarrhythmia or unmasking effect of radiofrequency application? Journal of Cardiovascular Electrophysiology, *Vol. 17, May 2006, pp. 516-19*

Post-ablation stroke risk

ANN ARBOR, MICHIGAN. Electrophysiologists at the University of Michigan report the results of a large study aimed at determining the incidence of thromboembolic events (ischemic stroke or transient ischemic attack – TIA) after radiofrequency ablation of atrial fibrillation. The study involved 755 afibbers (490 with paroxysmal and 265 with permanent afib) with an average age of 55 years (17-79 years). About 23% of the patients were women and 56% had one or more risk factors for stroke (congestive heart failure, hypertension, diabetes, age over 65 years, or a history of TIA or stroke). The patients underwent circumferential pulmonary vein ablation (Pappone method) using an 8-mm tip catheter. The procedure was repeated in 174 patients (23% repeat rate) and at the end of 12 months post-ablation, 77% of patients with paroxysmal afib and 66% of permanent afibbers were in normal sinus rhythm without the use of antiarrhythmics. The success rate after two years decreased to 73% and 62% respectively.

The patients were all treated with warfarin for at least 3 months prior to the procedure. Warfarin therapy was resumed immediately after the procedure and continued for at least 3 months, after which patients who were taken off were asked to take 81-325 mg/day of aspirin indefinitely. A thromboembolic event (TE) occurred in 7 patients (0.9%) within two weeks of the procedure and two TEs occurred 6-10 months after the procedure. The majority (78%) of the TE victims had one or more risk factors for stroke prior to ablation. The 0.2% incidence of late TEs is equivalent to the incidence expected among age-matched, otherwise healthy individuals without atrial fibrillation.

Among patients whose ablation was successful, warfarin therapy was discontinued for 79% of patients with no stroke risk factors and for 68% of those with one or more risk factors. None of these patients experienced a TE during 17-23 months of follow-up. The researchers conclude that the risk of a TE after radiofrequency ablation is 1.1% with most events occurring within the first two weeks following the procedure. They also express the opinion that discontinuation of warfarin therapy after a successful ablation is safe in patients with no risk factors and in most patients with risk factors. The data obtained during the study was insufficient to conclude whether patients older than 65 years of age or with a history of prior stroke could also safely discontinue anticoagulation after 3 months.

Oral, H, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation, *Vol. 114, August 22, 2006, pp. 759-65*

Editor's comment: The clear conclusion of this study is that a successful ablation reduces the risk of stroke to that of the general population. It is of some concern though that 4% of the patients who had been afib-free one year after the procedure no longer were so two years later. This indicates the need for periodic check-ups to ensure that afib has not returned – perhaps in an asymptomatic form.

Ablation - Outcome

Predicting ablation success

BORDEAUX, FRANCE. Electrical isolation of the pulmonary veins (PVI) is now standard practice in ablation procedures aimed at curing atrial fibrillation. In many cases, a PVI is sufficient to lead to complete abolition of future afib episodes, but in other cases, this unfortunately is not so. Studies have shown that the chance of ultimate success is much higher if afib cannot be induced after the PVI. However, in cases where afib is inducible (by pacing at the mid-coronary sinus, or at the right or left appendage), it is often possible to effect a cure by creating linear lesions at the mitral isthmus or at the roof of the left atrium joining the two superior pulmonary veins. Clearly, it would be highly desirable to be able to predict whether a simple PVI would be likely to cure a patient, or whether further ablation is likely to be required – or, in other words, to predict the likelihood of pacing after the PVI being able to induce afib.

Researchers at the Hopital Cardiologique du Haut-Leveque have now developed a protocol for estimating whether an afibber is likely to need more extensive ablation. Their study involved 181 afibbers (85% male with an average age of 54 years) who had suffered from paroxysmal atrial fibrillation (AF) for an average of 6 years prior to their procedure. The patients all underwent radiofrequency PVI (while in afib) and cavotricuspid isthmus ablation (to prevent right atrial flutter). Total procedure time was 2.4 hours with fluoroscopy time of 39 minutes and radiofrequency exposure of 49 minutes. After completion of the PVI it was possible to induce sustained AF (longer than 10-minute episode) in 54% of the patients. These patients were then treated with additional linear lesions increasing average procedure time to 3.6 hours, fluoroscopy exposure to 66 minutes, and radiofrequency exposure to 69 minutes.

The Bordeaux researchers compared age, gender, body weight, height, BMI, time since first afib episode, duration of longest episode, presence or absence of structural heart disease, hypertension, left ventricular ejection fraction, and extent of hypertrophy and left atrium size in the group where afib could not be induced after the PVI with those in the group where afib could be induced. They found that the duration of the largest (symptomatic) episode, left ventricular hypertrophy (septum thickness greater than 12 mm in parasternal long-axis view), and longitudinal left atrium diameter (greater than 57 mm) were independent predictors of the likelihood that AF could be induced after a PVI. Not having experienced afib episodes lasting longer than 12 hours was

associated with an 86% probability that sustained afib could not be induced after the standard PVI (86% sensitivity, 78% specificity). On the other hand, having experienced episodes longer than 48 hours made it a near certainty (97% probability) that sustained afib could be induced after the PVI, thus necessitating further ablation. The absence of left ventricular hypertrophy was associated with a 96% probability that sustained afib could not be induced, and a left atrium diameter (longitudinal) of less than 57 mm predicted that fib could not be induced with a 75% probability.

The researchers conclude that measuring left atrium diameter, the extent of left atrial hypertrophy, and enquiring about the duration of the longest episode experienced by a patient prior to ablation will assist in better planning of the procedure and a more realistic estimate of the chances of ultimate procedural success.
Rotter, M., et al. Clinical predictors of noninducibility of sustained atrial fibrillation after pulmonary vein isolation. Journal of Cardiovascular Electrophysiology, *Vol. 16, December 2005, pp. 1298-1303*

Editor's comment: This Bordeaux study underscores that all afibbers are not created equal, and also goes a long way toward explaining why a simple PVI is often not sufficient to effect a permanent cure.

Early recurrence of afib after PVI

BAD NAUHEIM, GERMANY. Several studies have shown that the average success rate (absence of afib with no medications) of pulmonary vein isolation (PVI) is about 50% with some specialized centers like Cleveland and Bordeaux doing much better and other centers doing significantly worse. There is, unfortunately, no agreement as to how success should be measured. Is it the total absence of symptomatic episodes observed by the patients after the PVI? Is it the absence of afib on occasional Holter recordings or ECGs performed after the PVI? How long should an afib episode last to be considered significant – more than 30 seconds or more than 2 minutes? Is a PVI a success if the patient's quality of life improves, or is strict absence of afib the only measure of success? No agreement exists on these points and this, of course, is bound to influence the success rates reported by various institutions.

German cardiologists recently reported on the outcome of 100 consecutive PVIs performed at the Kerckhoff-Klinik. Most (90%) of the 100 patients involved had no underlying structural heart disease with 85% having paroxysmal and 15% having persistent afib; 62% were men and the average age was 54 years (45-63 years). Radiofrequency (RF) ablation was used in the case of 63 patients, while the remaining 37 patients underwent a hybrid cryotherapy/RF ablation.

Early recurrence of afib (ERAF) was documented (with a portable recorder) in 30% of RF-treated patients and 25% reported symptomatic episodes. Corresponding numbers for the patients treated with the hybrid method were 43% and 35% respectively. The researchers found that patients with early recurrence who experienced a total of more than 6 hours of afib during the first 3 months after the PVI had a 100% probability of experiencing further episodes in the future – ie. of not being cured. In contrast, patients who experienced no ERAF during the 3 months following the PVI had a 65% probability of being completely afib-free and an 86% probability of their improvement remaining stable.

The overall probability of freedom from any symptomatic afib episodes over a 2-year period following the PVI was 50% for the RF group and 39% for the hybrid group. About 16% of RF procedure patients (19% of hybrid patients) experienced asymptomatic episodes after the first 3 months; however, these episodes generally lasted only between 1 and 6 hours and thus should not be a cause for concern as far as stroke risk is concerned. Quality of life scores improved significantly for patients who had undergone a completely successful procedure or whose afib burden (total time spent in afib over a 3-month period) was less than 12 hours. However, patients with an afib burden greater than 12 hours (per 3 months) experienced no improvement in quality of life score as compared to their score prior to the PVI.

The researchers conclude that an afib burden greater than 12 hours is an indication of failure as far as quality of life is concerned. They also suggest that symptomatic ERAF (episodes during first 3 months post-PVI) is highly predictive of late recurrence and should be used as an indicator for a repeat ablation.
Berkowitsch, A, et al. Usefulness of atrial fibrillation burden as a predictor for success of pulmonary vein isolation. PACE, *Vol. 28, December 2005, pp. 1292-1301*

Editor's comment: The findings of the German researchers are in accordance with the findings of our LAF Survey 9. In this survey we found that afibbers who experienced no episodes during the first 3 months after their PVI had a 63% probability of being completely afib-free (the German researchers corresponding number is 65%).

Real success rates for PVIs

LEIPZIG, GERMANY. Pulmonary vein isolation (PVI) is now the standard procedure for the curative treatment of atrial fibrillation. Success rates (no afib, no medication) as high as 95% have been reported, but most centers report cure rates of about 50-70%. Unfortunately, there is no common agreement as to how success should be measured. Does

absence of symptomatic episodes constitute success, or is it necessary to document the absence of afib via periodic Holter recordings or transtelephonic ECGs?

German researchers recently set out to answer this question in a study of 30 consecutive, highly symptomatic afibbers who underwent an electro-anatomically guided (Pappone) PVI procedure. The study participants (25 men and 5 women) with an average age of 56 years had suffered from AF for an average of 5 years and 37% of them had lone afib, while 50% had a history of hypertension, and 17% had coronary artery disease.

All participants underwent 7-day Holter recordings prior to the procedure, immediately after the procedure, and 3 and 6 months after the procedure. They were also equipped with a monitor that automatically transmitted a 12-lead electrocardiogram to a monitoring service every 2 days throughout the 6-month monitoring period and whenever the patient activated the recorder because of a symptomatic afib episode. Holter monitoring produced the following results:

	Percentage of Patients with AF Episodes	
	Total Documented	Asymptomatic
Prior to ablation	93%	10%
After ablation	80%	50%
After 3 months	58%	46%
After 6 months	54%	53%

Thus, according to the Holter monitoring only 46% of ablated patients were actually totally free of documented afib 6 months after the procedure. However, at the 6-month check-up about 70% of the group were free of afib if only symptomatic episodes were considered. About 31% of all afibbers who experienced episodes were completely asymptomatic. The mean episode duration among afibbers still experiencing episodes showed a gradual decline from an average of 31 hours prior to ablation to 22 hours post-ablation to 16 hours after 3 months and 5 hours after 6 months. A total of 2600 transtelephonic ECGs were recorded in the 30 patients. A total of 216 episodes were documented during 157 days with 25% of them being asymptomatic.

The German researchers conclude that the success rate of the PVI was about 70% if only symptomatic episodes are considered, but only about 50% if asymptomatic episodes were included as well. The high incidence of completely asymptomatic episodes is of concern in regard to the need for continued stroke prevention measures. However, the duration of

asymptomatic episodes tended to be quite short (average of 2 hours at the 6-month check-up), so blood clotting may not be a problem in the majority of cases.
Piorkowski, C, et al. Value of different follow-up strategies to assess the efficacy of circumferential pulmonary vein ablation for the curative treatment of atrial fibrillation. Journal of Cardiovascular Electrophysiology, *Vol. 16, December 2005, pp. 1286-92*

Long-term outcome of PVI for persistent AF
MESTRE, ITALY. Emanuele Bertaglia and colleagues at the Ospedale Civile di Mirano report on their follow-up of 74 persistent afibbers who had undergone circumferential pulmonary vein ablation (CPVA or Pappone method) for persistent AF (afib episodes lasting longer than 7 days). The average age of the patients was 61.5 years (49-78), 76% were men, average afib duration was 4.4 years (1-17), and all had tried at least 2 antiarrhythmic drugs (3.1 on average) with no success.

The ablation was performed using the CARTO anatomical mapping system and a cooled 3.5 mm Navistar catheter. Total procedure time averaged about 3.5 hours with a fluoroscopy time of about 28 minutes. All patients had their pulmonary veins isolated – 78% also had the right isthmus ablated (to prevent right atrial flutter), and 67% received an ablation line connecting the mitral valve to the left inferior PV (left isthmus). All patients continued on antiarrhythmic drugs for the first 7 months and were then taken off the drug or continued based on their response.

After a mean follow-up of 20 months, 70% of the patients were still in normal sinus rhythm (NSR) and were deemed to have been successfully treated. NOTE: 63% of these patients were either on amiodarone (18 patients) or Class IC drugs (15 patients). Of the 22 patients (30%) who relapsed into afib within the first 2 years, 19 did so within the first 12 months after the ablation procedure, while only 3 did so after 12 months. The researchers conclude that not having a relapse within the first 12 months and having suffered from persistent afib for less than 7 years are strong predictors of a successful outcome.

The researchers point out that the necessity of continuing antiarrhythmic drugs in this group of persistent afibbers was significantly higher than normally experienced among ablated paroxysmal afibbers. They make this very interesting statement concerning this finding, "It could be explained by the fact that, whereas in patients with paroxysmal AF elimination of triggers is often enough to eradicate the arrhythmia, in patients with persistent AF the role of atrial electrical and structural remodeling is predominant over triggers. So, the modifications of

anatomical and electrical substrate induced by circumferential ablation more often need to be aided by the continuation of antiarrhythmic drugs."
Bertaglia, E, et al. Long-term outcome of right and left atrial radiofrequency ablation in patients with persistent atrial fibrillation. PACE, *Vol. 29, February 2006, pp. 153-58*

Factors affecting last recurrence of AF following a PVI

TAIPEI, TAIWAN. It is barely 8 years since Professor Haissaguerre in Bordeaux first attempted pulmonary vein isolation (PVI) and only in the last 4 or 5 years have PVIs become widely accepted and performed. So, it is not too surprising that data regarding the ultimate long-term success of the procedure are only just emerging. Unfortunately, the news is not as encouraging as could be hoped for. Some studies have found recurrence rates as high as 50% after a seemingly successful PVI.

Researchers at the Taipei Medical University School of Medicine found a recurrence rate of 35% among 293 afibbers having undergone a seemingly successful first ablation. Of the 104 patients who experienced a late recurrence, 81 (78%) did so within one year after their PVI, while the remaining 23 (22%) did so more than one year post-procedure. Fifty of the 104 recurrence patients underwent a second ablation procedure during which careful electrophysiological (EP) measurements were repeated. Twelve of the patients (Group 1) had experienced their recurrence between 13 and 39 months (average of 26 months) after their PVI, while the remaining 38 (Group 2) had experienced their first afib episode post-ablation within 1 to 12 months (average of 3 months). The EP studies yielded the following intriguing information:

- At the baseline EP study (prior to the first ablation) Group 1 patients had fewer AF foci originating from the pulmonary veins than did those in Group 2 (67% vs 92%), but substantially more foci in the right atrium (50% vs 13%).

- At the repeat EP study (prior to the second ablation) Group 1 patients again had a lower incidence of pulmonary vein foci (50% vs 79%) and indeed of total left atrium foci (50% vs 97%). Most remarkably, the incidence of right atrium foci in Group 1 patients was 67% vs only 3% in Group 2.

- The majority of initiating foci (65%) in both groups were spots that had already been targeted in the first ablation, thus indicating that conductivity had been regained. The phenomenon of recovered conductivity was particularly pronounced at the pulmonary veins where 100% of foci

found in the study preceding the second ablation had already been "burned" during the initial ablation.

- After an average of 2 years (7-35 months) after the second ablation, 83% of group 1 patients were free of afib without the use of antiarrhythmics, while the remaining 17% were able to control their condition with the use of previously ineffective drugs. In Group 2 (13-61 months after second ablation) 74% were afib-free without drugs, while the remaining 26% achieved satisfactory control with antiarrhythmics.

The researchers conclude that right atrial foci play an important role in the very late (more than 1 year) recurrence of afib, while regained conductivity in pulmonary vein foci are most important in so far as late (less than 1 year, but more than 1 month) recurrence is concerned.
Hsieh, MH, et al. The different mechanisms between late and very late recurrences of atrial fibrillation in patients undergoing a repeated catheter ablation. Journal of Cardiovascular Electrophysiology, *Vol. 17, March 2006, pp. 231-35*
Lloyd, MS and Langberg, JJ. Recurrences of atrial fibrillation after ablation: When will this hydra meet its Hercules? Journal of Cardiovascular Electrophysiology, *Vol. 17, March 2006, pp. 236-37*

Latest ablation statistics
NEW YORK, NY. Researchers at the Montefiore Medical Center and the Albert Einstein College of Medicine have performed a thorough review of the latest literature dealing with ablation for atrial fibrillation. They reviewed over 200 articles dealing with procedure outcome and compiled data for over 23,000 AF patients who had undergone radiofrequency or surgical ablation for AF (lone or otherwise). The average full success or "cure" rate (no afib, no antiarrhythmics 6 months after ablation) for all patients was 63% with the full + partial success rate (less afib or no afib with medications) being 75%. The success rate was slightly better for the pulmonary vein antrum isolation (Natale) procedure at 67% cure and 76% cure or partial success. The fairly new approach substrate ablation (ablation of spots showing complex fractionated atrial electrograms) was quite successful with a cure rate of 75% and a cure + partial success rate of 87%. Surgical procedures such as the mini-maze had a cure rate of 67% and a full + partial success rate of 79%.

The average procedure time was about 4 hours and 25% of all procedures had to be repeated. PV stenosis occurred in 1.5% of procedures; however, only a very small number of the papers reviewed actually gave a number for the incidence of stenosis. Overall, 5.2% of patients

experienced one or more complications. The researchers point out that substrate ablation may well be the preferred procedure for patients with a high degree of abnormal atrial tissue such as is commonly found among persistent and permanent afibbers.
Fisher, JD, et al. Atrial fibrillation ablation: reaching the mainstream. **PACE**, *Vol. 29, May 2006, pp. 523-37*

Editor's comment: The results reported in this survey were reported in scientific papers by the institutions actually performing the ablations. Thus, it is likely that they reflect the performance at larger centers since individual EPs or EPs at small centers are perhaps less likely to report their experiences. The overall full success (cure) rate reported here of 63% and the full + partial success rate of 75% is actually very close to the average rates reported for the top 9 institutions in our LAF-9 Survey. These rates were 64% and 79% respectively. The repeat rate of 25% is also very close to the rate of 21% found in our survey.

Left atrium remodeling after ablation

LEIDEN, THE NETHERLANDS. There is substantial evidence that the left atrium tends to enlarge with the presence of afib. Now Dutch EPs report that this enlargement regresses after a successful PVI (pulmonary vein ablation), but continues if the ablation is unsuccessful. Their study involved 45 male and 12 female afibbers with an average age of 53 years (range of 45-61 years). The study participants had experienced afib for an average of 6 years (range of 1-11 years). Most (61%) had the paroxysmal variety, while 32% had persistent and 7% had permanent. The PVI was carried out using the CARTO electroanatomical mapping system (Pappone method) and a 4 mm irrigated ablation catheter. Lesion lines were placed outside the ostia of the pulmonary veins with additional lines drawn between the mitral annulus and the left inferior pulmonary vein (mitral isthmus line) and between the ostia of the left and right superior pulmonary veins (roof line). This procedure achieved immediate success in all patients, but 3 (5%) did suffer mild pericardial effusion.

After 3 months 68% of the patients were still in sinus rhythm, while still on antiarrhythmic drugs. It is of considerable interest to note that while 77% of the paroxysmal afibbers were in sinus rhythm after 3 months, only 28% of persistent and permanent afibbers had achieved this enviable state.

The Dutch researchers performed two-dimensional echocardiography 2 days prior to the procedure and at the 3-month follow-up visit. The LA anteroposterior diameter decreased from an average of 45 mm to an average of 42 mm in the group that was in sinus rhythm, but increased from 45 mm to 48 mm in the group whose ablation had been unsuccessful. Furthermore, both the LA end-systolic and end-diastolic

volumes decreased significantly (from 59 mL to 50 mL and from 37 mL to 31 mL respectively) in the successful group, but tended to increase in the group still in afib. The researchers conclude that the size of the left atrium decreases after a successful ablation, but increases with continuing afib.

Tops, L, et al. Effect of radiofrequency catheter ablation for atrial fibrillation on left atrial cavity size. American Journal of Cardiology**,** *Vol. 97, 2006, pp. 1220-22*

Editor's comment: The overall success rate of 68% is not impressive particularly considering that all the study participants remained on antiarrhythmics for the 3 months following their procedure. The fact that only 28% of persistent and permanent afibbers achieved a cure confirms my own belief that the electroanatomical (Pappone) approach is not appropriate for persistent and permanent afibbers.

PVI comes out the winner

Before the advent of pulmonary vein ablation (PVI) afib patients were often counseled to go on warfarin (Coumadin) and undergo direct current cardioversion (DCC) as needed to cope with their disorder. Other patients were counseled to receive an AV node ablation and pacemaker implantation (AVNA). Dr. Andrea Natale and his group at the Cleveland Clinic have now compiled data comparing afib recurrence rates and mortality rates for 138 patients undergoing PVI, DCC (139 patients), or AVNA (133 patients). The patients were age-matched (60-80 years of age) and had undergone their procedure during the period 1996-2004. The short-term recurrence rate (episodes less than 2 months after procedure) was 13% for PVI, 25% for DCC, and 37% for AVNA. The late recurrence rate (episodes between 2 and 12 months post-ablation) was 9% in the PVI group, 54% in the DCC group, and 48% in the AVNA group. Mortality within the groups was 1.4% for PVI, 31% for DCC, and 15% for AVNA. The authors of the study conclude that PVI has a very low recurrence and mortality rate compared to DCC and AVNA.

PACE, Vol. 29, Suppl 1, April 2006, Abstract #194, p. S95

Ablation normalizes ANP and BNP levels

NAGOYA, JAPAN. It has been reported that afibbers tend to have higher blood levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) than non-afibbers. There is also evidence that the levels are reduced after cardioversion or a successful maze procedure. Japanese researchers recently set out to see if elevated ANP/BNP levels would decline after pulmonary vein ablation (PVI). Their study involved 66

(54 men) paroxysmal afibbers with no underlying heart disease (lone afibbers). The average age of the study participants was 61 years (range of 51-71 years); they had suffered from afib for 1-7 years, had failed 2-4 class I or class II antiarrhythmic drugs, and experienced episodes that self-converted in less than 24 hours. Their average left atrial diameter was 35 mm (range of 25-45 mm).

The participants all underwent a segmental, ostial PVI targeting all 4 pulmonary veins and were followed up for 3 months after their last ablation. The follow-up included monthly 24-hour Holter recordings and ANP and BNP determination at baseline and 3 months. Three months after the initial PVI, only 53% of the study participants were still in normal sinus rhythm without the use of antiarrhythmic drugs. Nine (14%) of the unsuccessfully ablated patients underwent second and third procedures. Five became afib-free after the second procedure, and two achieved continuous normal sinus rhythm (NSR) after the third procedure.
The Japanese researchers made the following observations:

- At baseline, both ANP and BNP levels were elevated in 14 patients (21%) and in the remaining 52 patients (79%) only BNP level was elevated.

- There were no significant correlations between episode frequency and duration and ANP/BNP levels or left ventricular (LV) ejection fraction.

- There was a significant, but weak correlation between ANP and BNP levels and afib burden (episode frequency x duration) prior to the PVI.

- BNP level was positively correlated with left atrial dimension.

- Patients with elevated ANP levels tended to experience more episodes and a higher afib burden than those with normal levels.

- Both ANP and BNP levels decreased significantly after the first PVI whether ultimately successful or not (ANP from an average of 69 to 25 pg/mL and BNP from 58 to 23 pg/mL).

- In patients with elevated ANP only (at baseline) the ANP concentration returned to normal after the initial PVI.

- Average BNP levels decreased from 55.7 to 12.3 pg/mL in the 35 patients whose first PVI was successful. In contrast, it

decreased significantly less in the 7 patients who required additional PVIs (from 66.8 to 42.8 pg/mL)

- An enlarged left atrium at baseline was associated with a greater chance of the PVI being unsuccessful.
- No association was observed between ANP/BNP level at baseline and the outcome of the PVI.
- The decrease in afib burden post-PVI was proportional to the decrease in BNP, which eventually returned to normal level after a successful PVI.
- No asymptomatic afib episodes were observed during the Holter recordings.

The researchers conclude that ANP/BNP levels are elevated in paroxysmal afibbers even if they don't have structural heart disease. Both ANP and BNP levels decrease significantly after a PVI and a return to normal of BNP post-ablation is a good indication that the PVI was successful.
Yamada, T, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide levels after radiofrequency catheter ablation of atrial fibrillation. American Journal of Cardiology, *Vol. 97*, *June 15, 2006, pp. 1741-44*

Editor's comment: It is interesting that the procedural success rate was only 53% after the first PVI. This seems to be about the norm in other than top-rated institutions. It is to be hoped that more research will be done on the correlations between PVI success and BNP decrease. For example, if a BNP decrease to normal levels within the first month after the PVI would indicate ultimate success, this would go a long way toward answering the question, "was my ablation successful?" without having to wait the requisite 3 months.

Long-term success of RF ablation

BALTIMORE, MARYLAND. The outcome of a radio frequency (RF) pulmonary vein isolation (PVI) procedure for atrial fibrillation depends primarily on operator skill and experience, type of afib (paroxysmal, persistent, permanent), and the ablation protocol used (Haissaguerre, Natale or Pappone). A team of electrophysiologists at the Johns Hopkins Hospital now reports their experience with a group of 200 consecutive patients (67% male) who underwent either a segmental PVI (Haissaguerre method) or a circumferential, anatomically-guided PVI (Pappone method). The average age of the patients at time of ablation was 56 years (range of 45-67 years), 46% had paroxysmal afib, while 36% had persistent, and

18% had the permanent variety. Twenty-two percent had hypertension and 29% had structural heart disease, so a sizeable proportion were lone afibbers.

Eighty-seven (44%) of the study participants underwent a segmental PVI, while the remaining 113 underwent the circumferential procedure. All patients were followed for a minimum of 12 months (range of 15-37 months) with telephone interviews and, if indicated, ECGs every 3 months. Long-term success was defined as freedom from afib without the use of antiarrhythmics in the 6 months prior to evaluation. During the first 3 months after the procedure, 64% of all ablatees experienced one or more symptomatic afib episodes lasting longer than 10 minutes (early recurrence). Most (58%) experienced their episode(s) in the first month following the ablation, while the remaining 6% experienced it/them in the second or third month after the procedure.

Only 15% of patients with early recurrence went on to achieve long-term success (36% counting those who had repeat ablations). In contrast, 50% of those afibbers who remained afib-free for the first 3 months went on to achieve long-term success with an additional 9% demonstrating improvement (more than 90% reduction in symptomatic episodes with or without the use of antiarrhythmics).

The overall long-term success rate after a single PVI was 28% with an additional 7% demonstrating improvement. Thirty-two percent of the study population of 200 patients underwent one or more repeat ablations bringing the total long-term success rate to 41% with an additional 11% showing improvement. The two major variables affecting outcome were the type of afib and the procedure used. Paroxysmal afibbers experienced the best results with an overall success rate of 50% including repeat ablations. Persistent and permanent afibbers were grouped together and their combined ultimate long-term success rate was 34%. Afibbers who had been treated with the segmental approach had a 22% single procedure success rate (34% for paroxysmal and 5% for persistent/permanent) with 10% demonstrating improvement. Those who had undergone the circumferential PVI had a 32% single procedure success rate (40% for paroxysmal and 28% for non-paroxysmal) with 4% showing improvement. A first afib recurrence after one year was relatively rare at 4%. Major complications occurred during 21 procedures (7.9%) with 6 patients (2%) experiencing tamponade (piercing of the heart wall), 3 experiencing pulmonary vein stenosis, and another 3 experiencing a stroke. All complications occurred during or within 30 days of the procedure.

Cheema, A, et al. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. **J Interv Card Electrophysiol,** *Vol. 15, August 2006, pp. 145-55*

Editor's comment: The Johns Hopkins study found that 36% of afibbers who had an afib episode during the 3 months following their procedure went on to achieve long-term success. This correlates well with the 37% observed in my 2005 ablation survey. The 28% first procedure success rate at Johns Hopkins is also very similar to the average 31% rate (2004-2005 ablations) found in my survey. The success rates at top-rated institutions like Bordeaux, Cleveland Clinic, and Marin County Hospital (Dr. Natale) are, of course, much better than those reported by the Johns Hopkins team. According to a study reported in 2004 the long-term success rate at the Cleveland Clinic in Ohio for paroxysmal afibbers was 87%, while that for permanent (including persistent) afibbers was 78% for an overall success rate (after one year) of 83%. This included the 12% of patients who required a repeat ablation.[1] It is worth noting that the procedure used in Cleveland is a segmental procedure which the John Hopkins study found inferior to the circumferential procedure. This, once again, confirms my personal conviction that best results are obtained with the combination of a highly skilled operator using the segmental procedure. Less skilled operators, on the other hand, are likely to get better, but still inferior, results with the circumferential protocol.

[1] Bhargava, M, et al. Impact of age on the outcome of pulmonary vein isolation for atrial fibrillation using circular mapping technique and cooled-tip ablation catheter: A retrospective analysis. Journal of Cardiovascular Electrophysiology, Vol. 15, January 2004, pp. 8-13

Effect of PVI on left atrial function

CLEVELAND, OHIO. A study carried out at the University of Michigan concluded that circumferential pulmonary vein ablation (Pappone protocol) in paroxysmal afibbers is associated with a marked decline in left atrium (LA) ejection fraction. This could be of concern if this impairment of LA function, despite reversion to sinus rhythm, is severe enough to predispose to the formation of blood clots.

A team of EPs from the Cleveland Clinic and the Marin County General Hospital now report the good news that segmental pulmonary vein ablation (Haissaguerre and Natale protocol) does not result in a deterioration of LA function, but rather tends to improve it. Their clinical trial involved 125 consecutive patients with paroxysmal (60%) or persistent (40%) afib. NOTE: Permanent afibbers were excluded due to the impossibility of measuring their LA function in sinus rhythm prior to the ablation procedure.

The study participants, 73% of whom were men, had suffered from afib for an average of 6 years; 31% were hypertensive, 19% had coronary artery disease, and 15% had valvular hear disease. The participants all underwent pulmonary vein antrum isolation (PVAI) and 92% of these were

successful (no afib, no medications after 2 months). After excluding patients where imaging could not be carried out because of inability to image in sinus rhythm or the presence of AF symptoms, 67 patients were included in the final study. These patients underwent either TEE (at Cleveland Clinic) or EBCT (at Marin County) immediately prior to the PVAI and 6 months later. They also underwent Holter monitoring immediately following the procedure and at 3- and 6-month follow-up visits.

Transesophageal echocardiography (TEE)

Echocardiography uses ultrasound to evaluate the structure and function of the heart. The ultrasound transducer is usually applied over the heart region of the chest with the patient in the supine position. This technique, known as ***transthoracic echocardiography (TTE),*** can give a good indication of the size of the heart chambers, its ability to pump blood, and will show any valve abnormalities and other structural defects.

Transesophageal echocardiography (TEE) is similar to TTE except that the ultrasound transducer is shaped like a narrow cylinder and is swallowed during the procedure. Because the esophagus is right next to the heart TEE provides much clearer images than does TTE. It is particularly effective in spotting blood clots in the left atrium and left atrial appendage, and is also sometimes used during pulmonary vein ablation to prevent the accidental creation of an atrio-esophageal fistula (a hole between the heart and the esophagus). The most important parameters measured with TEE are:

- Left atrial diameter (LAD)
- Left atrial systolic area
- Left atrial diastolic area
- Blood flow through the mitral valve (TMP)
- Blood flow through the left atrial appendage (LAA)
- Blood flow through the pulmonary veins (PVF)

The important Peak A velocity measures the blood flow across the mitral valve (connecting the left atrium and the left ventricle) and can be taken as a measure of the strength of the atrium's contraction.

Cine electron-beam computed tomography (EBCT)

Computed tomography is an x-ray technique that uses multiple two-dimensional images to produce a three-dimensional representation of the body and its parts. It was developed in the early 1970s and has since undergone many improvements. One of the shortcomings of early CT scans was their inability to accurately depict moving organs such as the heart. This has now been overcome in the latest generation of CT scanners. While early scanners took 20-60 seconds to obtain a scan, the new EBCT scanners only require 50-100 milliseconds to "get the picture". This has made it possible to obtain clear pictures of the moving heart using an injected contrast medium (x-ray dye). Among the most important parameters measurable on an EBCT scan are:

- Left atrial systolic area and volume
- Left atrial diastolic area and volume
- Left atrial ejection fraction (%)

At the 6-month follow-up visit there was a clear, statistically significant decrease in left atrium diameter and area (both by TEE and EBCT) indicating that successful structural remodeling had taken place. Peak A velocity (measured by TEE) increased, on average, from 43 cm/sec pre-ablation to 62 cm/sec post-ablation indicating that the contractile force of the left atrium had improved as a result of the procedure. These improvements were more noticeable in persistent than in paroxysmal afibbers. The observed improvement in left atrial function was further supported by the finding that the left atrial ejection fraction, as measured with EBCT, increased from an average of 16.7% to 22.1%.

The researchers conclude that extensive ablation performed during a PVAI does not cause deterioration in LA function and may actually result in long-term improvement, especially in persistent afibbers.

David Callans, MD of the University of Philadelphia comments that it is possible that more extensive ablation (such as done in the circumferential or Pappone method) may reduce LA function to a greater extent. He also suggests that the left atrial ejection fraction, although improved after PVAI, may still be well below that found in a normal, afib-free population.
Verma, A, et al. Extensive ablation during pulmonary vein antrum isolation has no adverse impact on left atrial function. Journal of Cardiovascular Electrophysiology, *Vol. 17, July 2006, pp. 741-46*

Callans, DJ. The effect of catheter ablation of atrial fibrillation on left atrial transport function. Journal of Cardiovascular Electrophysiology, *Vol. 17, July 2006, pp. 747-48*

Editor's comment: It is indeed encouraging to learn that the segmental pulmonary vein isolation procedure (Haissaguerre and Natale protocol) using electrophysiological mapping does not harm the left atrium to the point of interfering with its function of acting as a "booster pump" for the left ventricle. It even appears from this latest study that LA function may actually improve after a PVI or PVAI. It is somewhat unfortunate that the authors of the study did not provide normal LA ejection fraction values as measured with ECBT. I have been unable to find such comparable values in a search of current medical literature.

Stroke Risk Factors

LAF does not increase stroke risk

ROCHESTER, MINNESOTA. Researchers at the Mayo Clinic have published a very important study regarding the correlation between lone atrial fibrillation (LAF) and stroke risk and overall mortality. The study is remarkable in that it followed the participants for 30 years and thus gives a good indication of the long-term prognosis for untreated LAF. The study involved 46 residents of Olmsted County who were diagnosed with LAF at an average age of 45.8 years (range of 34-58 years). None of the participants had coronary artery disease, hypertension, diabetes, mitral valve prolapse, congestive heart failure, or any other condition that would increase their risk of ischemic stroke (cerebral infarction). None of the participants were treated with warfarin. They were followed until death or July 1, 2002. At time of last follow-up the average age was 74 years (range of 63-85 years). At the beginning of the study 76% of participants had paroxysmal afib and 24% had the persistent variety; this changed to 59% paroxysmal and 41% persistent by the end of the study period. All participants were Caucasians and 83% were men.

The Mayo researchers made the following important observations:

1. The observed mortality rate among the afibbers over a 25-year period was substantially lower (15.9%) than the mortality expected in a group of age- and sex-matched white Minnesotans (32.5%).

2. The incidence of ischemic stroke (cerebral infarction) in the afib group was no greater (0.5%/person-year) than in the general population. The researchers conclude that, "This observation indicated that the pathophysiological mechanisms responsible for the development of a cerebrovascular event were unrelated to the continued presence of AF." In other words, LAF as such is not associated with an increased risk of stroke.

3. The volume of the left atrium (LAV) is an important indicator of the risk of adverse events such as stroke, heart attack (myocardial infarction), and congestive heart failure. A LAV (indexed for age and body mass) equal to or greater than 32 mL/m^2 was associated with a 4.46-fold increase in the probability of experiencing an adverse event.

4. All cerebral infarctions occurred in participants whose LAV prior to the incident was greater than 32 mL/m^2.

5. No correlation between age or the number of years afib had been present (duration) and LAV was observed; however, there was a highly significant correlation between persistent afib and enlarged LAV.

6. The average age at which a stroke occurred in the LAF group was 77 years, not significantly different from that observed in the general population.

7. Eighteen participants died during the study; 9 of cardiovascular disease, 4 of cancer, and 4 of a respiratory tract infection.

The researchers conclude that LAV is an important predictor of the likelihood that lone afibbers will suffer adverse events (stroke, heart attack, etc) during their lifetime. It is far more important than age and left ventricular ejection fraction. They suggest that only afibbers with a LAV less than 32 mL/m^2 should be classified as "lone". These afibbers had a benign clinical course during follow-up, while afibbers with an elevated LAV at diagnosis or later during follow-up experienced adverse events.
Osranek, M, et al. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. European Heart Journal, *Vol. 26, 2005, pp. 2556-61*

Editor's comment: The findings of the Mayo study are indeed encouraging. They confirm my long-held conviction that otherwise healthy lone afibbers are at no greater risk of stroke than is the general population and therefore does not warrant warfarin therapy. It is encouraging that the mortality among lone afibbers over 25 years of the study was less than half that found in the general population. The observation that left atrial volume (LAV) is an important predictor of future adverse events is intriguing. Hopefully, it will eventually lead to LAV being measured as part of the routine examination of afibbers.

Blood viscosity and stroke risk

FIRENZE, ITALY. There is evidence that a high blood viscosity (thick blood) may increase the risk of ischemic stroke. Blood viscosity, as a whole, affects the ease of general circulation, while erythrocyte (red blood cell) deformability affects circulation through the capillaries. Because red blood cells can only flow through a capillary (the smallest diameter blood vessels involved in nutrient and waste exchange with individual cells) one at a time and even then must be elongated to do so, it is clearly advantageous to have a high erythrocyte deformability index. Research

has shown that endurance athletes have significantly higher erythrocyte deformability indices than do sedentary people. The main reason for this is that red blood cells in endurance athletes tend to be replaced quicker than they are in sedentary people, thus creating a population of younger, more deformable cells.

Italian researchers have just reported on a study to determine if afibbers and afibbers who have suffered a stroke or TIA ("mini-stroke") have higher blood viscosity and lower erythrocyte deformability than does a control population of non-afibbers without cardiovascular disease. Their study involved 42 afibbers who had suffered an ischemic stroke, 20 who had suffered a TIA, 94 afibbers who had not suffered a stroke or TIA, and 130 age- and gender-matched healthy volunteers. About 60% of the afibbers were hypertensive and about 25% had coronary artery disease and/or left ventricular dysfunction. Average age of the study participants was 73 years and all afibbers were on oral anticoagulation.

After adjusting for gender, age, hypertension, left ventricular dysfunction, coronary artery disease, diabetes, elevated cholesterol level, smoking, hematocrit, fibrinogen, and C-reactive protein levels (hs-CRP), the researchers concluded that healthy controls had a significantly lower whole blood viscosity (at a shear rate of 94.5 seconds^{-1}) and a significantly higher erythrocyte deformability index than did afibbers who had not suffered a stroke. Afibbers who had not suffered a stroke, in turn, had a lower blood viscosity and higher erythrocyte deformability than did those afibbers who had suffered a stroke or TIA.

The researchers also noted a correlation between hypertension and reduced erythrocyte deformability, but observed no effect of ACE inhibitors, beta-blockers, diuretics, and calcium channel blockers on deformability. This would indicate that treating hypertension does not reduce the stroke risk attributable to reduced erythrocyte deformability. The researchers speculate that reduced erythrocyte deformability may be partly caused by a lack of nitric oxide availability and perhaps by inflammation or oxidative stress resulting in "premature aging" of red blood cells. They also suggest that adding a small dose of aspirin to oral anticoagulants in high-risk patients may be beneficial since aspirin has been found to improve erythrocyte deformability.
Cecchi, E, et al. Hyperviscosity as a possible risk factor for cerebral ischemic complications in atrial fibrillation patients. American Journal of Cardiology, *Vol. 97, June 15, 2006, pp. 1745-48*

Editor's comment: A large epidemiological study has shown that drinking 5 or more glasses of water every day cuts the risk of coronary artery disease in half as compared to drinking only 2 or fewer glasses of water every day. It is likely that this beneficial effect of adequate water intake is

closely linked to the fact that water, but not necessarily other fluids, reduces blood viscosity. It is also of interest that NO-ASA, a recently developed nitrogen oxide-releasing version of aspirin, has been found to reduce thrombosis (blood clotting).

Stroke Prevention

Warfarin interactions

HEIDELBERG, GERMANY. Warfarin (Coumadin) is widely prescribed for afib patients for the prevention of ischemic stroke. Its purported benefits are, however, to a large degree, offset by its tendency to cause internal bleeding and hemorrhagic stroke. For lone afibbers with no other risk factors for stroke the negative effects of warfarin therapy generally outweigh the benefits.

A team of researchers from Germany, Sweden and Switzerland has just concluded a study aimed at determining if the bleeding risks associated with warfarin usage are increased in patients taking other pharmaceutical drugs as well. Their study involved 4152 afib patients (aged between 40 and 84 years) who were on warfarin for non-valvular AF. During follow-up (for an average of 11 months) 133 patients died from internal bleeding and another 432 were hospitalized with serious bleeding. This corresponds to a warfarin-associated mortality rate of 3.5% a year and a serious bleeding rate of 12% a year. The researchers observed that 58% of all patients on warfarin had also been prescribed one or more of 88 specific drugs that are known to interact with warfarin. They also found that patients who were taking potentially interacting drugs experienced a 3.4-fold increased risk of serious bleeding. The use of a combination of warfarin and aspirin (75-325 mg/day) was associated with a 4.5-fold risk increase, while the concomitant use of acetaminophen (Tylenol, Paracetamol) was associated with a 3.8-fold increased risk at doses between 885-2900 mg/day taken for at least 4 weeks. Other particularly detrimental drugs were allopurinol (Zyloprim), amiodarone (Cordarone), levothyroxine (Synthroid), Metronidazole, Miconazole, and omeprazole (Prilosec). Taking Metronidazole or Miconazole during warfarin therapy was associated with a 40-fold increase in the risk of a serious bleeding event.

The researchers conclude that drug interactions are an independent risk factor for serious bleeding in patients on long-term warfarin therapy. They also point out that the practice of prescribing potentially interacting drugs is widespread.

Gasse, C, et al. Drug interactions and risk of acute bleeding leading to hospitalisation or death in patients with chronic atrial fibrillation treated with warfarin. Thrombosis and Haemostatis, *Vol. 94, September 2005, pp. 537-43*

Warfarin bleeding risk quantified

ST. LOUIS, MISSOURI. Many lone afibbers are counselled to take warfarin (Coumadin) although there is no evidence that doing so will reduce the risk of ischemic stroke (caused by a blood clot) for afibbers who do not have specific risk factors for stroke, more specifically, coronary artery disease, congestive heart failure, rheumatic heart disease, hypertension, advanced age, diabetes, a prior history of stroke or heart attack, or the presence of prosthetic heart valves.

Unfortunately, there is considerable evidence that taking warfarin is associated with a significantly increased risk of internal bleeding and hemorrhagic stroke (stroke caused by a burst blood vessel). Researchers at the Washington University School of Medicine have now developed a rating scheme for predicting the risk of internal bleeding for atrial fibrillation patients taking warfarin. They determined risk factors for warfarin-related bleeding incidents by studying the records of 1604 afibbers released from hospital on warfarin. They assigned one point to each of the following factors:

- Liver or kidney disease
- Alcohol abuse
- Cancer
- Advanced age (greater than 75 years)
- Reduced platelet count or function
- Uncontrolled hypertension
- Anemia
- Unfavourable genetic factors
- Excessive risk of falling
- Prior stroke

Patients who had already suffered an internal bleed were given an extra two points. Using this scheme ($HEMORR_2HAGES$) the researchers predicted the following annual incidence of bleeding requiring hospitalization for afibbers on warfarin:

# of Risk Factors	% Risk of Bleeding/Year
0	1.9
1	2.5
2	5.3
3	8.4
4	10.4
5 or more	12.3

Most of the bleeds (67.3%) were gastrointestinal hemorrhages, 15.3% were hemorrhagic strokes, and the remaining 17.3% were in other locations. The seriousness of the bleeds can be judged from the fact that 21.6% of the patients admitted for warfarin-induced bleeding died within 30 days. This is, no doubt, related to the fact that a hemorrhagic stroke is far more likely to be lethal than is an ischemic one and that a serious gastrointestinal bleed can quickly become fatal.

The researchers conclude that their new rating scheme, HEMORR$_2$HAGES, will be useful in assisting doctors and patients in judging the advisability of warfarin therapy in atrial fibrillation patients.

Gage, Brian F, et al. Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF). American Heart Journal, *Vol. 151, March 2006, pp. 713-19*

Heuschmann, Peter U, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German Stroke Registers Study Group. Archives of Internal Medicine, *Vol. 164, No. 16, September 13, 2004, pp. 1761-68*

Editor's comment: This study is clearly an important step forward in determining the risk/benefit ratio of warfarin therapy in afibbers. It is particularly illuminating to compare the risk for ischemic stroke according to the CHAD$_2$ score and the Kaiser Permanente Study with the risk of major bleeding according to the HEMORR$_2$HAGES scheme.

	Risk of Ischemic Stroke, %/year			Risk of Major Bleed, %/year
Risk Factor	CHAD$_2$ Original[1]	CHAD$_2$ Kaiser[2]	CHAD$_2$ Combined[3]	HEMORR$_2$HAGES
None	1.9	0.5	0.9	1.9
Hypertension or age over 75 yrs	2.8	1.5	1.8	2.5
Hypertension + age over 75 yrs	4.0	2.5	2.9	5.3
Prior stroke	4.0	2.5	2.9	2.5
Prior bleed	1.9	0.5	0.9	5.3

[1] Gage, BF, et al. Validation of clinical classification schemes for predicting stroke: results form the National Registry of Atrial Fibrillation. JAMA, Vol. 285, June 13, 2001, pp. 2864-70

[2] Go, As, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA, Vol. 290, November 26, 2003, pp. 2685-92

[3] Average of two estimates weighed by number of patients in studies.

Looking at the above comparison, it is clear that most afibbers with just one or two risk factors for ischemic stroke would be exposed to a greater risk of a serious adverse event by taking warfarin than by not taking it. It is abundantly clear that warfarin has no place in the treatment of afibbers with no risk factors, but a case can probably be made for recommending warfarin for afibbers who have already experienced an ischemic stroke. It is also important to remember that the HEMORR$_2$HAGES study found that 21.6% of patients admitted to hospital with warfarin-induced bleeding died within 30 days. In contrast, the mortality associated with an ischemic stroke varies between 5 and 25% depending on the nature of the treatment and how quickly it is received.

Warfarin implicated in osteoporosis

ST. LOUIS, MISSOURI. Vitamin K is a crucial element in the process of bone formation. As warfarin (Coumadin) is known to inhibit this action of vitamin K, it is relevant to ask the question, "Is long-term use of warfarin associated with an increased risk of osteoporotic fractures?" A team of researchers from Washington University School of Medicine and the NYU Medical Center now provides the answer. The researchers investigated the association between osteoporotic fractures and warfarin usage in over 14,000 Medicare beneficiaries who were hospitalized with atrial fibrillation. Most of the study participants (70%) had hypertension, 48% had heart failure, and 35% had a history of stroke. A total of 1005 of the study participants (6.9%) experienced an osteoporotic fracture during the 3-year study period. The researchers found that men who had been taking warfarin for a year or more had a 63% higher relative risk of experiencing an osteoporotic fracture when compared to men not taking warfarin. Hip fractures were most common (65% of all fractures) and were associated with a 30-day mortality of 39%. Women and men using warfarin for less than a year did not have an increased risk of osteoporotic fractures.

Other prominent risk factors for osteoporotic fractures were increasing age (63% increased risk per decade), frequent falls (78% increased risk), hyperthyroidism (77% increased risk), dementia, Parkinson's disease or schizophrenia (51% increased risk), and alcoholism (50% increased risk). On the other hand, the use of beta-blockers was associated with a 16% lower risk of osteoporotic fractures.

The researchers point out that patients taking warfarin are often advised to limit their intake of vitamin K rich green vegetables. They believe this may be poor advice and that ensuring an adequate intake of vitamin K-1 (found especially in green vegetables) and vitamin K-2 (present in fermented dairy and soy products, fish, meat, liver and eggs) would be more appropriate. They also caution that avoiding green vegetables may

lead to a folic acid deficiency and subsequent high levels of homocysteine, a known promoter of atherosclerosis.
Gage, BF, et al. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Archives of Internal Medicine, *Vol. 166, January 23, 2006, pp. 241-46*

Editor's comment: The results of this study support the findings of other studies that an adequate, but consistent, intake of vitamin K containing foods is advisable for patients taking warfarin. It would also be advisable to undertake an active osteoporosis prevention program including regular exercise and supplementation with vitamin D and calcium.

New guidelines for stroke prevention

DALLAS, TEXAS. New guidelines for the prevention of ischemic stroke (stroke caused by a blood clot) have been issued by the American Heart Association and the American Stroke Association. It is estimated that more than 700,000 strokes occur each year in the United States alone resulting in over 160,000 deaths. Over 70% of the strokes are first events making primary prevention particularly important. The guidelines list the following well-documented risk factors for ischemic stroke:

- Advanced age
- Black race
- Male gender
- Family history of stroke or TIA (transient ischemic attack)
- Low birth weight
- Cardiovascular disease
- Hypertension
- Cigarette smoking
- Diabetes
- Non-valvular atrial fibrillation
- Asymptomatic carotid stenosis
- Sickle cell disease
- High total cholesterol level
- Low HDL cholesterol
- A sodium intake above 2300 mg/day
- A potassium intake below 4700 mg/day
- Obesity (BMI above 30)
- Physical inactivity
- Postmenopausal hormone therapy

Other less well-documented risk factors include metabolic syndrome, alcohol abuse, sleep apnea, elevated homocysteine level, and for women at least, a high level of C-reactive protein. As far as atrial fibrillation is

concerned, the guidelines contain the following statements of particular interest:

- "*The absolute risk of stroke varies 20-fold among atrial fibrillation patients, according to age and associated vascular diseases*."

- "*Most patients with atrial fibrillation who are under the age of 75 years without prior stroke or TIA have a relatively low risk of stroke (1% to 2% a year) if given aspirin, and they do not benefit sufficiently from anticoagulation (with warfarin) to warrant its use for primary stroke prevention."*

The guidelines also recommend that AF patients with a $CHAD_2$ score of 0 (no congestive heart failure, no hypertension, no diabetes, no prior stroke or TIA, and under the age of 75 years) should be treated with aspirin (75-325 mg/day) and do not benefit from anticoagulation. The recommendation regarding the prophylactic (preventive) use of aspirin by afibbers is actually, at least as far as men is concerned, in contradiction to the main recommendation of the guidelines:

"*Aspirin is not recommended for the prevention of a first stroke in men. The use of aspirin is recommended for cardiovascular (including but not specific to stroke) prophylaxis among persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment. Aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment*."

The guidelines also confirm that an increased intake of fruit and vegetables is associated with a reduction in stroke risk, that a high intake of sodium (above 2.3 g/day or 100 mmol/day) increases risk, and that a high intake of potassium (over 4700 mg/day or 120 mmol/day) reduces risk. Regular physical exercise and maintaining the ideal body weight have also been found to be protective. [572 references]
Goldstein, LB, et al. Primary prevention of ischemic stroke. A guideline from the American Heart Association/American Stroke Association Stroke Council. Stroke, *Vol. 37, June 2006*

Editor's comment: The new guidelines confirm my position that lone afibbers with no additional risk factors for stroke should not be on long-term warfarin therapy. The reason is simple – for this category of afibbers the danger of suffering a serious hemorrhagic stroke when on warfarin is greater than the danger of suffering an ischemic stroke when not on warfarin.

Adherence to guidelines for anticoagulation

MAASTRICT, THE NETHERLANDS. The Euro Heart Survey enrolled 5333 atrial fibrillation patients in 35 countries in 2003 and 2004. Patients were enrolled in 182 university, non-university, and hospitals with cardiology clinics. Patients seen by individual cardiologists were not included. One of the aims of the survey was to evaluate how well the participating institutions adhered to the AHA guidelines for the management of atrial fibrillation (2001) in their prescription practices for oral anticoagulants (warfarin). The overall conclusion was that prescription patterns are generally not tailored to the patient's stroke risk profile. The major reason for prescribing oral anticoagulants (OACs) was valvular heart disease. A prior stroke/TIA, hypertension, age over 75 years, and coronary artery disease (CAD) were not associated with a higher level of OAC prescriptions, but antiplatelet agents (aspirin, clopidogrel) were frequently prescribed for coronary heart disease. The absence of a local clinic for measuring INR was closely related to fewer prescriptions for oral anticoagulants.

About 90% of the study participants had one or more underlying risk factors for stroke with the remaining being lone afibbers with no risk factors. In this group 40-50% were prescribed OACs despite the fact that neither the AHA guidelines, the ACCP guidelines, the $CHAD_2$ scheme, nor the Framingham stroke risk score call for this. The authors of the survey report concluded:

> "*Treatment needs to be tailored according to the patient's risk profile. In low-risk patients, OAC provides a minimal benefit in preventing thrombo-embolic strokes when compared with aspirin, which is largely offset by a higher risk of bleeding with OAC."*
>
> *"Of concern, this survey shows that OAC prescription for AF was quite high throughout all risk categories, irrespective of the stroke risk stratification scheme used, meaning that a large proportion of low-risk patients is at an avoidable increased hazard for bleeding and troubled with the inconvenience of constant INR monitoring with little chance of benefit."*

The authors also conclude that the type of AF (paroxysmal, persistent, permanent) should not influence the decision to prescribe OACs, but rather, the decision should be based strictly on the presence or absence of recognized stroke factors. They also found that the prescription of OACs prior to pharmaceutical or electrical cardioversion was somewhat haphazard, but OAC prescription around a catheter ablation (PVI) was quite high at 80-90%.

Nieuwlaat, R, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. European Heart Journal *advanced access published May 26, 2006*

Editor's comment: The main conclusion of interest to lone afibbers is that 40-50% of afibbers with no stroke risk factors were prescribed oral anticoagulants (warfarin) even though they should not have been according to the guidelines. There is no reason to believe that a similar situation would not exist in Canada and the US. Thus, it is clearly incumbent on each of us to familiarize ourselves with the guidelines and tactfully (more or less) remind our physician that we would like to be treated according to the guidelines, or at least ask for a valid explanation for why we should not be. The guidelines can be found at http://circ.ahajournals.org/cgi/reprint/104/17/2118

Odds and Ends

Optimizing algorithms for ICDs

BONN, GERMANY. Highly sophisticated, programmable pacemakers (ICDs) are finding increasing application in the management of paroxysmal atrial fibrillation. Their programs (algorithms) are based on the observation that most afib episodes are preceded by an increase in the number of premature atrial complexes (PACs). If the heart rate is increased by pacing when an increase in PACs is detected an afib episode can often be avoided.

A team of clinicians from 84 heart centers in 11 European countries has just reported the results of a study aimed at determining if different pacing algorithms would have different effects in a group of 126 paroxysmal afibbers who required a pacemaker implant because their normal heart rate was excessively low. After pacemaker implantation the recipients spent at least 6 weeks as a "run-in" period and then entered a 3-month diagnostic phase. During this phase the pacemaker was in normal dual-chamber pacing mode with the lower heart rate limit set to 60 beats/minute. The afib prevention algorithms were disabled. The purpose of the diagnostic phase was to determine each participant's baseline afib burden (time spent in afib per day) and to separate the participants into two groups. Group 1 (Trigger Group) consisted of 73 afibbers whose episodes were triggered by a sequence of more than 2 PACs/minute. Group 2 (Substrate Group) consisted of 53 afibbers whose episodes did not seem to be related to increased PACs (less than 2 PACs/minute). The researchers speculate that the members of the Substrate Group were more likely to have a damaged atria and therefore not be solely dependent on increased PAC activity as the initiator for an afib episode.

After establishing the baseline afib burden, the study participants entered the therapy phase during which their ICD was programmed either for continuous overdrive pacing (Substrate Group) or for PAC suppression pacing (Trigger Group). PAC suppression pacing involves raising the heart rate by 15 bpm upon detection of a PAC and maintaining the elevated heart rate for 600 beats before returning to non-pacing.

The researchers found that the median afib burden in the Trigger Group was reduced from 2.06 hours a day in the diagnostic phase to 1.49 hours a day in the therapy phase for a relative reduction of 28%. About 39% of participants reduced their afib burden by 70-96%. This "super response"

was significantly more common in the Trigger Group. The researchers conclude that selecting the PAC suppression algorithm may benefit a group of afibbers whose episodes are primarily initiated by an increase in PAC activity. No reduction in afib burden was observed in the Substrate Group with the use of continuous, overdrive pacing.
Lewalter, T, et al. Individualized selection of pacing algorithms for the prevention of recurrent atrial fibrillation: results from the VIP registry. PACE, *Vol. 29, February 2006, pp. 124-34*

Potassium and exercise testing

ROCHESTER, MN. Extremely elevated potassium levels are associated with an increased risk of ventricular fibrillation, which can be fatal. Researchers at the Mayo Clinic recently completed a study aimed at determining if exercise testing increases the risk of cardiac arrhythmias in patients with potassium levels outside the normal range. Their study included 10,272 exercise tests performed on 9,084 patients. All patients had their serum level of potassium measured less than 48 hours before the test. The majority (88%) was found to have a level between 3.6 – 4.8 mmol/L. Three per cent were hypokalemic (2.4 – 3.5 mmol/L), and the remaining 9% were hyperkalemic (4.9 – 6.1 mmol/L).

Most patients had one or more disease conditions (63% elevated cholesterol, 50% hypertension, 11% diabetes, 42% with a family history of coronary artery disease, and 54% with a history of smoking). Both ventricular and supraventricular (atrial) ectopy were common during exercise, but their frequency was not significantly different in the 3 groups. PVCs (premature ventricular complexes) occurred in about 42% of cases irrespective of potassium status, while PACs (premature atrial complexes) occurred in about 32% of cases. New onset atrial fibrillation and flutter were relatively uncommon at about 0.6%. NOTE: Patients who had already been diagnosed with afib or flutter were not counted as having had afib or flutter initiated by the testing.

Supraventricular tachycardia occurred in about 3% of cases and non-sustained ventricular tachycardia also occurred in about 3% of cases. Only one patient went into sustained ventricular tachycardia (potassium level of 4.9 mmol/L). This patient had a history of heart attack and angioplasty. It is interesting that 45% of the patients in the hypokalemic group were on a diuretic. Older, male patients with valvular regurgitation, poor ejection fraction, and/or coronary artery disease were at highest risk of developing atrial fibrillation or flutter during the test. Potassium status did not affect the risk. The researchers conclude that mild to moderate hypokalemia or hyperkalemia should not be a contraindication to exercise testing.

Modesto, KM, et al. Safety of exercise stress testing in patients with abnormal concentrations of serum potassium. American Journal of Cardiology, *Vol. 97, 2006, pp. 1247-49*

Editor's comment: It is unfortunate that the study did not include the measurement of intracellular potassium concentration. It is well established that intracellular concentration is far more indicative of the potential for arrhythmia than is serum concentration (only about 2% of the body's potassium stores are found in blood serum).

Potassium-enriched salt lowers mortality

TAIPEI, TAIWAN. There is ample evidence that a high intake of sodium chloride (table salt) is associated with an increased risk of hypertension (high blood pressure), especially among elderly people. Taiwanese researchers now report that using a potassium-enriched salt instead of plain table salt in meal preparation can materially reduce death from cardiovascular disease. Their clinical trial included 1981 World War II veterans with an average age of 75 years. The veterans were randomized into two groups – Group 1 (768 men) used a potassium-enriched salt (49% sodium chloride, 49% potassium chloride and 2% other salts) in meal preparation, while Group 2 (control group of 1213 men) used standard table salt (99.6% sodium chloride). The average daily intake of sodium was 5.2 grams in the control group and 3.8 grams in the experimental group (Group 1). The total extra intake of potassium chloride (from the enriched salt) in Group 1 varied between 1.3 and 2.5 grams/day (0.7 – 1.2 grams/day of elemental potassium).

The study participants were followed for an average of 2.6 years during which 504 died. This corresponds to an overall mortality rate of 9815 per 100,000 person years. Of these deaths, 15% were from cancer, 18% from cardiovascular disease (CVD), and about 10% from pneumonia. There was a significant difference in the CVD mortality between Group 1 (potassium salt) and Group 2 (control group, normal table salt). In Group 1 the mortality was 1310 per 100,000 person years as compared to 2140 per 100,000 person years in the control group, or a reduction of about 60% in CVD mortality in Group 1. The mortality from cerebral vascular disease was twice as high in the regular salt group as compared to the potassium salt group, and the mortality from heart failure was 3.3 times higher in the regular salt group. Veterans in Group 1 also tended to live longer than those in the control group and needed significantly less medical care than did the participants of the control group.

The researchers conclude that the beneficial effects observed in the study were likely due to a major increase in potassium intake and a moderate decrease in sodium intake.

Chang, HY, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. **American Journal of Clinical Nutrition**, Vol. 83, 2006, pp. 1289-96

Editor's comment: This study certainly confirms the beneficial effects of an increased potassium intake. A moderately increased potassium intake (about 10 mmol or 390 mg/day) has also been found to decrease stroke mortality by 40% and many afibbers have found potassium supplementation to be highly effective in reducing PACs, PVCs, and even afib episodes.

Magnesium improves bone strength

MEMPHIS, TENNESSEE. Many afibbers have found magnesium supplementation highly beneficial in preventing ectopic beats (PACs and PVCs) and even afib episodes. Now there is evidence that an adequate daily magnesium intake also materially improves the density of skeletal bone and helps prevent osteoporosis and hip fractures.

Researchers at the University of Tennessee measured bone mineral density (BMD) in a group of older men and women (black and white between the ages of 70-79 years). The 2038 participants were enrolled in the Health, Aging and Body Composition Study initiated in 1997. The researchers also determined the participants' daily intake of magnesium, calcium, potassium, vitamin D, and vitamin C. Less than 26% of the study group met the Recommended Daily Allowance (RDA) for magnesium (320 mg/day for women and 420 mg/day for men over the age of 70 years). Twenty-five per cent took a magnesium supplement providing an average of 83 mg/day of elemental magnesium. Black men and women had a significantly higher BMD than did white persons and did not benefit from higher magnesium intake.

White women with the highest magnesium intake had a significantly higher BMD than women with lower intakes with an increase in daily intake from 220 mg/day to 320 mg/day corresponding to an increase of 0.020 g/cm^2 in whole body BMD (after adjusting for other relevant variables). For white men, an increase from 320 mg/day to 420 mg/day corresponded to an increase of 0.010 g/cm^2 in whole body BMD. These increases are roughly equivalent to those that would result from increasing daily calcium intake by about 400 mg. The researchers speculate that the beneficial effects of an increased magnesium intake on bone density may be due to one or more of the following factors:

- Improved synthesis of vitamin D with subsequent suppression of parathyroid hormone function.

- Increased alkalinity of a diet high in magnesium and lower net acid production.
- Substitution of calcium with magnesium in the formulation of bone hydroxyapatite, resulting in greater structural strength. NOTE: Strontium may have a similar effect.

The researchers conclude that a higher magnesium intake through dietary change or supplementation may provide an additional strategy for preventing osteoporosis.
Ryder, KM, et al. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. Journal of the American Geriatrics Society, ***Vol. 53, November 2005, pp. 1875-80***

Editor's comment: The finding that 100 mg/day of elemental magnesium is as beneficial in regard to bone strength as is 400 mg/day of calcium is welcome news to those afibbers, notably vagal, who have found that calcium supplementation tends to increase the frequency of their episodes. I am not aware of any research on just how far one can go in replacing calcium with magnesium in the hydroxyapatite bone structure. However, it is quite possible that supplementing with 400-600 mg/day of highly absorbable magnesium (glycinate or citrate) may eliminate or vastly reduce the need for calcium supplementation in a normal diet.

Vitamin C helps prevent kidney damage

ATHENS, GREECE. Contrast agents (x-ray dyes) are widely used in CT scanning and procedures involving heart catheterization (angiography, angioplasty, and ablations for AF). Contrast agents contain large amounts of iodine and can be very hard on the kidneys. The incidence of contrast agent-induced nephropathy (abnormal kidney function) varies from 2-14% in the general population of patients to 20-80% in patients with pre-existing nephropathy. It is generally believed that contrast agents do their damage by increasing the production of free radicals in the kidneys.

Several clinical trials have found the antioxidant N-acetylcysteine useful in preventing contrast agent mediated nephropathy (CAMN), but other studies have failed to confirm any benefits. However, a recent meta-analysis of 7 randomized, placebo-controlled studies showed that, compared with hydration alone, N-acetylcysteine significantly reduced the risk of CAMN in patients with impaired renal function.

Now a team of British, Canadian and Greek researchers reports that vitamin C (ascorbic acid) is also effective in preventing CAMN. Their randomized, double-blind, placebo-controlled trial involved 231 patients scheduled to undergo coronary angiography or heart catheterization. All

patients had a baseline serum creatinine concentration of at least 1.2 mg/dL (106 micromol/L) and the average for the group was 1.4 mg/dL (125 micromol/L) indicating slight to moderate kidney impairment (normal range is 0.8-1.36 mg/dL or 70-120 micromol/L).

The study participants were assigned to receive a placebo or 3 grams of ascorbic acid at least 2 hours prior to the procedure followed by 2 grams in the night and morning after the procedure. All patients also received adequate hydration during the procedure (50-125 mL/h of normal isotonic saline solution infused intravenously). Placebo and ascorbic acid were administered in the form of chewable tablets. Creatinine concentration was measured before the procedure and 2-5 days after. CAMN was defined as an absolute increase in serum creatinine level of 0.5 mg/dL (44 micromol/L) or more, or a relative increase of 25% or more. The incidence of CAMN, according to this definition, was 9% in the ascorbic acid group and 20% in the placebo group.

The researchers conclude that, "ascorbic acid, a safe, well-tolerated, inexpensive, and readily available oral antioxidant, appears to prevent the complication of CAMN after invasive coronary imaging procedures in patients with preexisting renal dysfunction."
Spargias, K, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation, *Vol. 110, November 2, 2004, pp. 2837-42*

Editor's comment: Supplementing with vitamin C before and after an ablation (PVI) would seem to be a good preventive measure even for afibbers with no known kidney impairment.

Research Reports

Special Reports

LAF vs AF: Shape Matters

Patrick Chambers, MD

SIZE MATTERS! That has been the banner proclamation for Godzilla and mainstream medicine, when it comes to AF risk. However, the results of LAFS – 11 suggest that shape trumps size and is the primary determinant of LAF risk.

Before proceeding Hans and I would like to thank all of you that took the time out of your busy schedules to complete yet another survey. And I would personally like to thank Hans for allowing me the opportunity to exploit his wonderful resource, all of you. I believe you will find the objective data uncovered by the survey titillating and hope your reaction to the ensuing discussion of that data to be likewise.

What Is Lone Atrial Fibrillation?

Lone atrial fibrillation (LAF) is AF in the absence of structural heart disease (enlarged heart, rheumatic heart disease, coronary artery disease, valvular heart disease, congenital heart disease, etc.). Mitral valve prolapse, frequently encountered in the general population, is not generally considered to represent structural heart disease. Hypertension, which causes the heart to enlarge, is the biggest risk factor for AF in the U.S, according to the American Heart Association (AHA). Some studies on LAF include those with hypertension, while others do not.

Due to the increase in cardiovascular disease with age, once 65 is attained the “lone” is often dropped. Furthermore, aging results in progressive LENGTHENING of the atrial effective refractory period (AERP). NOTE: AERP is the rest period following the contraction of the heart muscle. The cell does not respond to stimulation during this period [1,2,3]. Parasympathetic and sympathetic stimulation can both trigger LAF, because they both cause SHORTENING of the AERP. This is why onset of true LAF after age 65 is most unlikely and why the mechanisms for LAF v. AF may differ [1].

What percent of AF is LAF? The answer to this question depends on what you consider to be organic heart disease and how hard you look for that disease. According to one study, “AF is associated with organic heart disease in 70% to 80% of such patients. AF can occur in the absence of detectable organic heart disease, so-called "lone AF," in about 30% of cases”[4]. “In material based on hospital observations, 35% of all fibrillation was described as being of paroxysmal type”[5]. “About 50% of the patients with paroxysmal AF are lone. This proportion falls to <20% in patients with persistent or permanent forms”[6]. So, these two studies

also translate to about 30% of AF being LAF. In other studies a more conservative figure is given. According to the AHA, only 5 to 15 percent of patients with AF have no apparent heart disease or identifiable contributing factor [7].

Because only about 5-30% of AF is lone, most studies on AF make no distinction. Instead AF categorization is limited to paroxysmal (spontaneously terminating and less than 48 hours duration for some v. less than seven days for others), persistent (medically or electrically cardiovertible) or permanent (not cardiovertible).

Could AF and LAF be two different diseases requiring different treatments? Previously differentiation between the two rested on an expensive battery of tests, e.g., EKG, chest radiograph, treadmill test, 24 Holter test, perfusion scan, … Perhaps there is an easier way. Cardiac structural disease may be reflected in body structure, which is much more readily measured. Hence, LAFS – 11 was undertaken in an attempt to explore this possibility and hopefully the results of this survey will underscore the legitimacy and utility of this approach.

Anthropometric Analysis

Anthropometry is the measurement and study of the human body and its parts and capacities. The anthropometric data from LAFS – 11 suggest that LAF and AF are most definitely distinct afflictions and shape not size is the critical parameter. The survey reveals that, whereas pear body shape (gynoid) is good and apple body shape (android) is bad, when it comes to cardiovascular disease risk, the opposite applies for LAF. Furthermore, age at onset/diagnosis, blood pressure and possibly specific lab data may provide further delineation.

RESULTS OF LAFS – 11

	LAFers		Normal Population Means	
	Men	Women	Men	Women
Respondents (77) by gender (%)	79.2	20.8		
Mean present age	58.9	63.6		
Mean age at diagnosis/onset	49.8	53.7		
Mean years of AF	9.1	9.9		
Mean height, inches[8]	71.4	66.6	69.2	63.8
Mean Body Mass Index (BMI)[8]	26.2	24.9	27.8	28.1
Mean waist: hip ratio (WHR)[9,10]	0.91	0.77	0.95	0.88
Mean waist: height ratio (WTR)[12]	0.51	0.47	0.53	0.55
Mean waist circumference (WC)[11]	36.6	31.2	38.8	36.3
Mean blood pressure, mm Hg	121/74			

Statistical analysis of the differences of the means between LAFers and the normal population on all of the above anthropometric measurements range from significant, i.e., p =. 01, (male WTR) to very significant, p < .001, (female BMI and height) to extremely significant, p < .0001, (everything else).

After elimination of several for probable structural heart disease a total of 77 respondents were included in the survey. This included 61 men and 16 women, a 4:1 ratio. Average present age is 59 for males and 64 for females, while the average age at onset/diagnosis is 50 for males and 54 for females (overall mean of 51). Curiously the latter is 50 for all VMAFers. There are many anthropometric measures of cardiovascular disease risk, BMI, WHR, WTR and WC [13]. So, data to calculate them all was requested. LAFers are taller with males and females both being about two to three inches taller than their average counterparts (LAF averages are 71.5" and 66.3" respectively). Regarding BMI, the average male weighed in at 26.2 kg/m2 (includes one BMI over 38), while for the average female BMI is 24.9. The frequency distribution curve for BMI is bell shaped. While BMI is the oft quoted barometer for assessing overweight and obesity, there has been much recently written on waist to hip ratio (WHR) [9,10]. For male LAFers this is .91 and for females it is .77 with an overall average of .88, well under the North American average WHR of .90. However, the latest data indicates that the waist to tallness ratio (WTR) is the most sensitive and specific standard for measuring obesity and related cardiovascular disease risk with limits of .55 for men and .53 for women [12]. WTR for LAFers is .51 for males and .47 for females. LAFers are not hypertensive with an average BP of 121/74. Much of the rest of the data was difficult to assimilate, but there was one other noteworthy result. Only seven LAFers have undergone intracellular mineral analysis, but all seven are either below normal or very near the lower limit of normal for intracellular magnesium. The normal range is 33.9-41.9 mEq/L, and that of LAFers ranged from 30.0-35.0 mEq/L. All of the height, weight, BMI, age, gender and BP results conform to those determined by LAFS – 5 undertaken in 2003.

After analyzing the data from LAFS – 11, a pattern began to emerge and additional data from earlier surveys proved relevant. LAFS – 1 (2001) revealed that 25% of all respondents (50) had hypoglycemia (idiopathic postprandial syndrome) and another 24% had symptoms of hypoglycemia, yet no one had diabetes. LAFS – 5 (2003) reported the prevalence of diabetes to be 0.6% amongst LAFers (v. 6% for the U.S. population). In LAFS –5 the prevalence of hypoglycemia amongst 140 LAFers with vagal or mixed type was reported to be 27% and the prevalence among 24 LAFers with adrenergic type was reported to be 42%.

So, what does this all mean? And what is the link between LAF and hypoglycemia? Hypoglycemia is generally due to either increased insulin sensitivity (decreased blood insulin and glucose levels) or increased insulin. It appears that LAF is highly correlated with increased insulin sensitivity and that this may be directly reflected in body shape. The following elaborates on this hypothesis.

Obesity and LAF

The risk of AF increases by 4% for every unit increase in BMI [14]. Since body size is related to heart size and larger atria more easily accommodate AF, the medical literature has linked this increased AF risk directly to increased heart size. This is why AF is often seen in syndrome X (metabolic syndrome) and in the tall, or so it has been reported [15,16]. But this is clearly not the case for LAFers, where increasing BMI over 26 kg/m2 is associated with decreasing LAF risk. Furthermore, the above weight and waist data reflect measurements taken on average eight years after onset/diagnosis. And, of course, these figures tend to go south as we age. In addition progression of episodes over this nine-year period may have restricted any preexisting exercise regimen. This would negatively impact ensuing weight and waist measurements. And finally delineation of LAF from AF can sometimes be quite difficult. Undoubtedly some of the latter may have been inadvertently included in this survey, compromising their anthropometric distinction.

Gender, Age, Blood Pressure and AF/LAF

The 4:1 male to female ratio is difficult to explain. However, LAFS – 11 does contain a clue. The mean age at onset/diagnosis of VMAF in females is a year less than that of male VMAFers. Whatever protective hormone may be at work in females appears to be effective predominantly against the adrenergic component. Age at onset/diagnosis of vagal/mixed/adrenergic types of LAF is 50.3/49.7/49.0 in males and 48.8/58.6/ in females. No female reported pure adrenergic type LAF.

Data from the Framingham Heart Study have established that the prevalence of atrial fibrillation rises with increasing age -- occurring in less than 0.5% of 25- to 35-year-olds, about 1.5% of people up to 60 years of age, and increasing to 9% in people aged over 75 years [17]. This is in contrast to the pattern for LAF where the frequency distribution curve for age at onset/diagnosis is bell shaped with a mean of about 50.6 years.

Hypertension is the biggest risk factor for AF. The relationship between insulin level and systolic/diastolic blood pressure persists after adjustment for body mass index, WHR, norepinephrine, age, smoking, physical activity level, and antihypertensive medication use [18]. Mean blood pressure amongst LAFers is 121/74 mm Hg; ie. well below the range for hypertension.

Hypoglycemia and AF/LAF

In one canine study the AERP was shortest under hypoglycemia in the left atrium and longest under hyperglycemia in the right atrium [19]. Other research indicates that ACTH mediates this through sympathoadrenal stimulation and catecholamine stimulated hypokalemia [20]. Hypoglycemia is a potent stimulant of ACTH secretion [21.22]. Hypokalemia is clearly aggravated by the additional action of increased ACTH driven aldosterone secretion.

According to the Merck Manual on Potassium Metabolism, "Numerous factors affect the movement of potassium between the intracellular and extracellular fluid compartments. Among the most important is circulating insulin level. In the presence of insulin, potassium moves into cells, thus lowering plasma potassium concentration…. Stimulation of the sympathetic nervous system also affects transcellular potassium movement. Beta-agonists, especially selective $beta_2$-agonists, promote cellular uptake of potassium…. High-circulating aldosterone levels lead to increased potassium secretion and kaliuresis" [23]. Insulin, catecholamines (adrenaline) and aldosterone all work to lower blood potassium.

Height and Insulin Sensitivity

Although endurance athletes are typically of average height, tall males also seem to be at increased risk for LAF (Bill Bradley, Akeem Olajuwon and recently 6'4" Mario Lemieux). Since insulin and glucose both inhibit growth hormone (GH) [24], those with increased insulin sensitivity (lower blood insulin and glucose levels) should be taller.

Tallness is a function of growth hormone (GH) secretion during the developmental stage. Growth hormone exerts its effect through insulin like growth factor 1 (IGF-1), produced by the liver. "Tall height and high BMI at 7 yr. were associated with low IGF-1 in adulthood but only in those subjects whose current BMI was below median. On further analysis these interactive effects were particularly strong for height in childhood and adult lean BMI (lean body mass/$height^2$). Serum IGF-I was positively correlated with fasting glucose, fibrinogen concentrations and blood pressure" [25]. Hence tallness appears to be associated with insulin/IGF-1 sensitivity. As an aside, increased IGF-1 levels have been directly linked with increased cancers of breast, colon, prostate, lung and ovary. Obese men and women demonstrated significantly more deaths due to these cancers, as well as cancers of the esophagus, liver, gallbladder, pancreas, kidney, endometrium, non-Hodgkins lymphoma and multiple myeloma than normal weight controls. The heaviest men were 52% more likely to die of cancer than thin/normal weight men; and the most obese women were 62% more likely to die than thin/normal weight women [26]. LAF

seems a small price to pay for extra protection against heart disease AND numerous cancers.

Body Fat Distribution and Insulin Sensitivity

Lower-body obesity in women has been associated with hypoglycemia and a high level of beneficial high-density lipoprotein (HDL). Insulin sensitivity is highest in those with moderate lower-body overweight (11.2), intermediate in controls (6.1) and lowest in those with upper-body obesity (2.6) [27]. Body fat distribution is a more relevant determinant of insulin resistance than obesity. Compared to the normal female, female LAFers appear to carry relatively more of their weight in their hips (WHR = .77). Perhaps female LAFers of normal weight are also relatively insulin sensitive compared to non-LAF females of normal weight.

Thigh fat may contribute to lipoprotein profiles that predict lower risk of cardiovascular disease [28,29]. However, a few LAFers appear to prefer weight lifting to aerobic endeavors. This may not be as beneficial to lipoprotein profile, as demonstrated by one study on HDL levels in professional football players [30]. Weight gain aggravates insulin sensitivity and weight loss improves it [31]. HDL is a surrogate for insulin sensitivity.

Autonomic Tone and Insulin Sensitivity

Our stomachs often remind us when we're hungry. This is because insulin induced hypoglycemia stimulates efferent vagal signals to the stomach. However, a recent study has shown that no simultaneous signals are sent to the heart [32]. Therefore, any role that insulin induced hypoglycemia might play in triggering LAF appears to be more related to subsequent electrolyte imbalance. On the other hand, insulin sensitivity clearly regulates cardiac autonomic tone [33]. These studies suggest that the role of parasympathetic tone in the possible genesis of LAF precedes hypoglycemia [33,34].

There appears to be a substance yet to be isolated, produced in the liver and released by parasympathetic signals, that sensitizes tissue to insulin. It is called hepatic insulin sensitizing substance (HISS)[35]. The HISS hypothesis has been proposed as a new paradigm for diabetes and obesity by Canadian pharmacologist Wayne Lautt [36]. Could this be the missing link connecting parasympathetic tone and insulin sensitivity in LAFers?

Exercise and Insulin Sensitivity/Autonomic Tone

"The proportion of sportsmen among patients with lone atrial fibrillation is much higher than that reported in the general population of Catalonia: 63% vs. 15%" [57]. The prevalence of lone atrial fibrillation in master orienteers was at least six-fold higher than in controls [58].

Physical fitness has also been shown to increase HDL and insulin sensitivity [37,38,39]. In fact HDL (or HDL/TG (triglyceride)) can be taken as a measure of insulin sensitivity [40]. Heart rate recovery after exercise is also related to HDL and can also be taken as a reflection of insulin sensitivity [41], further underscoring the link between cardiac autonomic tone and insulin resistance/sensitivity [42]. On the other hand obese patients have increased sympathetic activity and a withdrawal of vagal activity [43], and these autonomic disturbances improve after weight loss [44,45].

Obesity and Inflammation

Not only is body shape/size intimately tied to hypertension, insulin sensitivity, lipoprotein profile, and autonomic tone but also to inflammation [46]. Commonly used tests for detecting inflammation, e.g., high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), white blood cell (WBC) count, fibrinogen, are much more frequently elevated in the obese [46,47,48]. These inflammatory markers decrease with weight loss. It has been suggested that a WBC in the upper range of normal is yet another manifestation of the insulin resistance syndrome (syndrome X, metabolic syndrome) along with hypertension, increased cholesterol and increased triglycerides [49]. LAFers may have a white blood cell count at the lower limit of normal.

Inflammation and LAF

Although fibrosis and inflammation have been described in LAF and reactive oxygen species (ROS) generated by endurance sports has been suggested as causative, perhaps LAF precedes the inflammation, unlike in pathologic AF. After all, exercise and HDL are both anti-inflammatory [50] and AF by itself can produce a measurable increase in left atrial ROS [51]. Indirect support for this view may be found in Canadian and Spanish meta-analyses [52,53]. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) prevent recurrent and new onset AF in those with structural heart disease, but such findings have not been demonstrated for LAF with or without mild hypertension

Left atrial angiotensin II type 1 receptors (AT1s), but not AT2s are increased in LAFers [54]. On the other hand, pathologic AF is associated with decreased atrial AT1s and increased AT2s [55]. Furthermore, the decrease in AT1s is greater in permanent than paroxysmal atrial fibrillation. Why do the left atrial AT1s differ between LAF and AF? Angiotensin II/aldosterone are prominent players in cardiac remodeling and fibrosis. Therefore, increased left atrial AT1s in LAF should portend greater damage, yet ACEIs and ARBs confer no benefit. Recent research suggests a possible solution to this dilemma. Increased left atrial ATIs in LAF may be no more than a marker for mechanical stress and angiotensin II may not actually be involved [56].

LAF/AF both causes inflammation, whereas perhaps only AF may actually be caused by inflammation. The anthropometric data also support this interpretation.

Alcohol, Glutamate, Coffee and LAF

Alcohol has been well described as a trigger for LAF episodes (holiday heart syndrome). Alcohol-induced hypoglycemia often occurs during the fasting state. Hypoglycemia may result from alcoholic inhibition of gluconeogenesis (creation of glucose by the liver) [59,60] in combination with glycogen (storage form of glucose) depletion. "Light to moderate alcohol intake is associated with enhanced insulin sensitivity and this improvement in sensitivity results in higher HDL cholesterol levels" [61]. Furthermore, the acute effect of a moderate dose of alcohol on the heart is vagotonic [62].

In LAFS – 5 approximately 21% of 166 LAFers associated glutamate intake with initiation of episodes. L-glutamate appears to play a direct role in insulin release, although the precise mechanism remains elusive" [63,64].

Although caffeine has been widely reported to increase insulin resistance (small, short-term studies), long-term coffee consumption decreases insulin resistance. Two recent reports, one epidemiologic study and one meta-analysis, have confirmed this [65], even after adjustment for age, body mass index, and other risk factors [66]. Could coffee aggravate LAF by increasing insulin sensitivity?

Potassium and adrenergic LAF

The risk of AF can be quantified by the equation: wavelength (WL) = AERP x conduction velocity (CV). According to Moe's wavelet theory, the circumference of each wavelet is > WL and six or more wavelets appear to be required to sustain AF [67,68,69]. Both atrial dilatation and smaller wavelets provide this sustenance. Therefore, since shorter WL => smaller wavelets, shorter WL translates to greater risk of AF. Because adrenergic LAF (ALAF) or stress triggered LAF is associated with sympathetic tone, which causes relatively less AERP shortening (v. vagal tone) and increases CV, then ALAF requires additional arrhythmogenic input. Electrophysiologic studies show that increased dispersion may provide this arrhythmogenic shortfall [70]. Perhaps this is mediated by hypoglycemia. Hypoglycemia not only shortens AERP but also increases dispersion (heterogeneity) and both are potentiated by hypokalemia. The fact that 42% of ALAFers and only 24% of VMAFers (vagally mediated) are hypoglycemic supports this greater role for hypoglycemia in ALAFers.

The Na-K ATPase pump maintains intracellular potassium in the face of a 30:1 gradient with the extracellular space. The lower the blood potassium levels, the more this pump is challenged and the greater the leakage of potassium from within cells. This "conductance" of potassium forces faster repolarization and hence shortens the refractory period. Therefore, insulin-induced hypoglycemia and its ultimate impact on blood potassium appear to work in tandem with autonomic tone to shorten the AERP. Additional research has shown that low blood glucose increases dispersion of this refractoriness and that this is prevented by the administration of potassium [71]. Blood potassium may be lower in ALAFers (v. VMAFers), because ACTH is not only driven by hypoglycemia but also by stress. This stress mediated ACTH release leads to increased catecholamine and aldosterone secretion. An inability to maintain intracellular potassium in the face of a growing gradient may be at the heart of LAF. In ALAF the gradient may be greater but of shorter duration, whereas in VMAF the opposite may occur (less gradient but longer duration).

Potassium and vagal LAF

In VMAF it may not be the magnitude of the gradient that is critical but its duration, i.e., an extended period of lower range blood potassium. As Hans speculated on p. 63 of *Lone Atrial Fibrillation: Towards A Cure*, the flat or blunted glucose tolerance test curves associated with increased vagal tone may be implicated in LAF. These flat or blunted curves indicate extended periods during which blood glucose is in the lower range of normal. Frank hypokalemia or hypomagnesemia may not even be required for VMAF.

The prominence of nighttime episodes in VMAF may be due not only to increased nighttime vagal tone but also to the midnight diurnal nadir of blood potassium. "Plasma potassium values exhibit a circadian rhythm (average peak-to-trough difference 0.60 mmol/L, with lowest values at night) and also decrease postprandially because of insulin released in response to an ingested carbohydrate load" [72]. Slow leakage of intracellular potassium can also cause muscle cramps and twitching. Twenty one percent of 166 LAFers in LAFS –5 complained of leg cramps, especially at night.

Magnesium and LAF

Intracellular potassium is difficult to maintain in the face of low intracellular magnesium. Magnesium is necessary for proper functioning of the Na-K ATP requiring pump that performs this function. The fact that magnesium was either low or at the very lower limit of normal in seven of seven LAFers undergoing intracellular mineral analysis supports emphasis of its exalted status in preventing LAF episodes. However, the sampling is quite small and no sweeping conclusions can be drawn. Furthermore,

this pump is inhibited by digoxin and may explain why digoxin is problematic for LAFers, especially VMAFers [73,74].

According to magnesium expert Mildred Seelig, "Stress causes secretion of epinephrine (adrenaline) and corticosteroids (aldosterone) and results in magnesium loss in animals and in humans. The types of stresses that can increase magnesium needs can be physical (exhausting or competitive exercise, extremes of temperature, and accidental or surgical trauma), or psychological (anger, fear, anxiety, overwork and crowding)" [75,76]. To this list insulin induced hypoglycemia (idiopathic postprandial hypoglycemia) might be specifically added.

Magnesium also impacts cholesterol. According to her book *The Magnesium Factor*, magnesium inhibits HMG-CoA reductase, the rate-limiting step in cholesterol synthesis, thereby working to lower total cholesterol. Furthermore, the insulin to glucagon ratio also influences cholesterol metabolism by either stimulating (high ratio) or inhibiting (low ratio) the activity of this same enzyme [77]. Insulin sensitivity should result in a lower ratio and lower total cholesterol.

SUMMARY

In summary, body fat distribution is inextricably entwined with insulin sensitivity/resistance, lipoprotein profiles, autonomic tone and inflammation. The anthropometric data of LAFS-11 indicate LAFers to be quite distinct in their body shape. LAF (physiologic AF) appears to be the opposite of diabetes, and HDL cholesterol, total cholesterol, triglycerides, BP, WTR, WHR and age at onset/diagnosis may help to differentiate it from pathologic AF. Elevated total cholesterol in the face of normal BMI and WTR may indicate low intracellular magnesium, especially amongst VMAFers and especially if accompanied by nighttime muscle cramps and/or fasciculations (muscle twitching). Further delineation of the utility of these lab tests in differentiating LAF from AF awaits a future LAF survey (?LAFS – 12). Low blood glucose and potassium appear to conspire in creating an arrhythmogenic substrate. Low blood potassium may represent the final common pathway for both vagally mediated and adrenergic forms of LAF. LAF may represent physiologic AF primarily mediated by low potassium, whereas AF associated with structural heart disease is pathologic AF and predominantly characterized by visceral obesity, cardiac fibrosis and other age related changes.

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Fish Oils and Warfarin

Hans R. Larsen

Background

An increased intake of oily fish and long-chain polyunsaturated omega-3 fatty acids (fish oils) is generally beneficial and reduces the risk of ischemic stroke. For people on warfarin it is clearly important to know if it is safe to take both fish oils and warfarin.

Warfarin works by inhibiting the activation of vitamin K-dependent coagulation Factors V, VII and X in the extrinsic and common pathways of the coagulation cascade. Fish oil works primarily by inhibiting platelet aggregation, stabilizing atherosclerotic plaque, and reducing fibrinogen level, but there is some evidence that it also reduces Factors V and VII in both men and women and Factor X in women.[1,2]

There is no evidence that fish oil causes hemorrhagic stroke or internal bleeding, while there is abundant evidence that warfarin does.[3-7] Warfarin was originally developed as a rat poison and has two effects – it damages the integrity of blood vessel walls and inhibits the normal blood clotting action which would prevent the rat from bleeding to death. It would seem that a similar mechanism operates in humans.

The purpose of anticoagulants like warfarin and fish oil is to prevent blood from forming a clot or at least significantly increase the length of time it takes before a clot is formed in response to trauma or stagnation. There are several different tests for measuring clotting tendency, and it is somewhat unfortunate that the test in general use today, the prothrombin time (INR), is not an absolute measure of the blood's tendency to form a clot (thrombus), but rather a measure of the blood level of those coagulation factors that depend on vitamin K for their synthesis and the factors they, in turn, activate. In other words, the universal test today is primarily designed to measure blood level of warfarin. Aspirin, vitamin E, garlic and other natural antiplatelet/anticoagulant agents generally have no or very little effect on INR – and yet, these substances all have proven preventive effects against thrombus formation.

The problem is that the INR test only measures blood coagulation time in the extrinsic and common pathways. Retardation of the coagulation sequence by antiplatelet aggregation medications (aspirin, clopidogrel, ticlopidine), for example, will not affect INR because the sequence is halted in the intrinsic pathway before vitamin K-dependent coagulation factors become involved. Similarly, if the coagulation process is initiated via the intrinsic pathway and prekallikrein, Factor VIII or von Willebrand

Factor are blocked, the thrombus formation sequence will not proceed either, but the INR test, because it bypasses the intrinsic pathway, will not show that you are protected even though you clearly are.

It is clear that both fish oil and warfarin are effective anticoagulants and it is thus likely that taking both would be superior to either agent alone in preventing ischemic stroke. The question is, "Would taking both increase the risk of hemorrhagic stroke and internal bleeding?" As far as I know only three studies have investigated the possible interaction between warfarin and fish oil.

Clinical Studies

A group of Norwegian medical researchers found that fish oil supplementation did not increase the bleeding tendency in heart disease patients receiving aspirin or warfarin. The study involved 511 patients who had undergone coronary artery bypass surgery. On the second day after the operation half the patients were assigned in a random fashion to receive 4 grams of fish oil per day (providing 2 g/day of eicosapentaenoic acid, 1.3 g/day of docosahexaenoic acid, and 14.8 mg/day of vitamin E). At the same time the patients were also randomized to receive either 300 mg of aspirin per day or warfarin aimed at achieving an INR of 2.5-4.2. The patients were evaluated every 3 months and questioned about bleeding episodes for the duration of the 9-month study.

The researchers concluded that fish oil supplementation did not result in a statistically significant increase in bleeding episodes in either the aspirin group or in the warfarin group. Nosebleeds were somewhat more common in the fish oil + warfarin group, while gastrointestinal bleeding was more common in the warfarin group. None of the differences were statistically significant. They also found no significant long-term effects of fish oil on common parameters of coagulation and fibrinolysis – including bleeding time. They noted that the blood levels (serum phospholipid levels) of eicosapentaenoic acid and docosahexaenoic acid increased by 140% and 14% respectively in the patients taking fish oil. The serum triglyceride levels decreased by 19.1% in the fish oil group while no significant change was observed in the remainder of the patients.[8]

Researchers at the University of Texas Health Sciences Center have addressed the question, "Does fish oil supplementation change INR in patients on warfarin?" Their placebo-controlled, randomized, double-blind study included 11 patients with prosthetic heart valves, cardiomyopathy or deep vein thrombosis who were taking warfarin and had achieved stable INR values for at least 4 weeks. The participants were assigned to receive a placebo, 3 grams/day of fish oil (*MaxEPA*), or 6 grams/day of fish oil for a 4-week period. Their INR was measured twice weekly during the study period. INR values remained steady in all groups and there

were no significant differences in INR values between the groups during the trial. The researchers conclude that, "there does not appear to be a clinically significant interaction between warfarin and up to 6 grams/day of the fish oil supplement *MaxEPA* in terms of INR changes and bleeding incidence."[9]

Mitchell Buckley and colleagues at the Shawnee Mission Medical Center in Kansas recently reported the case of a 67-year-old woman whose INR increased significantly after she increased her daily dose of fish oil from 1 gram to 2 grams. The woman had serious health problems (TIAs, hypothyroidism, hyperlipemia, osteopenia, and coronary artery disease) and had experienced a heart attack necessitating angioplasty. She was taking several medications including warfarin, aspirin, levothyroxine, atorvastatin, bisoprolol, lisinopril, and conjugated estrogens. She was also supplementing with 400 IU a day of vitamin E and 1 gram a day of fish oil. The patient had been stable for a 5-month period at an INR of between 2 and 3 taking 1.5 mg a day of warfarin. In March 2002 she increased her fish oil dosage to 2 grams a day and a week later her INR measured 4.1. Upon returning to 1 gram a day of fish oil her INR dropped to 1.6. The researchers conclude that the higher dose of fish oil could have provided additional anticoagulation as expressed in a higher INR. There was no indication that the INR was affected by 1 gram a day of fish oil.[10]

Conclusion

There is no evidence that taking both warfarin and fish oil increases the incidence of bleeding. However, there is no clear consensus as to whether fish oil affects INR. One small study found that 3 and 6 grams a day of fish oil had no significant effect on INR, whereas a single case study found that 2 grams a day increased INR significantly. Thus, it would appear that supplementing with 1 gram a day of fish oil while on warfarin is safe and does not affect INR.

It is not clear whether higher fish oil intakes may affect INR, so it is advisable to increase INR monitoring frequency when changing one's daily fish oil intake. It is possible, but certainly not proven, that taking fish oil and warfarin together may reduce the amount of warfarin required to keep the INR in the therapeutic range.

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Living with Warfarin

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Anticoagulation with warfarin is not recommended for afibbers with no underlying heart disease or other risk factors for stroke.[1,2] However, in patients with a history of prior stroke or TIA (transient ischemic attack) and in those with prosthetic (artificial) heart valves the use of warfarin is likely to be beneficial overall. Many patients with less serious stroke risk factors such as hypertension and diabetes are also prescribed warfarin although it is somewhat doubtful whether the reduction in ischemic stroke risk outweighs the increase in the risk of serious bleeding and hemorrhagic stroke. A recent study of atrial fibrillation patients on warfarin found that the risk of major bleeding was 2.5% a year in the case of uncontrolled hypertension. [3] This compares to an ischemic stroke risk of 1.5-2.8% a year when not on warfarin.[4,5] This is not a significant difference.

The study, involving 1604 afibbers released from hospital on warfarin, found that most of the major bleeding events occurred in the gastrointestinal tract (67.3%). Hemorrhagic strokes accounted for 15.3% of the bleeding events, and the remaining 17.3% were in other locations. The seriousness of the bleeds can be judged by the fact that 21.6% of the patients admitted for warfarin-induced bleeding died within 30 days. In comparison, only 6-10% of patients admitted to hospital for ischemic stroke die while in hospital, most of them through errors in the administration of thrombolytic agents.[6]

While it is thus not at all clear that anticoagulation with warfarin produces an overall benefit in the majority of patients, it is nevertheless widely prescribed and many patients need to live with it for the remainder of their lives. For those patients it is clearly important to know what the adverse effects of warfarin are, and how to protect against them.

ADVERSE EFFECTS

The most serious adverse effect of warfarin is the potential for major gastrointestinal bleeding and hemorrhagic stroke or bleeding in the brain. A recent study of 1604 afibbers released from hospital on warfarin observed a 5% a year risk of a major bleed and a 21.6% chance of dying from this bleed within 30 days.[3] Warfarin usage has also been linked to arterial calcification (atherosclerosis) and long-term use to an increased risk of osteoporosis. Other less common adverse effects include skin necrosis sometimes requiring amputation, and ocular (eye-related) bleeding.

GASTROINTESTINAL BLEEDING AND HEMORRHAGIC STROKE

Warfarin was originally developed as a rat poison. It works in two ways – in effective doses it increases the permeability of the capillaries (smallest blood vessels) thus allowing blood to seep out of the vessels and into the organs and surrounding body cavity. Secondly, it prevents the vitamin K-dependent clotting activity, which would normally stop the leak until it can be repaired. If nothing is done the animal (or human) will eventually die from loss of blood.[7-9] To understand the intricacies of this process and find possible ways of preventing it, it is necessary to develop a basic understanding of the function and construction of blood vessels.

Blood vessels

Blood is "the river of life". It carries nutrients to and receives waste from each individual cell in the body. It begins its journey in the main arteries emanating from the heart's left ventricle. As it flows through smaller and smaller arteries it eventually reaches the arterioles, which control the flow of blood to the tissues. Each arteriole, in turn, can serve hundreds of the smallest blood vessel of all, the capillary. The diameter of a capillary is so small that red blood cells can only pass through one at a time. About 10 billion capillaries lace all body tissues bringing blood to within reach of every cell. Capillary walls are highly permeable and while they will not, in normal circumstances, allow the passage of blood itself, they readily allow the transfer of oxygen, nutrients, hormones, carbon dioxide, and waste products between the cell and the blood flowing through the capillary. After the exchange with the cell has taken place the capillaries become part of the venous system with the blood flowing through venules and veins before returning to the right atrium.

In order to achieve the required permeability, the walls of the capillaries are, of necessity, very thin. As a matter of fact, they consist of just one layer of epithelial (lining) cells held in place by a "skeleton" of cross-linked collagen fibers embedded in a matrix of laminin which "glues" the lining cells to the collagen "net". The collagen/laminin structure supporting the single layer of epithelial cells is also known as the basement membrane and is a component of all blood vessels whether large or small.[10,11]

Research involving snake venom and matrix metalloproteinases has clearly shown that hemorrhage (blood seeping out of blood vessels) is caused by destruction of the collagen fibers forming the backbone of the basement membranes.[12] In other words, for red blood cells to be able to get through the collagen "net" it must first be broken. Although I am not aware of any specific research concerning the mechanism by which warfarin causes hemorrhage, it would have to do so by degrading the collagen network and perhaps the laminin matrix as well. Thus, an obvious way of preventing warfarin-induced bleeding would be to

strengthen the basement membrane and ensure that the raw materials for repairing it are readily at hand.

Prevention of hemorrhage

Perhaps the most "famous" disease involving internal bleeding is scurvy. Scurvy is now known to be caused by a vitamin C deficiency, but before this was understood scurvy epidemics devastated the ancient populations in Egypt, Greece and Rome, and until the 18th Century caused numerous deaths in Europe as well. In 1536 when the French explorer Jacques Cartier arrived in Newfoundland native Indians advised him to give his men, who were dying from scurvy, a potion made from spruce tree needles. This potion would have been very high in vitamin C and actually cured most of Cartier's crew. In 1742 British naval commander James Lind described the miraculous effects of citrus juice on sailors suffering from scurvy and by the late 1700s all British navy ships carried citrus fruits (especially limes from which the term "limey" originates) to avoid scurvy outbreaks.

There is now substantial evidence that vitamin C works its bleeding preventing magic by promoting the synthesis and deposition of both collagen and laminin.[13-15] There is also direct evidence that vitamin C helps prevent gastrointestinal bleeding resulting from regular aspirin use. German researchers found that combining aspirin (acetylsalicylic acid) with vitamin C (ascorbic acid) significantly reduces the number of microscopic blood leaks normally observed in the stomach when taking aspirin.[16] Another group of German researchers found that aspirin causes gastric mucosal damage and micro-bleeding both before and after *H. pylori* eradication. Buffering the aspirin with vitamin C resulted in significantly less stomach lining damage and bleeding both before and especially after *H. pylori* eradication.[17]

Thus, it would appear that ensuring an adequate daily intake of vitamin C is an important step in reducing and quickly repairing warfarin-induced breakdown of the basement membrane. Since vitamin C is used up and excreted fairly quickly, taking three or four doses of 500 mg of vitamin C throughout the day is the ideal way to ensure a constant and adequate level in the blood stream. Patients with hemochromatosis (iron overload) should only supplement with vitamin C under the supervision of a competent health care provider and should probably limit their intake to 200 mg three or four times daily.

Collagen is the most abundant protein in the human body so it is clearly important to also ensure an adequate intake of the amino acids (lysine, alanine, and proline) that make up the collagen structure. Cheese, eggs, lima beans, potatoes, milk, meat, and brewer's yeast are good sources of lysine, and meats are good sources of proline, which can also be

synthesized in the liver from other amino acids. Alanine can be obtained from meat, poultry, fish, eggs, avocado, and dairy products. Lysine, proline and alanine are also available as individual supplements.

Mathias Rath MD, a former associate of the late Linus Pauling, has formulated a supplement specifically designed to ensure optimum collagen production and repair.[18] The formula contains vitamin C and other dietary antioxidants and minerals as well as proline and lysine. Dr. Rath reports that it is effective in preventing and reversing atherosclerosis, but I am not aware of any research that has studied its possible effects in preventing warfarin-induced bleeding.

Green tea and grapeseed extract have also been found to inhibit the collagen-destroying action of metalloproteinases, and green tea on its own has been found to significantly reduce the risk of a certain type of hemorrhagic stroke involving bleeding on the surface of the brain (subarachnoid hemorrhage).[19,20]

There is also some, still controversial evidence, that supplementation with the amino acid arginine may enhance collagen synthesis and deposition.[21-23]

It would thus appear that the risk of warfarin-induced bleeding and hemorrhagic stroke can be materially reduced by supplementing with vitamin C and the amino acids proline and lysine. Green tea may also be helpful because of its significant content of vitamin K, but large amounts should not be consumed without appropriate monitoring of INR.[24,25] There is no evidence that vitamin C interferes with the anticoagulation effect of warfarin.[26] As a matter of fact, low blood levels of vitamin C have been associated with a substantially increased risk of both ischemic and hemorrhagic stroke. Finnish researchers have found that men with a plasma vitamin C level below 28.4 micromol/L have twice the risk of experiencing a stroke (hemorrhagic or ischemic) when compared to men with a level above 65 micromol/L. The association was particularly pronounced among hypertensive men where low vitamin C levels were associated with a 2.6 times higher risk and among overweight men where low levels were associated with a 2.7-fold risk increase.[27] Tissue saturation with vitamin C (about 70 micromol/L in plasma) can be achieved by supplementing with 300-500 mg of vitamin C three times daily.

ARTERIAL CALCIFICATION

Arterial calcification is commonly associated with atherosclerosis and involves the deposition of calcium phosphate (hydroxyapatite) on artery walls. Atherosclerosis is a major risk factor for ischemic stroke so it is

indeed ironic that warfarin has been implicated in the formation of arterial calcification. Australian researchers have reported that rats treated with warfarin develop extensive arterial calcification and concluded that, "It is likely that humans on long-term warfarin treatment have extrahepatic vitamin K deficiency and hence are potentially at increased risk of developing arterial calcification."[28] US doctors recently reported the case of an otherwise healthy man who developed extensive calcification of the coronary arteries after long-term warfarin treatment. They conclude, "that physicians prescribing long-term warfarin treatment should consider arterial calcification as one of its potential consequences."[29] Dutch researchers have confirmed that a vitamin K deficiency, such as would be induced by warfarin treatment, increases the risk of arterial calcification and conclude that the current RDA for vitamin K is too low.[30]

Unfortunately, the common advice given by physicians to their warfarin-treated patients is to avoid dark green leafy vegetables (the major dietary source of vitamin K) and to strictly avoid vitamin K-containing supplements – thus guaranteeing a vitamin K deficiency.

Fortunately, this advice may be about to become obsolete. British researchers recently reported that minimizing vitamin K intake while on warfarin might be precisely the wrong thing to do. Their study involved 26 patients (stable) whose INR had remained within the therapeutic range for at least 6 months without a change in warfarin dosage. The daily vitamin K intake of these patients was compared to that of 26 patients (unstable) whose INR had been varying considerably (standard deviation of INR values greater than 0.5) over a 6-month period and thus requiring continuous adjustment of warfarin dosage. All participants carefully weighed their food intake for two 7-day periods and completed detailed food diaries. Analysis of the data showed that the unstable patients had a significantly lower average daily intake of vitamin K (K_1) than did stable patients (29 versus 76 micrograms/day). As a matter of fact, the daily vitamin K intake of the unstable patients was significantly lower than the daily intake of 60-80 micrograms estimated for the general UK population. The researchers conclude that INR levels can be stabilized by increasing daily vitamin K intake. They point out that even a daily increase in vitamin K intake of 100 micrograms has comparatively little effect on INR (reduction of about 0.2). While it would be theoretically possible to improve the consistency of daily vitamin K intake through a strictly controlled diet, it is unlikely that this would be a viable solution. The researchers conclude their report with the statement, "Daily supplementation with vitamin K could be an alternative method in stabilizing anticoagulation control, lessening the impact of variable dietary vitamin K intake. We are currently evaluating this possibility."[31]

Johannes Oldenburg, a German medical researcher, concurs and suggests that a continuous low-dose intake of vitamin K may stabilize the INR and subsequently reduce risk of bleeding complications.[32]

Natural vitamin K comes in two forms – phylloquinone (vitamin K1) and menaquinone (vitamin K2). Phylloquinone is found in dark green vegetables like spinach, broccoli and kale. Green, but not black tea is also a rich source of phylloquinone. Menaquinone is found in meats, butter, cheese and fermented foods (especially natto) and can also be produced by conversion of vitamin K1 in the intestinal tract. This conversion, however, is compromised after a course of antibiotics. The RDA for total vitamin K intake is 90 micrograms/day for women and 120 micrograms/day for men, and is essentially the amount required for the synthesis of coagulation factors in the liver. The RDA does not consider that vitamin K (especially K2) is also required outside of the liver (extrahepatic), particularly to ensure healthy bones and blood vessels.[30]

The main role of vitamin K is to act as a cofactor for the conversion of glutamate into gamma-carboxyglutamate. Matrix Gla protein (MGP) is derived from gamma-carboxyglutamic acid residues and is a powerful inhibitor of arterial calcification.[30,31] There is evidence that oxidative stress and warfarin inhibit the synthesis of MGP.[33]

Dutch researchers have observed that vitamin K1 tends to accumulate in the liver where it is used in the synthesis of coagulation factors, whereas K2 preferentially accumulates in the artery walls where it participates in the production of MGP which, in turn, inhibits arterial calcification. Unfortunately, warfarin inhibits the intestinal conversion of K1 to K2, thus explaining why warfarin promotes arterial calcification. The researchers also observed that menaquinone, but not phylloquinone supplementation prevented warfarin-induced arterial calcification in rats.[31]

Another group of researchers from Maastricht University in the Netherlands has reported that a high intake of menaquinone (vitamin K2), but not phylloquinone (vitamin K1) is associated with a significantly reduced risk of arterial (aortic) calcification and coronary heart disease (CHD). The epidemiological study included 4800 participants in the Rotterdam Study. The researchers found that the average daily intake of vitamin K1 was 250 micrograms, while that of vitamin K2 was only about 29 micrograms. Study participants with a vitamin K2 intake of more than 32.7 micrograms/day had a 41% reduced risk of CHD, a 57% reduced risk of dying from CHD, and a 26% reduction in overall mortality when compared to those with an intake below 21.6 micrograms/day. Participants with a high menaquinone intake also had a 52% reduced risk of severe arterial calcification. Phylloquinone intake was not associated

with decreased risk of CHD, CHD mortality, overall mortality or arterial calcification.[35]

University of Wisconsin researchers have found that, while warfarin is highly effective in blocking the recycling of vitamin K1, it has little effect on the activity of vitamin K2.[36]

Considering the above findings it is tempting to conclude that daily supplementation with menaquinone (vitamin K2) would be highly beneficial in reducing arterial calcification (whether warfarin-induced or not), CHD, and overall mortality without impacting on warfarin's role in reducing the level of coagulation factors. In other words, supplementing with moderate amounts of vitamin K2 should not affect INR levels. Clinical trials, of course, should and hopefully will be carried out to substantiate or negate this hypothesis.

Vitamin D may also play a role in the prevention of arterial calcification. Researchers at the UCLA School of Medicine have reported that the degree of vascular calcification observed in a group of patients at moderate risk for CHD was inversely proportional to the blood level of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D. They suggest that this form of vitamin D may play a role in inhibiting vascular calcification.[37] Dutch researchers support this observation with their finding that supplementation with vitamin D and vitamin K1 has a beneficial effect on the elastic properties of the arterial vessel wall.[38]

Other researchers have, however, found that very large (20 million IU/day or more) doses of vitamin D may actually induce arterial calcification (at least in rats).[39,40] Thus, it may be best to avoid supplementing with more than the dose known to be free of adverse events (2000 IU/day).

A magnesium deficiency, especially if combined with a high exposure to trans-fatty acids, has been found to increase the risk of arterial calcification in cell culture experiments [41] and supplementation with a combination of magnesium and potassium citrate has been found to reduce arterial calcification in rats.[42]

It would thus appear that supplementation with vitamin K, vitamin D and magnesium and potassium citrate can materially reduce the risk of warfarin-induced arterial calcification. It is, of course, necessary to monitor INR very closely if embarking on vitamin K2 prophylactic therapy and it would also appear wise to limit daily vitamin D intake to 2000 IU or less. The most effective form of vitamin K for prevention of arterial calcification is menaquinone (vitamin K2). However, in view of the finding that supplementing with vitamin K (vitamin K1) may help stabilize INR

levels, it may be advisable for warfarin-treated patients to use a 50:50 mixture.

OSTEOPOROSIS

Osteoporosis is characterized by a decrease in bone mass and density, causing bones to become fragile and increasing the risk of fractures. In the United States 26% of women 65 years or older, and more than 50% of women 85 years or older have osteoporosis. Over 1.5 million fractures, requiring about 500,000 hospitalizations and costing the health care system about 12 billion dollars, occur every year as a result of osteoporosis.[43] Men are not immune to osteoporosis, but the incidence is significantly lower than among women.[44]

Vitamin K is a crucial element in the process of bone formation, so it is relevant to ask the question, "Is long-term use of warfarin associated with an increased risk of osteoporotic fractures?" A team of researchers from Washington University School of Medicine and the NYU Medical Center recently investigated the association between osteoporotic fractures and warfarin usage in over 14,000 Medicare beneficiaries who were hospitalized with atrial fibrillation. Most of the study participants (70%) had hypertension, 48% had heart failure, and 35% had a history of stroke. A total of 1005 of the study participants (6.9%) experienced an osteoporotic fracture during the 3-year study period. The researchers found that men who had been taking warfarin for a year or more had a 63% higher relative risk of experiencing an osteoporotic fracture when compared to men not taking warfarin. Hip fractures were most common (65% of all fractures) and were associated with a 30-day mortality of 39%. Men using warfarin for less than a year did not have an increased risk of osteoporotic fractures. Osteoporosis risk was not increased in women irrespective of duration of warfarin usage.

The researchers point out that patients taking warfarin are often advised to limit their intake of vitamin K rich green vegetables. They believe this may be poor advice and that ensuring an adequate intake of vitamin K-1 (found especially in green vegetables) and vitamin K-2 (present in fermented dairy and soy products, fish, meat, liver and eggs) would be more appropriate. They also caution that avoiding green vegetables may lead to a folic acid deficiency and subsequent high levels of homocysteine, a known promoter of atherosclerosis.[45]

Although this study did not find an increased risk of osteoporosis among female warfarin users, it is possible that an association still exists, but is masked by other, more important, risk factors such as loss of estrogen production after menopause. This hypothesis is supported by the recent

finding by Australian researchers that children on long-term warfarin therapy also experience a marked reduction in bone density.[46]
To better understand the role of vitamin K in osteoporosis and to suggest ways of preventing it, it is necessary to first gain a broad understanding of the process of bone formation.

Bone formation
Bones consist of a matrix of hydroxyapatite (calcium phosphate) and other minerals embedded in a cross-linked collagen matrix. The formation and maintenance of the bone structure is an ongoing, dynamic process. Up until the age of about 30 years the process involves mainly bone formation, but after this bone formation and bone resorption develop a delicate balance, which if bone resorption becomes dominant can lead to osteopenia (a forerunner of osteoporosis) and osteoporosis. There are two main types of cells involved in the process – osteoblasts which promote the formation of new bone structure by increasing calcium content, and osteoclasts which promote the resorption (demineralization of old bone) by releasing calcium into the blood circulation. Bone formation and resorption are also known as bone remodelling and take place continuously in the entire skeleton. The concentration of calcium in the blood is maintained within very narrow limits using the bone structure as a reservoir. The hormone calcitonin promotes the transfer of calcium into the bones, while parathyroid hormone (PTH) promotes the release of calcium from the bones.

Vitamin D is important in controlling PTH level with a deficiency leading to higher PTH concentration and subsequent demineralization. There is some evidence that an estrogen deficiency makes the osteoclasts more sensitive to PTH. Vitamin K is important in the synthesis of the gamma-carboxylated protein, osteocalcin. A deficiency of osteocalcin is associated with impaired bone formation (remineralization). Calcium, magnesium, boron, and zinc are all important constituents of the bone matrix with calcium being needed in by far the greatest amounts.

The main effect of warfarin as far as osteoporosis is concerned is that its long-term use leads to impaired remineralization due to its interference with the vitamin K-dependent synthesis of osteocalcin. Thus, the main players in the "osteoporosis drama" are calcium, vitamin D, vitamin K, magnesium, boron, and zinc. Maintaining appropriate levels of these components can go a long way in preventing osteoporosis in both men and women whether on warfarin or not.

Prevention of osteoporosis
Due to the devastating nature of osteoporosis and its enormous cost to the health care system, a great deal of research has gone into finding ways of preventing it. The standard medical approach to osteoporosis

prevention and treatment involves the life-long use of bisphosphonates such as etidronate (Didronel), alendronate (Fosamax), and raloxifene (Evista) interspersed with calcium and vitamin D supplementation. These drugs work primarily by decreasing bone resorption, in orders words, they result in "old bones". Bisphosphonate therapy is usually effective, but carries the risk of significant side effects, among them necrosis (rotting) of the jaw bone.[47] Merck & Co., the manufacturer of Fosamax is currently facing several class action suits launched by Fosamax users who developed severe necrosis after undergoing dental work.[48]

Fortunately, it is eminently possible to achieve effective and safe osteoporosis prevention through exercise, proper food choices, and supplementation with natural products.

Exercise

There is little doubt that physical inactivity leads to loss of bone mass – even in highly fit astronauts. There is also evidence that a structured program of load-bearing exercise such as regular walking can help prevent osteopenia and its progression to osteoporosis, especially if accompanied by supplementation with calcium and vitamin D.[49,50] Just recently Dr. Rittweger of the Institute for Biophysical and Clinical Research into Human Movement in the UK suggested that high strain rate exercises (weightlifting), while being beneficial in the prevention of osteopenia, may actually increase the risk of fractures in full-blown osteoporosis.[51] So, while high strain rate exercises may be appropriate for younger people, a more moderate program such as regular walking may be better suited to older people. In any case, the program to be effective needs to be accompanied by a proper diet, judicious supplementation, and avoidance of coffee, alcohol, smoking, and soft drinks (colas) which have all been proven to increase the risk of osteoporosis.[52]

Vitamin D

Several studies have shown that vitamin D deficiency is widespread. Researchers at Boston University School of Medicine found that 52% of postmenopausal women with osteoporosis had abnormally low vitamin D (25-hydroxyvitamin D) levels and commensurate high levels of PTH.[53] Vitamin D deficiency was more prevalent in women whose daily intake of dietary vitamin D was less than 400 IU. Swiss researchers recently reported that 64% of postmenopausal women with osteoporosis had a vitamin D deficiency and elevated PTH.[54]

The connection between vitamin D deficiency and osteoporosis was first reported by Meryl LeBoff and colleagues at Brigham and Women's Hospital in Boston. Their 1999 study found that 50% of women admitted with acute osteoporosis-related hip fracture were vitamin D deficient.

They suggested that supplementation with vitamin D and accompanying suppression of PTH may reduce future fracture risk and help the healing of existing fractures. They concluded that vitamin D deficiency among the elderly is entirely preventable and recommended supplementation with calcium and 800 IU/day of vitamin D.[55]

Australian researchers have observed that vitamin D deficiency is also a major cause of osteoporosis and hip fractures among men. Their study involved 41 men (60 years and older) who were admitted with hip fractures. Known risk factors for osteoporosis and hip fracture were determined and compared to those of two control groups – one a group of 41 inpatients, the other a group of 41 outpatients all without hip fractures and aged 60 years or older. The researchers found that men in the hip fracture group had significantly lower blood levels of vitamin D (25-hydroxyvitamin D) than did men in the control group. Sixty-three per cent of the men in the hip fracture group had a subclinical vitamin D deficiency (<50 nmol/L serum 25- hydroxyvitamin D) as compared to only 25 per cent in the control group. The researchers also noted that men with hip fractures and hospital in-patients had lower levels of calcium and testosterone than did the out-patient controls. About 89 per cent of the men with hip fractures and the in-patients were diagnosed with hypogonadism (low testosterone levels). The researchers conclude that a vitamin D deficiency is a major cause of hip fractures in elderly men.[56]

It is clear that vitamin D deficiency, irrespective of calcium status, is critical risk factor for osteoporosis and associated bone fractures. Thus, it is fortunate that several clinical trials have concluded that vitamin D supplementation is effective in fracture prevention. Researchers at Harvard School of Public Health, after evaluating 14 reliable studies of oral vitamin D supplementation, concluded that daily supplementation with 700-800 IU of vitamin D reduced hip fracture risk by 26% and overall non-vertebral fracture rate by 23%. No benefit was observed with a daily dose of 400 IU (current RDA for women under the age of 70 years).[57]

A group of researchers at Harvard Medical School studied over 72,000 postmenopausal nurses for 18 years and found that those whose daily vitamin D intake exceeded 500 IU had a 37% lower risk of hip fracture than did women whose intake was less than 140 IU/day. They found no benefit of a high daily intake of milk or calcium on its own. The researchers point out that about 60% of the women in the survey had vitamin D intakes below those recommended by the Food and Nutrition Board (400 IU for women between the ages of 51 and 70 years and 600 IU for women older than 70 years). They also point out that the amount of vitamin-D produced by exposure to sunlight decreases significantly with age (due to thinning of the skin) and the use of sunscreens. They further suggest that the reason why milk showed no significant protective effect

may be due to its content of vitamin A which recently has come under scrutiny in regard to its possible role as a negative factor in bone health. The researchers conclude that women should ensure an adequate daily intake of vitamin D either through the use of supplements or through increased consumption of fish such as salmon or sardines.[58]

The importance of daily supplementation with vitamin D is becoming increasingly clear. A team of American and Swiss researchers recently concluded that a daily intake of at least 1000 IU is required in order to achieve reasonable protection against the risk of osteoporosis, fractures, falls, and colon cancer. They suggest that an increase in the current RDA is warranted.[59] Dr. Reinhold Vieth and colleagues of the University of Toronto go even further. They found that 62% of supposedly healthy Canadians were deficient in vitamin D and that a daily intake of 4000 IU (100 micrograms/day) was needed to bring their level of 25(OH)D, the active metabolite of vitamin D, to the desirable level of 75 nmol/L. The researchers conclude that 4000 IU/day of vitamin D3 is a safe and desirable intake, but very specifically caution that their findings regarding vitamin D3 (cholecalciferol) cannot be applied to the synthetic version of vitamin D2 (ergocalciferol), the form most often used in North America. Vitamin D2 is far more toxic than vitamin D3 and produces unique metabolites not generated by D3. The researchers are very "down" on vitamin D2 and say, "It is an anachronism to regard vitamin D2 as a vitamin."[60]

Vitamin D and calcium

An adequate intake of calcium is clearly essential in achieving and maintaining sufficient bone mass due to the simple fact that calcium, in the form of hydroxyapatite, constitutes the major part of the bone structure. In combination with vitamin D it is effective in preventing bone loss and fractures. Ten years ago French researchers discovered that daily supplementation with 1200 mg of calcium and 800 IU of vitamin D3 (cholecalciferol) for 3 years reduced the number of hip fractures in a group of 3270 elderly women by 23%. The researches also noted that the bone density in calcium/vitamin D supplemented women increased by 2.7% over an 18-month period, while it decreased by 4.6% in the placebo group.[61] Since 1996 several other studies have verified the benefits of supplementation with calcium and vitamin D. In 1998 researchers at Johns Hopkins Medical School concluded that, "Optimal intakes of both calcium and vitamin D are relatively cost-effective, safe, and easily implemented approaches to maintain existing bone mass and assist in the prevention of fractures."[62]

Dutch researchers report that 1000-1200 mg/day of calcium (elemental) plus 800 IU/day of vitamin D is effective in the prevention and treatment of osteoporosis.[63] German researchers, after evaluating several

randomized, prospective, placebo-controlled clinical trials, conclude that supplementation with 800-1500 mg/day of calcium plus 400-1200 IU/day of vitamin D reduces the risk of falls and fall-related fractures in the elderly.[64] Indeed, the evidence that supplementation with calcium and vitamin D is beneficial in preventing and treating osteoporosis is incontrovertible.

It is, however, becoming increasing clear that a supposedly adequate calcium intake does not guarantee the absence of osteoporosis. The calcium must not only be ingested, it must also be absorbed and its excretion minimized. In other words, it is not the calcium intake per se that is important, but rather how much of it is actually retained in the body. Researchers at the University of Pittsburgh have found that the intake of fat and fiber significantly influences calcium absorption. Their study involved 142 healthy pre-menopausal white women who had enrolled in the Women's Healthy Lifestyle Project in 1995-96. The women had blood samples drawn three hours after consuming apple juice containing labeled (isotope) calcium. The blood samples were analyzed for calcium, 1,25 dihydroxyvitamin D (the active from of vitamin D), and PTH. The researchers found that about 35% (17-58%) of the labeled calcium had been absorbed. It was clear that women with a higher fat intake and a lower intake of fiber absorbed significantly more calcium than did women with less fat and more fiber in their diet. Women with high blood levels of vitamin D also showed increased absorption while women who consumed alcohol had decreased absorption. There is also some indication that a higher total calcium intake is associated with a lower rate of absorption. The researchers caution that it may only be certain types of fiber (eg. wheat bran) that inhibit calcium absorption. Fiber found in green leafy vegetables such as kale, broccoli, and bok choy may not be detrimental to absorption. They found no indication that genetic differences among the women were in any way related to calcium absorption. The researchers express the hope that their findings will encourage a second look at the current standard recommendation to emphasize a low-fat, high-fiber diet.[65]

The rate of excretion of calcium is also an important factor in determining its effectiveness in osteoporosis prevention. Dr. Christopher Nordin of Australia's Institute of Medical and Veterinary Science points out that is not the total calcium intake which determines bone strength (density), but rather the difference between what is taken in and what is excreted. Research has shown that for each gram of animal protein consumed one milligram of calcium is lost in the urine. This means that a 40-gram reduction in animal protein intake reduces the urinary calcium loss by 40 mg which, in turn, corresponds to a reduction in calcium requirements of 200 mg (assuming an absorption of 20%). A reduction in sodium (salt) intake of 2.3 grams also reduces urinary calcium loss by 40 mg lowering

requirements by another 200 mg. So a person with a low intake of protein and salt might have half the calcium requirements of a person eating a typical North American diet. This and the fact that developing countries generally get more sunshine (vitamin D) than developed countries go a long way towards explaining the difference in the incidence of osteoporosis and bone fractures between different cultures and individuals. Dr. Nordin concludes that there is no single, universal calcium requirement, only a requirement linked to the intake of other nutrients especially animal protein and sodium.[66]

Dairy products like milk, cheese and yogurt are the richest sources of calcium followed by collards, spinach, beans, sardines and canned salmon. There is some indication that milk may not be an optimum source of calcium for older people. Researchers at the Boston University School of Medicine have studied the effectiveness of various sources of supplemental calcium in preventing bone loss in older women. Their study involved 60 postmenopausal women aged 65 years or older who did not suffer from osteoporosis and whose daily calcium intake from their regular diet was less than 800 mg/day. The women were randomly assigned to three groups. Group 1 supplemented with four 8-ounce glasses of vitamin D-fortified milk per day, group 2 took a 500 mg calcium carbonate supplement twice a day with meals, and group 3 took a placebo twice a day with meals. Bone density measurements of the spine (L2-L4) and thighbone (greater trochanter[GT]) were done at six-month intervals for a two-year period. After two years women in the placebo group (average daily calcium intake was 683 mg) had lost an average of 3% of their baseline bone mineral density in the trochanter area. This loss occurred exclusively during the winter months. Women in the milk group had an average daily calcium intake of 1028 mg and lost 1.5% of their bone density in the GT area. Women who supplemented with calcium carbonate tablets increased their daily intake to 1633 mg and suffered no bone loss in the GT area. The women in the supplement group also increased the bone density in their spine and femoral neck area by about 3%, while the placebo group women lost about 0.3%, and the milk group about 1.8%. The researchers conclude that 1000 mg/day of supplemental calcium is required in order to prevent bone loss in older women living in northern latitudes. They also point out that an adequate vitamin D intake (600-700 IU/day) is essential in order to prevent bone loss during the winter.[67]

Other researchers, however, have found that calcium is equally well absorbed from skim milk, calcium-fortified orange juice, and calcium carbonate tablets.[68] The most commonly used calcium supplements are calcium carbonate and calcium citrate. A comprehensive study comparing the bioavailability of calcium carbonate and calcium citrate found that calcium citrate was consistently better absorbed whether

taken on an empty stomach or with a meal.[69] Other research has shown that calcium carbonate is extremely poorly absorbed by people with low stomach acid even if taken with meals.[52] Inasmuch as low stomach acid (achlorhydria) is a common condition among older people, calcium citrate, calcium malate or calcium fumarate are all much better choices than calcium carbonate. Natural oyster shell calcium, dolomite, and bone-meal products should be avoided due to the potential for lead contamination and poor absorbability.[52]

As an added bonus, supplementation with vitamin D and calcium has also been found to reduce systolic blood pressure by about 10%.[70] Calcium citrate supplementation is also effective in reducing LDL cholesterol (the "bad" kind) and increase HDL cholesterol (the "good" kind").[71] LAF Survey 3 observed that some vagal afibbers who supplemented with calcium experienced longer episodes than average.[72] Thus, vagal afibbers may have to experiment with calcium sources and dosages to find a protocol that works for them.

Calcium

The evidence that calcium supplementation on its own (without vitamin D) increases bone mass and helps prevent osteoporosis is somewhat sparser and more controversial. A 1998 study at the Boston University School of Medicine concluded that 2 x 500 mg of calcium carbonate taken with meals for two years improved bone density in the spine and femoral neck area by about 3%.[67] However, researchers at the Harvard Medical School found no benefit of calcium supplementation on its own.[52] It is quite likely that vitamin D status could explain the differences and also quite conceivable that an adequate vitamin D intake is actually more important than an increased calcium intake. However, as far as I know, no clinical trials have addressed this question.

In any case, there would seem to be little advantage in consuming more than the RDA (1200 mg/day) of calcium and a great advantage in ensuring that this intake is accompanied by a vitamin D3 intake of at least 1000 IU/day.

Magnesium

Magnesium is a hugely important mineral, especially for afibbers. Its many vital functions have been discussed in detail in Conference Room Sessions 14 and 14A and will not be repeated here.[73,74] Suffice it to say that calcium and magnesium are intimately linked and that a high calcium to magnesium ratio can be detrimental and lead to hypertension and other conditions involving the cardiovascular system.[75]

Legumes, tofu, seeds, nuts, whole grains, and green leafy vegetables are good sources of magnesium. Magnesium glycinate (chelated magnesium)

is the most bioavailable and best tolerated supplement. Magnesium citrate is also highly available, but may cause loose stools. The common form of magnesium used in supplements, magnesium oxide, is essentially useless in that only about 4% of the ingested amount is actually absorbed.[76]

About half of the body's magnesium stores can be found in bones, so it is clearly a very important mineral as far as osteoporosis prevention is concerned. Magnesium deficiency is, unfortunately, very common. A recent study found that 74% of a cohort of 2000 elderly men and women did not consume the recommended 400 mg/day. This same study also concluded that a high magnesium intake is associated with a significantly higher bone density in older white men and women. Every 100 mg/day extra intake of magnesium was found to correspond to a 2% increase in whole-body bone mass. This compares to an approximate 2% increase per 400-mg/day increase in calcium consumption. It is thought that magnesium may act as a buffer for the acid produced by the typical Western diet and may also replace calcium in the hydroxyapatite part of bone, thus resulting in a stronger structure.[77] There is also evidence that magnesium suppresses bone resorption (demineralization) at least in younger people.[78]

Other minerals

A high salt diet has been found to significantly increase urinary calcium excretion and bone loss. Supplementing with 90 mmol/day of ***potassium*** citrate (3500 mg of elemental potassium) will prevent this detrimental effect.[79]

Boron is also a very important mineral in osteoporosis prevention. Researchers at the U.S. Department of Agriculture found that women who supplemented with 3 mg of boron daily reduced the amount of calcium excreted in their urine by 44%. The conclusion of the study was that boron improves the metabolism of calcium and magnesium.[80]

A low dietary intake of ***zinc*** and accompanying low blood levels has been associated with an increased risk of osteoporosis in women. Researchers at the University of California have found that an adequate zinc intake is equally important for men. Their study involved 396 men aged between 45 and 92 years who had their bone mineral density (BMD) measured at baseline (in 1988-1992) and 4 years later. Plasma zinc level correlated well with the total intake from diet and supplements. The average daily intake was 11.2 mg and the mean plasma zinc concentration was 12.7 micromol/L. The researchers observed that men with a low zinc intake and plasma concentration were significantly more likely to have osteoporosis of the hip and spine.[81]

Vitamin K

Vitamin K is essential in the synthesis of osteocalcin, the hormone that promotes bone formation. Several epidemiological studies have concluded that a vitamin K deficiency (such as would be induced by warfarin therapy) causes reductions in bone mineral density and increases the risk of fractures. Other studies have shown that the concurrent use of menaquinone (vitamin K2) and vitamin D substantially reduces bone loss. There is evidence that the average dietary intake of vitamin K is insufficient to ensure optimum osteocalcin production and that the RDA should be increased.[82] Supplementation with vitamin K (preferably K2) would, thus, be important for afibbers on warfarin.

Conclusion

Osteoporosis is widespread and of particular concern for afibbers on warfarin. It is clear that moderate exercise combined with an appropriate intake of vitamin D, calcium, magnesium, boron, zinc, and vitamin K can substantially reduce the risk of bone loss and fractures.

SKIN NECROSIS

Warfarin-induced skin necrosis is a rare, but serious disorder which primarily affects middle-aged, obese women. The disorder has a prevalence of less than 0.1%. Skin necrosis usually appears in breast, buttocks or thighs of women and on the penis of men. If it is going to occur it would usually do so within the first 3 to 6 days after starting warfarin therapy. It is thought to be associated with a sharp drop in protein C and factor VII experienced in some patients following initiation of therapy. The disorder manifests itself by large bleeding skin eruptions and may require extensive surgery and even amputation. The risk of skin necrosis can be reduced by avoiding large initial doses of warfarin and by increasing dosages slowly. In some cases, it is possible to reverse the condition with rapid intervention with vitamin K infusions. Skin necrosis is a serious condition and its symptoms and the symptom of its close cousin, “purple toes” should not be ignored.[83]

EYE DAMAGE

Massive bleeding in the eye in patients with age-related macular degeneration (AMD) is a devastating event. Dutch researchers have found that warfarin treatment increases the risk of serious bleeding in AMD patients and recommend that warfarin therapy for such patients only be prescribed when absolutely essential.[84]

WARFARIN INTERACTIONS

The efficacy and safety of warfarin therapy depends on maintaining a reasonably constant INR (International Normalized Ratio) between 2.0

and 3.0. An INR below 2.0 is less effective in preventing ischemic stroke and at an INR of 3.0 or higher the risk of a hemorrhagic stroke outweighs the risk of an ischemic stroke.[2] Numerous drugs, herbs, and foods affect the action of warfarin by either increasing or decreasing its anticoagulation effect. It is clearly important to be aware of these interactions so as to avoid large swings in INR and the accompanying risks of over- or under-coagulation. Warfarin interacts with at least 90 common drugs and several herbs. A list of the most significant interactions is given below.

Interactions that **potentiate** warfarin's effect

Highly probable

Drugs	Foods & Herbs
Acetaminophen (Tylenol)	Boldo/fenugreek mixture
Ciprofloxacin	Fish oil
Citalopram	Mango
Diltiazem	Quilinggao
Entacapone	
Fenofibrate	
Miconazole	
Sertraline	
Voriconazole	
Zileuton	

Probable

Amoxicillin	Danshen
NSAIDs	Dong quai
COX-2 inhibitors	Grapefruit juice
Fluorouracil	
Fluvastatin	
Fluvoxamine	
Gemcitabine	

Interactions that **inhibit** warfarin's effect

Highly probable

Cholestyramine	
Mercaptopurine	
Mesalamine	
Ribavirin	
Trazodone	

Probable

Azathioprine	Ginseng
Bosentan	
Dicloxacillin	
Ritonavir	

There are no credible studies supporting an interaction between warfarin and the following drugs and food – alcohol, antacids, atenolol, clopidogrel, fluoxetine (Prozac), metoprolol, naproxen, psyllium, ranitidine, vitamin E, atorvastatin (Lipitor), coenzyme Q10, ginkgo biloba, ibuprofen, and influenza vaccine.[85] However, it is a good idea to maintain a reasonably steady intake of coenzyme Q10 and vitamin E since the literature supporting a lack of interactions is not entirely consistent.

The Canadian researchers who compiled the listing point out that there are now so many potential interactions between warfarin and other drugs that it would be impossible for a physician or pharmacist to remember them all. They recommend that doctors prescribing other drugs to patients on warfarin keep in mind that many drugs in the following groups can increase or inhibit the effect of warfarin:[85]

- Antibiotics and antifungal agents
- Cardiovascular drugs (including propafenone, amiodarone, and cholesterol-reducing drugs)
- Painkillers
- Anti-inflammatories
- Central nervous system drugs (citalopram, sertraline)
- Gastrointestinal drugs (cimetidine, omeprazole)
- Anabolic steroids

A team of researchers from Germany, Sweden and Switzerland studied 4152 afib patients who were on warfarin therapy for non-valvular atrial fibrillation. During follow-up (for an average of 11 months) 133 patients died from internal bleeding and another 432 were hospitalized with serious bleeding. This corresponds to a warfarin-associated mortality rate of 3.5% a year and a serious bleeding rate of 12% a year. The researchers observed that 58% of all patients on warfarin had also been prescribed one or more of 88 specific drugs that are known to interact with warfarin. They also found that patients who were taking potentially interacting drugs experienced a 3.4-fold increased risk of serious bleeding. The use of a combination of warfarin and aspirin (75-325 mg/day) was associated with a 4.5-fold risk increase, while the concomitant use of acetaminophen (Tylenol, Paracetamol) was associated with a 3.8-fold increased risk at doses between 885-2900 mg/day taken for at least 4 weeks. Other particularly detrimental drugs were allopurinol (Zyloprim), amiodarone (Cordarone), levothyroxine (Synthroid), Metronidazole, Miconazole, and omeprazole (Prilosec). Taking Metronidazole or Miconazole during warfarin therapy was associated with a 40-fold increase in the risk of a serious bleeding event.

The researchers conclude that drug interactions are an independent risk factor for serious bleeding in patients on long-term warfarin therapy. They

also point out that the practice of prescribing potentially interacting drugs is widespread.[86]

INR CONTROL

An obvious way of improving the safety and efficacy of warfarin therapy is to control the INR within close limits. Doing this, by going to a clinic or medical laboratory weekly or more frequently, is clearly inconvenient, time-consuming and expensive. Fortunately, there are now several home testing kits that provide quick and accurate results for INR and prothrombin time. *INRatio* by HemoSense is probably the most reliable and accurate. It must be prescribed by a physician and its cost may be reimbursed by Medicare in the US (http://www.hemosense.com).

SUMMARY

Warfarin (Coumadin) is an effective anticoagulant, but has the potential for serious adverse effects – notably internal bleeding, hemorrhagic stroke, arterial calcification, osteoporosis, and skin necrosis. Fortunately, as detailed in this report, it is possible to greatly reduce the risk of adverse events by judicious supplementation, avoidance of drugs and herbs that interact with warfarin, and maintaining close control of INR through monitoring at home.

The most important supplements for patients on long-term warfarin therapy are:

Supplement	Suggested intake
Vitamin C	500 mg 3-4 times daily with meals
Vitamin D3(1)	1000-2000 IU daily
Vitamin K*(2)	100 micrograms daily
Magnesium (elemental)(3)	100-200 mg 3 times daily
Calcium (elemental)(4)	200 mg 3 times daily
Potassium (elemental)(5)	2-3 grams daily
Boron	3 mg daily
Zinc	15 mg daily
Proline	500 mg daily[18]
Lysine	500 mg daily[18]
Green tea*(6)	4-6 cups daily

* These supplements should only be taken with a doctor's approval and require close INR monitoring.

(1) Please note that many supplements such as multivitamins, calcium, magnesium and vitamin K also contain vitamin D. Total intake from all sources should not exceed 2000 IU/day.
(2) The preferred form of vitamin K is vitamin K2 (menaquinone). However, if the intake of green leafy vegetables is low and INR is fluctuating significantly then a mixture of vitamin K1 (phylloquinone) and vitamin K2 is preferable.
(3) Taurine (3 x 1000 mg/day) may be helpful in ensuring optimum efficacy of magnesium. Magnesium supplementation is not advised in patients with kidney failure.
(4) Total daily calcium intake from diet and supplements should not exceed 1200-1500 mg.
(5) This amount can be obtained from 6-7 daily servings of fruits and vegetables. Supplementation is not advised in patients with kidney failure.
(6) It is likely, but not proven, that a similar benefit can be obtained through supplementing with green tea extract in capsules.

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Special Reports

Cleveland Clinic Foundation Atrial Fibrillation Summit

October 14-15, 2005

Summary Report & Observations

by Jackie Burgess, RDH

The Conference attracted a capacity audience of 500 Electrophysiologists, Cardiologists, Cardiac Surgeons, Internists and AF Nurses from the US, Canada and several other countries. It was my privilege to attend.

A detailed report from my notes on each presentation can be viewed at http://www.afibbers.com/forum/read.php?f=6&i=17509&t=17509#reply_17509 starting with the very first post and working chronologically forward. I encourage readers to do this since it is impossible to condense all the important comments from my 60 pages of notes. The format allowed 20-30 minutes for each speaker. A minor amount of time followed for Q&A. Some topics were presented in debate form with brief summary rebuttals and questions. Some notes are direct quotes. My personal observations are at the end.

To view the entire agenda and presenters while still available online, go to https://www.clevelandclinicmeded.com/summit/atrial/faculty.htm

OPENING REMARKS

Eric Topol, MD,
Chairman of the Dept. of Cardiovascular Medicine - Cleveland Clinic

"Now that it has become clear that ablating or electrically isolating the pulmonary veins may be curative for some patients with atrial fibrillation, the challenge in going forward is how we can validate and extrapolate this for the future. In order to 'beat' atrial fibrillation, some of the key issues that need to be grappled with include:

- Randomized trials large enough and definitive to prove the efficacy of PVI vs. Medical therapy; there is a desperate need and only one study, currently.
- Determine the appropriate endpoints for 'cure' and what is the long-term efficacy of the available treatments? When can we say it's cured?
- What is the relationship between atrial transport, stroke risk and the need for systemic coagulation?
- Does closure of the Left Atrial Appendage (surgically or percutaneously) really reduce the risk of stroke beyond that achieved by arrhythmia termination alone?
- How long after PVI is anticoagulation required? It's really unknown.
- How can the procedure(s) be refined to be much more practical?
- Is total electrical isolation of the PVs necessary?
- What are the biologic mediators – genes, inflammatory proteins, channelopathies and pathways that predispose to atrial fibrillation (and stroke)?
- Can a better understanding of the biology lead to the identification of new targets and personalized management of AF?

With the continuation of the "Graying of America, "we will continue to see AF increase. We estimate that 25 – 30% of the population will have AF if they live long enough and that the projected number of people with afib will be about double to 5.6 million by the year 2050. Of major concern is the stroke risk that accompanies AF.

What's coming in the future or Beyond Radio Frequency Ablation?

There is a need to find chemical freedom from stroke. There is a heated debate about closure and incomplete closure of the LAA and whether incomplete increases risk of stroke. Do certain types of AF respond better to certain therapies? ie, electrophysiology or surgery? Cryo is definitely being looked at as is a new balloon device. The stent is also a consideration for each pulmonary vein where it provides electrical isolation. Interesting work is being explored with the Vagus Nerve as the new AF target. And, the possibility of potent, anti-inflammatory drugs promises potential.

Conclusion: "Beating Afib is the new frontier of Cardiovascular Medicine."

PULMONARY VEIN ANATOMY – WHAT HAVE WE LEARNED?

Francis E. Marchlinski, MD,
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University of Pennsylvania Healthcare System - Philadelphia, PA

Ablations began in the '70's and by the late 90's, EPs came to recognize what cardiac surgeons have always understood – how complex the anatomy is and why it's critical to understand anatomy variations to prevent complications. With the development of appropriate tools, we can prevent complications. Special caution needs to be taken of anatomy either by anatomic mapping (CARTO) or electrical mapping, especially in the relationship of the PVs to the esophagus. It's important to address the risk of collateral damage. We must titrate energy delivery and watch lesion bubble formation to reduce risk of damage to the esophagus.

We know from histology that atrialization occurs in 100% of veins with Afib and 85% without AF; PV atrialization is the rule with or without atrial fibrillation [Atrialization: atrial muscle enters the pulmonary veins (PV) but is not unique to AF]. We know the degree of PV fibrosis affects atrial fibrillation. Is atrialization the result of AF? Anatomy is highly variable and this knowledge is critical.

We know 95% of triggers originate in the pulmonary vein or pulmonary ostium, but as we moved outside the veins and into the antrum and into the adjacent tissue to get away from the stenosis risk, another consideration became important - the collateral damage risk such as to the esophagus. [Antrum: The posterior aspect of the pulmonary veins is thought to blend into the posterior left atrial wall with a funnel shape, referred to as the "antrum" by investigators from the Cleveland Clinic (Ohio).]

Catheter Ablation of Atrial Fibrillation: Pulmonary Veins Antrum Isolation-Demonstration Case

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Dr. Natale gave two separate presentations involving his PVAI techniques. Both involved video walk-throughs with his pointing out significant points on techniques, anatomy, and precautions. Questions from the audience were clarified by visual examples and explanations. Following are just a few of the very important points covered. Others can be viewed at the aforementioned site with my complete notes. He stopped during the

slides to narrate techniques to avoid collateral damage such as a laryngeal nerve palsy, and how to avoid the phrenic nerve with pace/mapping. He showed an image of phrenic and how, by placing an inflated balloon to push the heart away from the phrenic nerve, damage is avoided. Mentioned using cryo when close to the mitral annulus. Cautioned to be mindful of posterior energy exposure to prevent damage to the esophagus.

Intracardiac Echocardiography Guidance system. (ICE) Value and efficacy demonstrated. Invaluable for accuracy, efficacy and safety of the patient, ICE allows for real-time direct visualization of the pulmonary veins, location of the atrial-venal junction and assurance of the catheter tip location within the pulmonary vein antrum and more. It provides a clear visualization of the transseptal puncture which leads to a critical finding regarding safety.

He identified by ICE image the formation of a clot soon after the transseptal puncture. He said the prevalence of clot formation is so common that they now use a heparin flush before and after the puncture to reduce this occurrence. He showed several examples of the catheter tip with a clot dangling from the end or a clot that had dropped off and was just lying in the atrium. And, he showed a gauze 2x2 on which the catheter tip had been wiped and the many clot fragments that had accumulated. Very graphic.

ESOPHAGEAL FISTULA (EF) is an unintentional burn through the atrium into the esophagus, a serious and critical problem with severe and dire consequences; one that can rarely be corrected by surgical means. Considerable time was devoted to showing the proximity of the back wall of the atrium and the esophagus indicating how easy it is to accidentally cause injury because of the extremely thin heart wall and using too much heat. They have had no EFs at the CCF.

THERMAL MONITORING The importance of adding the thermal monitoring device down the esophagus to a location behind the atria was emphasized. This is now standard in their ablation procedures for tissue temperature control to prevent EFs and provide another view of the area since knowing all the anatomical variances and locations helps prevent mistakes.

Tissue temperature monitoring is critical since even though the energy source is stopped, the tissue continues to heat. The importance of starting with a low energy and ramping up along with the observance of microbubbles to indicate maximum tissue heating was discussed in great detail and pointed out in these video clips with the ICE guidance showing the microbubbles like a little puff of smoke on the screen. Right along with

this demonstration was a comparison of what happens with too much heat…formation of holes and craters and irregularly shaped defects in the heart tissue.

A question was asked on how to control microbubbles; the reply was – start low, like 20 – 25 W and titrate slowly. The thought is to minimize excessive use of power to prevent fistula and stroke. He noted that people with lots of scar/fibrosis create more bubbles. On the power issue, he said problems can occur even as low as 10-20 W and added that 50 W is not safe.

PVI vs. PV ANTRUM ISOLATION Antrum is a newer technical term to describe the area of atrium wall farther away from the ostia; he says come out into the antrum and ablates to get away from the stenosis risk. Their ablation procedure ablates the Pulmonary Vein Antrum and the Superior Vena Cava. Between 90 and 95% of all trigger signals or potentials are seen in the area of the PV and the objective of this procedure is "isolation of the antrum."

When flutter occurs after ablation, it was the opinion that ablation scars were either incomplete, not deep enough, or had been so superficial, that nerve conduction recovered.

Regarding paralysis – he commented it was important to pace to be sure the phrenic nerve wasn't captured and paralysis caused. He said they had never seen paralysis, and explained that in some cases (18-20%), they can't completely isolate because of the phrenic nerve location.

The new irrigation catheter is being studied so far with good results. No strokes and it allows increased efficiency (faster).

His final statement included: "We have proven isolation is important."

DEBATE: RATE CONTROL VS. RHYTHM CONTROL: DO WE KNOW THE ANSWER?

Pro:
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Paicenza, Italy

Referencing the AFFIRM study results, his opinion was that a high heart rate is the most important issue. Most patients (77%) are treated for rate. [but he acknowledged that most patients esp. younger, prefer to be treated for rhythm control.] He said it is difficult to treat AF with one strategy because AF is the final result of underlying conditions such as hypertension, hypertrophy, and congestive heart failure. The AFFIRM

patients were not very symptomatic and those who could not be cardioverted were also excluded. Pacemaker has poor affect on fibrillation – rate is similar whether rate or rhythm.
Concluding statement: The majority of AF patients come to the MD to ask for a better QoL (Quality of Life). Give them what they do ask by dropping down the ventricular rate. (by rate control.)

Debate: RATE CONTROL VS RHYTHM CONTROL: DO WE KNOW THE ANSWER?

Con:
J. Marcus Wharton, MD,
Professor of Medicine -Director of Clinical Cardiac Electrophysiology
Medical University of South Carolina - Charleston, SC

Early on, rate control was the only method used for AF. We are better now at rate control than years ago but we have even better methods than pharmacology. The AFFIRM study says to treat the symptoms but how easily is this really achieved? The comment was "Relatively" and we must remember that this study population group was either asymptomatic or mildly symptomatic. Control is even harder in the symptomatic. The study says 34% didn't achieve NSR. AFFIRM says 80% of patients are treated by rate control. We are interested in long term NSR. AFFIRM found increased incidence of stroke in rhythm rather than rate, but this was due to the discontinuation of warfarin. We need to stay on warfarin for an indefinite period of time, even if asymptomatic.

We have to consider the costs of rate control. We still have stroke risk (.1%) and intracranial hemorrhage (.3%) along with the high nuisance of side effects (>50%) and decreased quality of life, which is especially true for younger, more active individuals where the significant side effects do affect activity and quality of life since some side effects for some patients are severe; rate control in ventricular problems is limited

Rate control isn't as bad as everyone says; when it works, it's good; often better than anti-arrhythmics but we need to eliminate the negative aspects of pharmacology. Keep patients in NSR and they feel better. If we can get rid of drugs or improve pharmacological results, patients will function better physically and mentally. Rate vs. Rhythm is a Pharmacological treatment. However, Catheter Ablation is clearly superior to pharmacological treatment and allows freedom from drugs and reduces risks and eliminates the negative aspects of pharmacological treatment.

Conclusion: Our goal should be to maintain NSR. It's important to maintain NSR for survival of patients. The risk of asymptomatic afib is relatively high. Our long-term goal 100 years from now should be to get rid

of the need for warfarin altogether. Let's get rid of anti-arrhythmics altogether. In a retrospective analysis of the AFFIRM study (Pappone's group), there is indication of direct long-term survival benefits with ablation and getting rid of anti-arrhythmic drugs. Our goals should be rather than using anti-arrhythmics to use more advanced technology to maintain NSR.

COMPLICATIONS OF PULMONARY VEIN ISOLATION –
What is the risk and what can we do about it?

Douglas L. Packer, MD
Co-Director Electrophysiology and Arrhythmia Ablation Laboratory
The Mayo Clinic - Rochester, MN

Damage depends on temperature of the catheter tip and tissue temperature. Tissue temperature becomes much higher than the temperature readings and; once the tissue is heated, it continues on heating. This is of special concern in areas such as PV, esophagus and atrial tissue. Don't turn on to a high degree and expect to control tissue damage.

We control this by using Intracardiac Echocardiography guidance (ICE) and watching microbubbles. When see them, turn down the power. The use of this ultrasound is very important and even then, in some cases, we may not see microbubbles and still have stenosis and the temp can be in the area of 80-100˚ which is much too high.

We have incidence of severe stenosis down around 1% at Mayo which is what Dr. Natale at the CCF also confirms; both use ICE guidance.

Even with stenosis, patients can be asymptomatic or in patients who are initially symptomatic, they tend to be less symptomatic in time. Severe stenosis requires a second procedure of dilation or stenting.

Diaphragm – paralysis: Doesn't happen very often. Mostly avoidable. The phrenic nerve poses a problem and is very easy to damage. It only takes 44˚ to fry the phrenic. Depending on the severity of damage, it can resolve in between 6 and 16 months. The pathway of the phrenic is such that it wraps back behind the RSPV orifice making it very difficult to avoid. Time of application is very sensitive. He maps out the phrenic around 10–20 ma and notes where the whole thing is and paces during the whole time in some cases such as a balloon ablation. Perforation or tamponade – national registry to keep track of (use ICE for surveillance)

Stroke in progress– 0.5 to 2.5%. We should worry when we see sheaths dangling anything (like clots). Like Dr. Natale, we watch with ultrasound

and give incremental heparin dosing during the ablation. Is fluoroscopy adequate? Maybe, but it's clear, Mayo's stroke rate is 0.5% using ICE and we think it helps.

Atrial Esophageal Fistula -- unsure how many known occurrences – at least 30; devastating consequences. Esophagus moves substantially during the case so prelim CT scan doesn't mean much. The use of temperature probe provides an additional view and helps define the esophagus (in addition to ICE). Didn't think barium helpful enough to avoid problems. How do you treat esophageal fistula? - - not much experience – very uncertain. Surgical? May be too late even then. Endoscopy could be dangerous.

Conclusion: Be very careful and know where you're heading.

RELATIONSHIP BETWEEN THE LOCATION OF AUTONOMIC GANGLIONATED PLEXUSES AND SITES RECORDING COMPLEX FRACTIONATED ATRIAL ELECTROGRAMS DURING AF

Warren M. Jackman, MD
Professor of Medicine
Univ. of Oklahoma Health Science Center -Cardiac Arrhythmia Research Institute
Oklahoma City, OK

Dr. Packer presented a paper explaining the finding of ablation sites in the right and left atria exhibiting complex fractionated atrial electrograms (CFAE) during AF which suggests there are additional factors important to the success of the ablation procedure besides PV isolation and continuous linear lesions.

One candidate for this factor is the intrinsic cardiac autonomic nervous system. Each of the different ablation procedures apply radio frequency current near the major left atrial clusters of autonomic ganglia or the axons extending between the clusters and the PVs. These clusters are located in the epicardial fat pads and are referred to as ganglionated plexi (GP) by Armour, et al. The possibility that some of the ablation effects may result from destroying GP or their axons is supported by the report by Pappone, et al, identifying a significant increase in short-term ablation success if a vagal response occurred during the RF applications indicating heating of a GP.

Autonomic ganglia are present over much of the epicardial surface of the right and left atria. There may be 7 major clusters of autonomic ganglia (GP) on the atria in humans.

They are testing the ability to localize and ablate GP in patients with AF. This hypothesis is supported by a number of findings.

PULMONARY VEIN ISOLATION IS NOT NECESSARY FOR ABLATION OF ATRIAL FIBRILLATION

Fred Morady, MD
Director, Clinical Electrophysiology Laboratory
University Hospital - University of Michigan - Ann Arbor, MI

The rationale for PV isolation in patients with AF is to eliminate premature depolarizations that trigger AF and to eliminate bursts ('drivers') of tachycardia that contribute to the perpetuation of AF. Circumferential PV isolation was first used by Pappone and although it encircles the pulmonary veins (PV), very often, is not complete isolation and was successful. He showed studies by various EPs with no attempt to isolate PV. Triggers are often still present, so why not AF? They had frequent PACs but no longer had AF. He says not all triggers originate in PV and PVI may not be enough and to check other areas and ablate where necessary. About 28% of triggers occur outside the PV; such as posterior LA wall, Superior Vena Cava, Ligament of Marshall, Coronary Sinus, and acknowledges the success of CCF ablations were because their procedure encompasses many of the extra trigger areas.

His approach is tailored to the patient, not just one particular lesion path but he acknowledges that the PVs play an important role. He said it is important to induce AF or you'll never know where all the drivers are. He said, each case is different and I believe a tailored approach is best.

RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION USING STEREOTAXIS TECHNOLOGY

Gabriele Vicedomini, MD
Department of Cardiology Electrophysiology and Cardiac Pacing Unit
Hospital San Raffaele, Milan, Italy

Dr. Vicedomini emphasized the need for what I would term 'user-friendly equipment' reducing greatly the learning curve and also reducing typical procedure time from 480 minutes to 60 minutes. Remote magnetic navigation for AF is safe and feasible with the shortest learning curve suggesting that AF ablation can be performed even by less experienced operators in low volume centers; ie, Auto Mapping, Auto Navigation to selected points or lines – the computer controls the ablation parameters and end points. Safety benefit: Less pressure on the catheter; "may" have fewer esophageal fistulas, soft contact of catheter tip but very stable, full contact all the time.

"THE ORIGIN OF SURGICAL ABLATION and WHERE WE ARE TODAY"

Ralph J. Damiano, Jr. MD
John M. Shoenberg Professor of Surgery- Chief of Cardiac Surgery
Washington University School of Medicine - St. Louis, MO

[Clarification - many patients who have opted for a surgical ablation procedure also had concomitant surgery, as in mitral valve repair].

Dr. Jim Cox performed the first Maze procedure in 1987. Cox Maze III procedure is what he settled on which involves a myriad of surgical incisions in the right and left atrium. The theory being, this would block signals, but he ended up isolating all PV and the entire back of the LA felt to be responsible for AF back in the 80's which has shown, in time, to be extremely important in preventing AF.

We have learned the Maze III full maze lesion set for whatever reason seems to be effective in restoring sinus rhythm and is particularly effective in preventing stroke. Summary follow up report of the cut-and-sew method and long-term efficacy indicates what they experienced at Washington U (that is - 200 patients with a median follow up for 5 year and some, for 14years which was the lone maze at 14 years,) 92% had freedom from AF. Pretty spectacular results. In concomitant maze procedure (mitral or coronary surgery) 10 years – 97% AF free.

Why not just keep doing this? Only 80% in the lone maze were actually afib free and medication free and I think most patients would not view as complete success unless off medications. Some of the concomitant surgical patients (about 25%) were still on antiarrhythmic drugs.

In the lone maze, there has been only one late stroke in entire group (was in NSR at the time) – pretty remarkable and has been verified by other institutions across the country as well – average follow 5-1/2 years and 200 patients. We now use the Maze IV procedure using ablation devices with two simple incisions, with whole array; bipolar radio frequency is very quick…less than a minute. Still use cryo lesion at the annulus.

What we don't know: No one knows the significance of each individual lesion of the Cox Maze procedure. It appears bi- atrial is more effective than single atrial procedure, but both are more effective than PVI.

One problem in surgeries is we do not know the mechanism of AF in each individual, and that does not allow us to tailor a procedure for each patient as Dr. Morady does and has made tremendous progress with his tailored electrophysiology approach. To get 100% success for lone AF, probably we need to have better understanding of the mechanisms of AF

in order to develop that procedure and this will take development and refinement of clinical diagnostic technology - tremendous progress is being made along that line as you have seen with the pre op mapping. We should continue with limited lesion sets which are working and do a better job of risk stratifying of patient's report atrial diameter, duration of actual AF duration; and carefully state the exact procedure rather than a Maze or Mini-maze – whatever that is. There are lots of types and we need to be careful with reporting results.

In conclusion, looking back on my 20 years experience with atrial fibrillation, it could be said…. "The more you learn about atrial fibrillation, the less you are likely to know." There is a diverse group of patients with a spectrum of complex arrhythmias AF and one procedure probably isn't applicable for all.

Randall K. Wolf, MD
Professor of Surgery, Division of Cardiac Surgery
Section of Cardiothoracic Surgery - University of Cincinnati, Cincinnati, Ohio

He began with a video of a live heart, in an open chest cavity, beating in atrial fibrillation, and commented that many allied health people outside of surgery don't have the opportunity to view the chaotic arrhythmia but cardiac surgeons see it every day. He said it was clear why patients are so symptomatic. [For me, it was sad to view that heart and it brought back vivid memories of how badly I felt so many times and for so long while in afib. It's difficult to imagine that it isn't fatal.]

Dr. Wolf said when they interview patients, they describe all the options including the least invasive – catheter ablation – and says the Cox Maze has the best results. Dr. Wolf has worked with Dr. Jackman and agrees with the approach of partial cardiac denervation and the genesis of afib. By focusing on ganglia plexii, high frequency stimulation of fat pads is routine in every case. They use a standard EP catheter; do transmural lesions in veins and find the ganglia plexii. His mapping is very similar to mapping done by Dr. Jackman's at U of Oklahoma.

He said it is very important to divide the Ligament of Marshal (LoM) and is leery of right-side-only 'minimally invasive' approaches that don't take care of that and the LAA. The only way to do that is be on the left side. They find that signals are often in the LoM. The Left Atrial Appendage (LAA) is always excised.

He believes this procedure will revolutionize the treatment of paroxysmal AF. It has a high cure rate. They try not to do large atriums or patients with 20 years of AF… and they do remove the LAA.

SHOULD SURGERY BE CONSIDERED FOR TREATMENT OF LONE ATRIAL FIBRILLATION?

David J. Callans, MD,
Professor of Medicine -Director, Electrophysiology Laboratory
University of Pennsylvania - School of Medicine - Philadelphia, PA

CONCESSIONS

- Progress in surgical ablation of AF has been impressive and should be encouraged.
- Surgical ablation during concomitant cardiac procedures can treat patients that are probably not well served by catheter ablation.
- Technology available for surgical ablation is more advanced than that for catheter ablation.

However,

- Catheter ablation for patients with early lone AF is safe and effective.
- Lone AF is an electrophysiologic disease and ablation should not be "one size fits all'.
- There are limited data regarding stand-alone surgical ablation (post MAZE III).

PROBLEMS WITH CATHETER ABLATION

- Incidence of stroke – around 1% - need a procedure with no risk of stroke
- His own experience no strokes in last 320 cases with increased ACT
- Pulmonary vein stenosis – about 1.6% - essentially eliminated with ICE guidance
- Atrial-esophageal fistula – about 0.01% -
- EPs lack of uniform approach
- Inconsistent follow up and reporting of complications; no formal registry

PROBLEMS WITH SURGICAL ABLATION

(His comment: patients more ill and have worse AF. Difficult comparison)

- Limited data regarding stand-alone AF ablation
- Post-operative AF about 40% - expect lower with off pump, stand alone.
- Atrial-esophageal fistula – around 1% (unipolar energy)
- Surgical mortality/morbidity
- Lack of uniform approach – technology fest
- Inconsistent use of anti-arrhythmic agents

- Complete avoidance of post-operative monitoring – (Dr. Wolf is starting intensive monitoring and he salutes him for this)
- No registry

WHERE DO WE GO FROM HERE? Adversarial relationships are unproductive; atrial fibrillation is a syndrome; surgical and catheter ablation will both have defined roles in patient treatment; nonpharmacologic therapy has been applied to <1% of the AF population – so there is plenty of work for everyone.. More data is necessary; need to set up registry; analogy to the STS registry surgeons have a registry for coronary disease.

His opinion: Surgical ablation is not appropriate for Lone Atrial Fibrillation. There is a lack of outcome data …there is a significant morbidity including pain in these patients. He says, "I was concerned about all those things going into holes in these patients."

SURGICAL TREATMENT OF ATRIAL FIBRILLATION WITH MITRAL VALVE DISEASE

Marc Gillinov, MD,
Surgical Director - Center for Atrial Fibrillation
Department of Thoracic and Cardiovascular Surgery - The Cleveland Clinic -Cleveland, OH

Mitral valve disease is common and progressively age-related. By ages 60 – 70, about 20-40% already have preexisting AF in addition to the mitral disease. Just because its there isn't a reason to treat but this is: "if mitral regurg is treated and stenosis is treated but the AF is not, then the patient is left with increased risk of stroke and death. The incidence of mitral valve disease with AF increases with age. By age 80, 40% of patients have mitral valve involvement.

Stats show MAZE people live longer than living with AF. With Maze, 99% of patients are free from stroke compared to about 70% with no maze. Most patients throughout the country are not treated for AF when they go in for mitral valve or coronary disease. They leave with untreated AF. We are a bit different here at the Clinic; we attempt to treat both in most patients as most have valve disease. Lone AF is not an indication for surgical treatment but newer treatments such as Dr. Wolf's may change that.

The Maze Procedure is extremely successful, but it is a big deal and patients often choose a less invasive approach. Takes time; lots of suture marks, but is successful and risk of stroke is reduced to about zero, in time. There is some morbidity as with all open-heart surgical procedures.

Summary: AF is a tenacious, erratic disease evolving over a lifetime, and brief post-interventional follows-ups over period of months should be

interpreted cautiously. There are several dozen new technologies in development today which will probably available in 2006. We look to the future of tailoring surgical procedures for individual patients and hope to be able to assess the results and look patients in the eye some day and say…."you are cured of atrial fibrillation."

PATHOGENESIS AND GENETICS OF ATRIAL FIBRILLATION

David Van Wagoner, PhD. – Topic: INFLAMMATORY MECHANISMS OF ATRIAL FIBRILLATION

There are numerous associations between cardiovascular events and a systemic inflammatory state. In the examination of the inflammatory mechanism in AF, a common theme is emerging about the role of inflammation pathways, cellular and tissue response to inflammation and the result is adaptive changes in the heart. Risk factors associated with AF include, aging, hypertension, valvular disease (stretch) CAD, dyslipidemia, diabetes, autonomic imbalance, SVT (high rate electrical activation) and cardiac surgeries, along with elevated C-reactive protein levels indicative of inflammation, cell infiltration and tissue injury. Inflammatory changes in AF lower NO and increase PAI-1 and promote thrombus formation in the LAA, stroke and death. CRP is a marker of inflammation and predicts the extent of scarring and also success of ablation.

The common mechanisms of AF are sympathetic stimulation related to rate and stretch; structural remodeling related to hypertrophy, apoptosis and fibrosis; electrical remodeling and vagal stimulation.

Mina K. Chung, MD, Electrophysiologist - Topic: GENETICS OF ATRIAL FIBRILLATION

Atrial fibrillation is an arrhythmia in which identification of underlying humoral or genetic factors might be beneficial. Genetic, biochemical or hormonal factors may contribute to the development or perpetuation of AF. Familial forms of AF have been reported. Parental atrial fibrillation increases the risk of AF in offspring. A gain-of-function mutation in the beta subunit of a potassium channel has also been associated with familial atrial fibrillation and a mutation in a sodium channel gene, has been associated with early dilated cardiomyopathy and atrial fibrillation. A study of familial Wolff-Parkinson-White Syndrome links metabolic instability with the electrical instability that promotes atrial fibrillation. Further study is needed to identify genetic factors that are more relevant to larger populations of atrial fibrillation and to better understand the pathogenesis

Bruce Stambler, MD – Topic: ATRIAL ANTIARRHYTHMIC EFFECTS OF SELECTIVE ALDOSTERONE BLOCKADE IN HEART FAILURE

Elevated Aldosterone (ALD) can have major deleterious effects on the heart since it leads to inflammation and myocardial fibrosis. Elevated ALD leads to cardiac fibrosis which leads to increased collagen synthesis and collagen deposition which leads to myocardial fibrosis which means LV stiffness and LVD and ultimately congestive heart failure.

The impact of elevated ALD includes: cardiovascular disorders and heart failure, myocardial fibrosis and remodeling, vascular injury and fibrosis, vascular compliance lowered, impaired baroreceptor function, catecholamine potentiation, prothrombic effects (incr. PAI-1), sodium reabsorption and water retention, K+ and Mg2 loss, progressive renal disease, heart rate variability. All these are contributory to cardiovascular disorders including pathways leading to AF, Atrial tachyarrhythmia and atrial flutter and hypertension, heart failure, stroke, ischemia, end stage renal failure.

Conclusions: the use of eplerenone as a selective aldosterone blockade in CHF, suppresses inducibility of sustained atrial tachyarrhythmias; prolongs atrial ERPs; attenuates diastolic dysfunction; is more effective than ACE inhibition with benzepril in suppressing atrial arrhythmias, prolonging ERP and attenuating diastolic dysfunction; has its effects on inducibility of atrial arrhythmias and prolongation of ERP reversed by isoproterenol.

DEBATE: MORE TECHNOLOGY OR MORE EXPERIENCE: WHAT DO WE NEED FOR PERCUTANEOUS ABLATION?

Pro:
Atul Verma, MD, FRCPC
Southlake Regional Health Center - Staff Electrophysiologist
University of Toronto, Newmarket, Toronto, Canada

THE ANSWER LIES IN TECHNOLOGY - MY ARGUMENT
We know a lot about the technique. There is a convergence in technique. Operator experience plateaus. We have enough "experience". Major barriers or limitations to widespread use are practical ones and the answer to these limits lies in technology.

"Ever since the Bordeaux group perfected the technique, and despite all the arguing and debates out there, PV isolation has remained the cornerstone or bedrock procedure for ablation. PVI has remained a very consistent and enduring theme since 1998. As recently as last year, Karl Heinz Kuck, using the double lasso technique found if you can get true

isolation in all pulmonary veins you can get incredibly high success rates (95%) in paroxysmal atrial fibrillation.

Fluoroscopy can be very challenging – it's two-dimensional and doesn't really give you a good feel for all variations of anatomy. With the development of real time imaging technology and procedure, the ICE monitor, we now have a better understanding of anatomy and keep the ablation pathway as well. Incidence of severe stenosis is dropping to almost zero and this topic went from hot to passé. Today's vexing issue is esophageal injury and we alter that in terms of time and power to minimize injury and with the latest technology.

Fluoroscopy time is a concern for both EP and patient. The day is right around the corner when not only will we see the left atrium but also the lasso within the left atrium and the ablation path in relationship to the lasso. We will see our catheters or lassos moving on real 3D CT or MRI images and we may never have to push on another fluoroscopy pedal again.

Con:
Gregory K. Feld, MD
Professor of Medicine - Director, Cardiac Electrophysiology Program
University of California - San Diego Medical Center -San Diego, CA

Drs. Feld and Verma discussed the debate beforehand and decided the number of cases you do is not that critical and rather than more experience, he feels a better description would be – "more knowledge" is needed for his position in this debate.

Certainly without technology, we wouldn't be anywhere. Technology has been rapidly advancing but we are ahead of ourselves. I'm not sure we have a good understanding of the potential mechanisms of AF and how they pertain to the patient. With all the different procedures there seems to be some convergence and consistency in approach but we still may not be appropriately targeting our individual patients with a specific procedure. And I propose that more experience and KNOWLEDGE will allow us to do that.

Regarding PV electrical activity triggering AF certainly it is one of the most important mechanisms specifically in paroxysmal AF patients. There may be non-electrical activity triggers as well as mechanical, but it's not entirely clear. Whether this is due to localized re-entry or other factors, research doesn't clearly tell us which mechanism may underlie the triggering in the PV. May be non PV electrical activity may be local reentry, local scarring or the old historical info on multiple wavelet bands maintaining afib leading to electrical remodeling or regional scarring.

Certainly with the various types of technology available we can get a better handle on the types of mechanisms involved in various cases.

Multiple approaches and potentially multiple mechanisms, and at first blush, the success rates look very good, but there is even more data out there to show that we may be too optimistic about these success rates; we need more careful assessments with outcomes with event monitoring. In paroxysmal cases the success outcomes are higher, but certainly in persistent, these rates are lower. While the success rates are good, further improvement is still possible. And further efficacy will require greater experience and greater knowledge and not necessarily more technology.

Closing Remarks

Are We Curing Atrial Fibrillation?

Antonio Pacifico, MD
Founder and Chairman – Texas Arrhythmia Institute – Houston, TX

Dr. Pacifico presented the skeptic's view of the successful treatment of atrial fibrillation by all current methods. Tragically, not long after the Summit, he was killed in a plane crash and Dr. Steven Hao of Marin General offered this insight to his well-known role as skeptic.

"The passing of Antonio Pacifico is a true loss to the field of cardiology/electrophysiology and all those who knew him. His insights/discussions were always carefully crafted to provide perspective and inspire scientific thought, both necessary to rein in unbridled enthusiasm. He will be missed."

Following are my notes and I urge you to read his short published paper at the afibbers.com web site, especially if considering an ablation procedure http://www.afibbers.com/forum/read.php?f=6&i=19014&t=19013#reply_19014

We have not long enough follow-ups to say 'cured'. Patients are just asymptomatic. He first challenged the Cox and modified procedures with these points:

- Stroke risk – incomplete evaluation.
- Failure rate of sinus node function is high and this is not being assessed.
- No random trial for efficacy and safety of these procedures.
- Post-procedure – pts wear a Holter for 7 days – this is not long enough to proclaim a cure or anything else.

- Method to detect arrhythmia recurrences not clearly described.
- Not enough being assessed.
- As stated in his published opinion, he repeated concern about silent atrial fibrillation with up to 50% asymptomatic afib recurrences.
- 70% of the reporting data comes from only three groups with a mean age of less than the majority of the patient population.
- Important to look at left atrial function since, in time, the atrium is enlarged; stroke concerns.
- He expressed concern over long procedures over 90 minutes; the average time is 2-3 hours of fluoroscopy time.

And his parting remarks left questions unanswered: …. "If we are ablating heart tissues for hours (and the area isn't that large to begin with), what amount of tissue is left unscarred? Are we endangering future lives?"

My Observations

Among the many videos I viewed last October, some images are still vividly present in my memory. Among my impressions are:

Many video examples of a fibrillating heart; small wonder we feel as badly as we do.

It was also obvious there is no one uniform technique; rather the judgment of either the cardiac surgeon or the EP is extremely important based on their experience with certain situations and history of the patient emphasizing the importance of going to a highly practiced and skilled professional.

Demonstration and discussion of placement of catheters, the proximity of the esophagus and the pulmonary vein burns to explain why esophageal fistulas are such a threat. No question; this procedure does not belong in the hands of the inexperienced. Amazing they are able to accomplish all they do - safely.

Saw a video of an excised LAA that was described as 'didn't know its job was done'…it lay there on a gauze pad still beating. A new (to me) area of potentials or drivers: The Ligament of Marshall, highly arrhythmogenic. The excision of this ligament in the Maze procedure eliminated AF. (As did the excision of the LAA.) The Ligament of Marshall is responsible for adrenergic stimulation of AF. Several presenters emphasized the

importance of removing this ligament and showed many views of the size and shape both before and after excision.

Silent arrhythmia was mentioned by every speaker. It was very obviously of great concern. It even permeated the group discussion at my table at lunch.

When you see videos of the pulsing heart and the many catheters all pulsing inside in concert to each beat during a procedure, it reminded me of tiny dancing sea plants or little snakes curved at the tips and all affected positionally by each contraction of the heart. To then, imagine that a burn is delivered accurately is certainly a test of skill.

One of the EPs said ...this is not an art, but rather a science and we need to get back to delivering the science. IMHO I would tend to disagree and say it is definitely a combination of both. In the hands of the unskilled or inept, the science would mean nothing.

The lack of any reference to nutritional intervention was so powerful it was deafening; to my ears only, of course. I didn't expect otherwise. I was very much the lone ranger at that convention for the nutritional aspect.

My original impression was confirmed again as I completed this report. There is a wide collection of opinions amongst the experts as to which method of ablating heart tissue is most effective. There certainly was no one who proclaimed definitely a cure would be guaranteed with either a surgical or electrophysiological approach, although the surgeons were much more confident of 'cures.' However, that opinion was deflated a bit by some stats indicating some surgical patients are still on heart drugs. It was apparent to me that while ablation for AF has come a long way and many of us are enjoying the results of that success, Dr. Topol's comment on "Beating Afib is the New Frontier of Cardiology" was most appropriate.

In the meantime, as Hans has indicated in his surveys, the most success seems to be with the doctors and facilities doing the most number of cases. This may change significantly when the new technology arrives that provides more user-friendly equipment that relies less on operator skill and knowledge but for now, whether it's electrophysiology or surgical, if heading for an ablation, my advice is to choose the most knowledgeable and experienced in the field and do your due diligence. I don't think anyone should rush to have any ablation procedure unless all other options have failed. My forum posts give a wealth of references for research by the top cardiac AF specialists.

Review of 2006 Guidelines for Management of Patients with Atrial Fibrillation

Hans R. Larsen

A group of experts from the American College of Cardiology, American Heart Association, and European Society of Cardiology has published a new set of guidelines for the management of patients with atrial fibrillation. These guidelines supersede those issued in 2001.

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. It is estimated that about 2.3 million people in North America and about 4.5 million in the European Union have AF. Most of these have associated structural heart disease, but 10-30% have what is known as "lone" AF. Lone AF was originally defined as being simply AF with no underlying structural heart disease; however, the 2006 guidelines narrow this definition. The term "lone" AF now applies to individuals younger than 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. The term "nonvalvular" AF refers to cases without mitral valve disease, prosthetic heart valve, or valve repair. The terms paroxysmal (terminating spontaneously within 7 days), persistent (episodes lasting longer than 7 days, but amenable to cardioversion), and permanent (lasting longer than one year and either not amenable to cardioversion or cardioversion foregone) have not been materially changed.

The guidelines cover the acute treatment of AF, rhythm and rate control, prevention of recurrence, and stroke prevention (antithrombotic therapy). There is also brief mention of maze surgery and catheter ablation, which are considered primarily as approaches to be tried if drug therapy fails.

Clinicians (cardiologists and electrophysiologists) should distinguish clearly between a first-detected episode, which generally requires no treatment and recurring episodes which may. Among the highlights of the guidelines are:

Acute treatment of an AF episode

Most episodes of AF terminate spontaneously, but if they do not attempts at electrical or pharmacological (drug-based) cardioversion should be made in a hospital setting. Pharmacological cardioversion is more effective the quicker it is initiated and loses its effectiveness if more than 7 days have elapsed since the onset of the episode. Flecainide

(Tambocor) and propafenone (Rythmol) are most often used for pharmaceutical conversion, although there may be cases in which dofetilide (Tikosyn), ibutilide (Corvert), or amiodarone (Cordarone) are deemed desirable. The drugs can be administered intravenously or orally. Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. It is now also accepted practice for lone afibbers to use the "pill-in-the-pocket" or "on-demand" approach to terminate paroxysmal episodes in a home setting. It is recommended that a beta-blocker or a calcium channel blocker (verapamil, diltiazem) be taken prior to taking the Class IC antiarrhythmic (flecainide or propafenone) in order to prevent rapid AV conduction in case atrial flutter is also present.

Electrical cardioversion involves the delivery of an electrical shock(s) synchronized with the intrinsic activity of the heart. It is performed in a sedated and, preferably, fasting state. Electrical cardioversion is usually performed within 48 hours of the onset of an episode, or after 3 weeks of anticoagulation with warfarin. A further 4 weeks of anticoagulation post procedure is necessary in order to prevent an embolic stroke precipitated by the heart's return to normal sinus rhythm. It is also acceptable to perform electrical cardioversion after ensuring, via transesophageal echocardiography (TEE), that there are no clots or clot precursors (SEC) in the left atrium prior to the procedure. It is very important to ensure that serum potassium level is within the normal range before attempting cardioversion. Low potassium levels are associated with a significantly poorer success rate for the cardioversion.

Maintenance of sinus rhythm

If episodes are infrequent and well-tolerated drug therapy is usually not indicated. However, if episodes are more frequent and highly symptomatic then antiarrhythmic therapy should be considered. The first choice drugs for vagal afibbers are flecainide and disopyramide (Norpace, Rythmodan). Propafenone is not recommend because its (weak) intrinsic beta-blocking activity may aggravate vagally-mediated paroxysmal AF.

Editor's comment: Some vagal afibbers have reported good results with propafenone. Whether or not it is effective or detrimental may depend on the speed with which it is metabolized in each particular case.

The first line treatment for adrenergic afibbers is usually a beta-blocker, but flecainide, propafenone or sotalol may be tried if the beta-blocker does not prove up to the task. Combinations of Class IC antiarrhythmics and beta-blockers or calcium channel blockers may also be efficacious in some individuals.

Rate rather than rhythm control may be a viable alternative for older patients in permanent and fairly asymptomatic AF. Rate control can be achieved with beta-blockers or calcium channel blockers (verapamil, diltiazem). It is desirable to achieve ventricular (pulse) rates of between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise. There is not evidence that afibbers assigned to rate control rather then rhythm control have a greater incidence of ischemic stroke.

Stroke prevention

The guidelines for antithrombotic therapy (stroke prevention) have changed considerably since the issuance of the 2001 guidelines. While the 2001 guidelines allowed for lone afibbers with no risk factors for stroke to forego any stroke prophylaxis or take a daily aspirin, the 2006 guidelines require that all patients diagnosed with AF take either aspirin or warfarin even if they have no risk factors. Actually, the guidelines are not clear on this point. Another section (page 705) states, "*Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications*." And on page 706 the following two statements appear:

- "*In patients with AF younger than 60 y without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established*."

- "*Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease (lone AF) or any risk factors for thromboembolism*."

So, it would seem that the option of no antithrombotic therapy is still open for lone afibbers.

Patients with only one moderate-risk factor (age over 75 years, hypertension, diabetes, or recent onset heart failure) may take aspirin or warfarin (target INR 2.5), while patients with two or more moderate-risk factors, or one high-risk factor (previous stroke, TIA or embolism, mitral stenosis, prosthetic heart valve) are advised to take warfarin (target INR 2.5). The same guidelines apply to patients with atrial flutter. The selection of antithrombotic therapy should not be influenced by whether the patient has paroxysmal, persistent, or permanent AF, but should be based strictly on the absence or presence of stroke risk factors.

ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation – Executive Summary. **Circulation**, *Vol. 114, August 15, 2006, pp. 700-52*
http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1

Editor's comment: One of the more controversial changes in the 2006 guidelines is the increased emphasis on the use of aspirin for stroke prevention. There is actually no evidence that aspirin is effective for the prevention of a first stroke (primary prevention) and the FDA has repeatedly refused to label the drug for this application. Aspirin is by no means innocuous and causes thousands of hemorrhagic strokes and serious internal bleeds every year. Thus, the "daily aspirin" ritual should not be embarked upon lightly, but only after careful study of the pros and cons in each particular case. An excellent start for this is the report "*Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence for the U.S. Preventive Services Task Force*" by Michael Hayden, MD et al. published in the **Annals of Internal Medicine**, Vol. 136, No. 2, January 15, 2002, pp. 161-72.
http://www.annals.org/cgi/reprint/136/2/161.pdf

Ablation/Maze Survey – 2006

2006 Ablation/Maze Survey

The evaluation of the 2006 ablation/maze survey turned out to be a very major undertaking. With 335 afibbers responding to almost 100 questions about their ablation, maze or other procedures close to 35,000 data points had to be extracted, arranged and evaluated.

The volume of data is clearly good as far as being able to draw valid conclusions, but less desirable as far as being able to present the data and conclusions in a readable and comprehensible format. I am fairly certain that this survey is the largest ablation survey ever done in the "real world". In other words, a survey in which the information is provided by the patients who underwent the procedures rather than by the EPs or institutions that performed them. Please note that the survey only relates to symptomatic episodes of atrial fibrillation.

This report has been divided into five major sections: –

- Definition of Terms
- Evaluation of Background Data
- Initial Procedure Results
- Procedure Outcome
- Patient Outcome
- Performance Rating

Definition of Terms

Types of Atrial Fibrillation

- **Paroxysmal –** Episodes occurring intermittently and tending to terminate spontaneously - usually within 48 hours.
- **Persistent** – Episodes lasting longer than 7 days and not terminating spontaneously, but can be terminated with chemical or electrical cardioversion.
- **Permanent** – Constant (chronic, 24/7) afib not amenable to effective termination by cardioversion.

- **Adrenergic** – Episodes occurring almost exclusively during daytime, often in connection with exercise or emotional or work-related stress.
- **Vagal** – Episodes tending to occur during rest, at night or after a meal. Alcohol and cold drinks are common triggers.
- **Mixed (random) –** Episodes occur anytime and do not consistently fit the adrenergic or vagal pattern.

Procedures

- **Focal ablation** – The original radiofrequency (RF) ablation procedure in which specific active foci of aberrant impulses are located and ablated.
- **Pulmonary vein ablation (PVA) –** An ablation procedure in which a ring of scar tissue is placed just inside the pulmonary veins where they enter the left atrium. The original PVA carries a high risk of pulmonary vein stenosis, so it is rarely used in its original form anymore. Thus, the term PVA is now associated with ablation around the pulmonary veins when a more specific description (SPVI, CAPVI or PVAI) is not used by the EP or the exact type of pulmonary vein isolation procedure is not known by the respondent.
- **Segmental pulmonary vein isolation (SPVI or Haissaguerre procedure) –** In this procedure electrophysiological mapping (using a multipolar Lasso catheter) is used to locate the pathways taken by aberrant impulses from the pulmonary veins and these pathways are then eliminated by ablation around the veins approximately 5 to 10 mm from the ostium of the veins.
- **Circumferential anatomical pulmonary vein isolation (CAPVI or Pappone procedure) –** In this procedure anatomical mapping (CARTO) is used to establish the exact location of the pulmonary veins. Two rings of lesions are then created in the left atrium - one completely encircling the left pulmonary veins and another completely encircling the right pulmonary veins; the two rings are usually joined by a linear lesion.
- **Pulmonary vein antrum isolation (PVAI or Natale procedure) –** This procedure is a variant of the Haissaguerre procedure. It involves locating aberrant pathways through electrophysiological mapping (using a multipolar Lasso catheter) and ablating these pathways guided by an ultrasound (ICE) catheter. The ablation is performed as close as possible to the outside edge (antrum) of the junction between the pulmonary veins and the atrial wall. All four

pulmonary veins as well as the superior vena cava (if indicated) are isolated during the procedure.

- All three variants of the PVI procedure may be followed by focal ablations involving other areas of the atrium wall or creation of linear lesions in order to eliminate sources of afib located outside the pulmonary veins.
- **Cryoablation –** In this procedure a nitrogen-cooled, rather than electrically-heated, catheter is used to create the ablation lesions.
- **Maze procedure** – The original surgical procedure, the full maze or Cox procedure, used a cut-and-sew protocol for creating lesions forming a "maze" that conducted the electrical impulse from the SA to the AV node, while at the same time interrupting any "rogue" circuits. The cut-and-sew method has now largely been replaced by the use of RF-powered devices, but cryosurgery, microwave application, and high-intensity focused ultrasound (HIFU) have all been tried as well and are preferred by some surgeons. Creating the full set of maze lesions usually requires open-heart surgery and the use of a heart/lung machine.
- **Mini-maze procedure –** The so-called mini-maze procedure also involves lesions on the outside of the heart wall, but access to the heart is through incisions between the ribs rather than via open-heart surgery. The mini-maze may involve the creation of the full maze set of lesions, but usually focuses on pulmonary vein isolation. The procedure does not involve the use of a heart/lung machine and lesions are created by the application of RF energy or cryoablation.
  Right atrial flutter ablation – This procedure involves the application of radiofrequency energy to create a block of the cavotricuspid isthmus in the right atrium so as to interrupt the flutter circuit. A right atrial flutter ablation is usually successful in eliminating the flutter, but rarely helps eliminate atrial fibrillation and may even, in some cases, cause the development of atrial fibrillation.
- **Left atrial flutter ablation –** Left atrial flutter is a common complication of ablation for atrial fibrillation. It most often resolves on its own, but if not it may be necessary to re-enter the left atrium, locate the offending circuit, and block it via radiofrequency catheter ablation.
- **AV node ablation + pacemaker –** In this procedure the AV node (the ventricular beat controller) is isolated from any extraneous impulses through cauterization of surrounding tissue, and the ventricles are fed their "marching order" through an implanted pacemaker. The procedure does not eliminate atrial fibrillation, but makes it substantially less

noticeable. Patients who have undergone AV node ablation and pacemaker installation are entirely dependent on the pacemaker and are usually on warfarin for life.

Statistical Terms

- **Mean** – The average value for a group of data, i.e. the sum of the values of all data points divided by the number of data points.
- **Median** – The value in the middle of a group of data, i.e. the value above which half of all individual values can be found and below which the remaining 50% can be found.
- **Statistical significance** – In this study average values are considered different if the probability of the difference arising by chance is less than 5 in 100 using the two-tailed t-test. This is expressed as "p" being equal to 0.5 or less. Lower values of p are indicative of a greater certainty that observed differences are truly significant.

All statistical tests were carried out using the *GraphPad Instat* program (GraphPad Software Inc, San Diego, CA).

Definition of Success

The success of the procedures is (unless otherwise noted) judged after the last reported ablation (initial or touch-up). It is defined in two ways:

Subjectively – The afibber's own opinion as to whether the procedure was completely successful, partially successful, not successful, or too early to tell

Objectively – The following criteria are used to define success objectively:

- Complete success – No afib episodes, no antiarrhythmics, consistent sinus rhythm
- Partial success – No afib episodes, but on antiarrhythmics
- Failure – Afib episodes still occurring
- Uncertain – Cases where insufficient data was available or where less than 6 months had gone by since the procedure.

Overview of Procedures

The procedures used to cure atrial fibrillation can be divided into two groups – **catheterization procedures** and **surgical procedures**. Both types involve the creation of lesions on the heart wall (right and/or left atrium) in order to stop the propagation of impulses not involved in conducting the heart beat "signal" from the sino-atrial (SA) node to the atrio-ventricular (AV) node.

Catheterization procedures create the lesions from the inside via an ablation catheter threaded through the femoral vein and are performed by electrophysiologists (EPs). Surgical procedures create the lesions from the outside and access is either through incisions between the ribs or may involve open-heart surgery and the use of a heart/lung machine. Surgical procedures are carried out by cardiothoracic surgeons.

The overwhelming majority of catheterization procedures use radiofrequency (RF) energy to create the lesions, but some EPs prefer the use of nitrogen-cooled catheters (cryoablation) rather than RF-powered ones due to their reduced risk of creating pulmonary vein stenosis.

The original surgical procedure, the full maze or Cox procedure, used a cut and sew protocol for creating lesions forming a "maze" that conducted the electrical impulse from the SA to the AV node, while at the same time interrupting any "rogue" circuits. The cut and sew method has now largely been replaced by the use of RF-powered devices, but cryosurgery, microwave application, and high-intensity focused ultrasound (HIFU) have all been tried as well and are preferred by some surgeons.

The so-called mini-maze procedure also involves lesions on the outside of the heart wall, but access to the heart is through incisions between the ribs rather than via open-heart surgery. The mini-maze may involve the creation of the full maze set of lesions, but usually focuses on pulmonary vein isolation. The procedure does not involve the use of a heart/lung machine.

Most of the rogue electrical impulses that create afib originate in the area where the pulmonary veins join the left atrium. Thus, all catheterization procedures aimed at curing afib involve electrical isolation of the pulmonary veins from the left atrium wall. Depending on the origin of the afib, catheterization procedures may also involve ablations of the superior vena cava and coronary sinus (thoracic veins), linear ablation of the left atrial roof, and a standard cavotricuspid isthmus (right flutter) ablation.

Surgical procedures, except for the full maze, also focus on isolating the pulmonary veins, but in addition may involve lesion creation at specific spots located by mapping, removal of the left atrial appendage, and disconnection of the ligaments of Marshall – a potent source of vagal input.

The catheterization procedures covered in this part of the survey are left atrial flutter ablation, right atrial flutter ablation, cryoablation, and AV node ablation + pacemaker installation. The surgical procedures covered are the maze procedure and the so-called "mini-maze" or minimally invasive maze procedure. The main difference between the full maze and the mini-maze procedure is the method of access to the heart. The maze involves a 6-12" long cut through the breastbone, while the mini-maze provides access through two or more 2" incisions between the ribs. Another important difference is that the maze procedure requires the use of a heart/lung machine, while the mini-maze does not.

Evaluation of Background Data

Distribution of Procedures

Three hundred and thirty-five afibbers responded to the survey and provided details of a total of 493 procedures distributed as follows:

TABLE 1

	Number of Procedures				
Procedure	1st	2nd	3rd	Further	Total
Focal ablation	23	11	1	0	35
Pulmonary vein ablation (PVA)	64	24	4	0	92
Segmental pulmonary vein ablation	41	24	7	0	72
Circumferential pulmonary vein ablation	42	13	2	4	61
Pulmonary vein antrum isolation	66	20	3	0	89
RF procedure not specified	41	15	2	1	59
Total RF ablation procedures	77	107	19	5	408
Cryoablation	4	2	0	0	6
Maze procedure	10	1	2	0	13
Mini-maze procedure	18	1	2	1	22
Right atrial flutter	18	5	2	1	26
Left atrial flutter	2	3	2	1	8
AV node ablation + pacemaker	6	2	1	1	10
Total non-AF procedures	58	14	9	4	85
GRAND TOTAL	**335**	**121**	**28**	**9**	**493**

The majority of procedures (83%) were radio frequency (RF) ablation procedures aimed at curing atrial fibrillation. Thirty-seven per cent of the 335 respondents underwent a second procedure, 9% a third procedure, and 3% underwent further procedures. The most widely used AF ablation procedure was the generic pulmonary vein ablation (PVA) followed by the pulmonary vein antrum isolation (Natale), the segmental PVI (Haissaguerre), and the circumferential PVI (Pappone).

General Background of Respondents

TABLE 2

Demographics	Male	Female	Total
Gender distribution	77%	23%	100%
Average (median) age*	57	57	57
Age range (present)	27-78	26-86	26-86
AF confirmed by diagnosis	95%	97%	95%
Underlying heart disease	11%	8%	10%
Mitral valve prolapse	6%	8%	7%
Mitral valve regurgitation	11%	13%	11%
Median age at diagnosis	47	49	48
Age range (at diagnosis)	5-74	8-79	5-79
Median age at last procedure	56	56	56
Age range (last procedure)	26-85	26-78	26-85

* at time of completing survey

There are no significant differences between males and females as far as demographic variables are concerned.

Afib Type

A total of 279 respondents had provided detailed information regarding their type of AF (adrenergic, mixed, vagal). The distribution was as follows:

TABLE 3

Type of AF	Male,%	Female,%	Total,%
Adrenergic	8	3	7
Mixed	48	53	49
Vagal	24	31	25
Total paroxysmal or persistent	80	87	81
Permanent	20	13	19
TOTAL	**100**	**100**	**100**

The majority of respondents (81%) had paroxysmal or persistent AF, while 19% were in permanent AF. The proportion of permanent afibbers in this sample would thus seem to be somewhat higher than in our total database (14% among 625 afibbers), while the prevalence of vagal AF is somewhat lower (34% of total database). Mixed (random) AF was the most common type followed by vagal, permanent and adrenergic.

Afib Frequency

Three hundred and twenty-three respondents had provided information about their episode frequency. The distribution was as follows:

TABLE 4

Afib Frequency*	Male,%	Female,%	Total,%
Permanent	19	10	17
Daily	21	26	22
Twice weekly	24	25	24
Weekly	13	10	12
Twice a month	9	13	10
Monthly	6	6	6
Every 2 months	0	1	1
Every 3 months	3	7	4
Every 6 months	2	1	2
Once a year	1	0	0
Less than once a year	2	1	2

* prior to first procedure

The majority of respondents (75%) experienced episodes at least once a week and 39% were in afib every day (including permanent afibbers). Only 9% of those seeking a cure through ablation or surgical procedures had episodes less frequent than once a month. This indicates that most afibbers only opt for a procedure when the frequency of episodes becomes intolerable or permanent AF becomes a reality.

The median duration of paroxysmal episodes was 9.5 hours with a wide range of from a few minutes to 120 hours. There was no statistically significant difference in episode frequency and duration between paroxysmal afibbers taking antiarrhythmics or blockers and those taking no medications on a continuous basis.

Use of Antiarrhythmics and Blockers

The majority of respondents (86%) were taking one or more drugs on a continuous basis to reduce their episode frequency and duration, or ameliorate the effects of their permanent AF. The popularity of the various drugs among the 335 afibbers who had provided information about AF type and drug use is presented below.

TABLE 5

Drug	Adren. %	Mixed %	Vagal %	Perm. %	Unknown %	Total %
Beta-blockers	5	13	9	17	14	**13**
Calcium channel block.	5	4	4	17	5	**7**
Amiodarone	0	9	7	15	20	**11**
Digoxin	0	1	0	2	2	**1**
Disopyramide	5	2	4	2	0	**2**
Dofetilide	0	6	0	4	11	**5**
Flecainide	16	17	23	13	20	**18**
Propafenone	5	15	13	4	11	**11**
Sotalol	32	13	10	9	2	**11**
Combination A	5	2	4	0	0	**2**
Combination B	0	1	0	2	4	**1**
Other (incl. combin.)	11	5	1	6	2	**4**
No drugs	16	12	24	11	11	**14**
TOTAL, %	100	100	100	100	100	100
No. in group	19	136	70	54	56	335

Combination A – antiarrhythmic + beta-blocker
Combination B – antiarrhythmic + calcium channel blocker

Flecainide (Tambocor) was the most prescribed antiarrhythmic and was used on a continuous basis by 18% of respondents. Beta-blockers were the second most popular drugs followed by propafenone, sotalol and amiodarone. About 35% of permanent afibbers were, as would be expected, solely on beta-blockers or calcium channel blockers. However, a rather astounding 49% were on antiarrhythmics, which would not be expected to benefit permanent afibbers. It is encouraging to see the low usage of digoxin (Lanoxin) which should never be used by lone afibbers.

Over 40% of vagal afibbers (paroxysmal or persistent) were on drugs with beta-blocking properties (beta-blockers, propafenone, amiodarone and sotalol) on a continuous basis. These drugs are generally contraindicated for vagally-mediated AF. Flecainide was the most prescribed drug for

vagal afibbers followed by propafenone, sotalol, beta-blockers, and amiodarone. Sotalol was the most popular drug for adrenergic afibbers, while flecainide was the most prescribed drug for mixed afibbers. Fourteen percent of all respondents used no drugs to manage their afib.

As would be expected in a group of afibbers awaiting ablation or maze procedure, the drugs were clearly not effective in preventing episodes or in lessening the overall burden of the afib. The following table shows the average values for afib frequency, duration and burden (frequency x duration) for a group of 223 paroxysmal afibbers during the 3-month period preceding their first procedure.

TABLE 6
Episodes 3 months prior to procedure

		# of Episodes		Duration of Episodes,hrs.		Burden,hrs.	
Drug	# in Group	Mean	Median	Mean	Median	Mean	Median
Beta-blockers	30	35	25	13	9	282	190
Calcium chan. block.	12	31	19	16	15	580	156
Amiodarone	20	36	19	16	12	361	180
Dofetilide	11	56	90	20	16	774	540
Flecainide	50	33	25	16	7	364	149
Propafenone	32	31	25	15	8	289	176
Sotalol	29	27	25	18	10	390	150
No drugs	39	35	25	17	10	529	300

NOTES – Episodes per 3 months estimated as follows:
Daily = 90 episodes per 3 months
Twice-weekly = 25 episodes per 3 months
Weekly = 13 episodes per 3 months
Twice-monthly = 6 episodes per 3 months
Monthly = 3 episodes per 3 months
One every 2 months = 1.5 episodes per 3 months
One every 3 months = 1 episode per 3 months
One every 6 months = 0.5 episode per 3 months
One every year = 0.25 episode per 3 months
Burden = # of episodes over 3 months x duration in hours

There was no statistically significant difference in episode burden between using no drugs or using a blocker or antiarrhythmic. Dofetilide (Tikosyn) was significantly less effective in easing overall afib burden than were beta-blockers, amiodarone, flecainide, propafenone and sotalol. In view of the potential serious side effects of dofetilide, its use should probably be restricted.

Thirty-six of 253 paroxysmal afibbers (14%) were using the on-demand (pill-in-the-pocket) approach in an attempt to shorten their episodes. Median episode duration with flecainide was 9 hours (range of 1 – 80 hours), 14 hours with propafenone (range of 2 – 90 hours), and 17 hours with other approaches. This compares to a median episode duration of 9 hours (range of 0.1 – 96 hours) when not using the on-demand approach. Thus, in this group of afibbers, 80% of whom were using antiarrhythmics or blockers on a continuous basis, the use of the on-demand approach did not seem to confer any benefit. It is possible that the main beneficiaries of this approach will be afibbers who are not taking antiarrhythmics on a regular basis.

Radiofrequency Ablation

Demographics

A total of 277 afibbers underwent a RF ablation for atrial fibrillation as their first procedure. The majority of the 275 respondents who knew their type of afib had the paroxysmal form (78%), 6% had persistent afib, while the remaining 16% were in permanent afib. Among the 179 paroxysmal afibbers who were aware of the initiating circumstances for their episodes, 61% characterized themselves as mixed, 31% were vagal, and 8% were adrenergic.

The median age of respondents at the time they completed the questionnaire was 57 years with a range of 26 to 86 years. The median age at diagnosis was 47 years for men and 50 years for women with a range of 5 to 79 years. The median age at the latest procedure was 55 years for men and 56 years for women with a range of 26 to 85 years. The average (median) number of years between diagnosis and last procedure was 6 years for men and 7 years for women with a range of 0 to 48 years.

Twenty-four percent of respondents were female. Seven percent of respondents had been diagnosed with heart disease, 6% with mitral valve prolapse (MVP), and 11% with minor mitral valve regurgitation.

Respondents with reported heart disease were diagnosed with afib significantly later in life than those without heart disease (54 versus 46 years of age) and underwent their ablation later (60 versus 55 years of age).

Initial Procedure Results

Only afibbers who had undergone their first RF ablation at least 6 months prior to completing the survey questionnaire were considered in this evaluation in order to avoid making premature conclusions as to success. Thus, 247 afibbers who knew their afib type (paroxysmal, persistent, permanent) and the outcome of their first ablation were included. Results are presented in the table below.

TABLE 7
Results of Initial RF Procedure

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Ablation Results				
Adrenergic	12	42	0	58
Mixed	104	43	5	52
Vagal	49	39	4	57
Not sure	30	23	17	60
Total paroxysmal	195	39	6	55
Persistent	15	27	20	53
Permanent	37	38	0	62
Grand total	247	**38**	**6**	**56**
Adverse event rate	247	**29**	**53**	**51**
Other Possible Variables				
Underlying heart disease	20	35	0	65
Mitral valve prolapse	14	29	14	57
Minor MV regurgitation	30	53	3	43
Outcome for males	189	41	3	56
Outcome for females	58	28	17	55
Demographics		years	years	years
Present age, median	247	58	54	57
Age at diagnosis, median	247	49	45	47
Years of AF	247	6	6	7

The overall rate of complete success (no afib, no antiarrhythmics) was 38%. The rate of partial success (afib controlled with antiarrhythmics) was 6%, and the overall failure rate was a disappointing 56%. There was no significant difference in failure rate for the 3 types of AF (adrenergic, mixed and vagal). The failure rate for permanent afibbers tended to be slightly higher than for paroxysmal afibbers, as did the failure rate for

afibbers with underlying heart disease and mitral valve prolapse. However, none of these differences reached statistical significance.

The difference in outcome for male and female afibbers was not statistically significant, nor did present age, age at diagnosis, or years of AF correlate with success/failure. The difference in the percentage of procedures accompanied by adverse events was, however, significantly different (p=0.004) between successful procedures (29%) and failures (48%) indicating that a failed procedure is more likely to be accompanied by adverse events than is a successful one.

The success rate (38%) observed in this survey is clearly disappointing, as is the high rate of adverse events. However, as previous surveys have shown, both the success and complication rates are highly dependent on the skill and experience of the EP performing the procedure.

Fifteen afibbers underwent their first RF ablation at the age of 70 years or older. The rate of complete success was 46%, partial success was 7%, and the failure rate was 47%. Thus, based on this very small sample, RF ablations in elderly afibbers are not less successful than those in younger ones.

Success Rate vs. AF Severity

It is conceivable that the success rate might be affected by the severity of the AF (frequency and duration of episodes).

TABLE 8
Success Rate vs. Afib Severity

Parameters	# in Group	Complete Success,%	Partial Success,%	Failure,%
Episode frequency				
Permanent	37	38	0	62
Daily	49	27	4	69
Weekly or twice-weekly	93	42	4	54
Monthly or twice-monthly	37	41	11	49
Less than once a month	22	50	18	32
Episode duration				
Less than 10 hrs	86	40	6	55
10 - 24 hrs	66	38	8	55
Longer than 24 hrs	31	45	3	52
Permanent	37	38	0	62

Episode duration, somewhat surprisingly, did not play a statistically significant role in determining the outcome of the first ablation. Episode frequency, however, showed a statistically significant linear correlation with outcome. Afibbers with daily episodes experienced more than twice the failure rate of afibbers who experienced episodes less than once a month. This would indicate that increasing frequency would be a warning that an ablation would be a good idea.

Second and Third Procedure Results

Only afibbers who had undergone their second and third ablations at least 6 months prior to completing the survey were included in this tabulation in order to avoid making premature conclusions as to success. Results are presented in the table below.

TABLE 9
Outcome of 2nd and 3rd Ablations

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Procedure outcome				
1st procedure	247	38	6	56
2nd procedure	89	37	10	53
3rd procedure	17	41	6	53
Total/Average	**353**	**38**	**7**	**55**

The outcome of the second and third procedures is not significantly different from those of the first procedure, thus supporting the claim by many EPs that a follow-up procedure is not materially different from the initial procedure. The remainder of this section will thus combine the results for the 358 RF ablation procedures for which the outcome is known (including 5 fourth, fifth and sixth procedures).

Procedure Outcome

Popularity of Procedures

It is clear that focal ablation has declined markedly in popularity over the years in the group surveyed. The popularity of the various procedures aimed at isolating the pulmonary veins have, on the other hand,

increased. The two most popular procedures over the period 1998-2006 were the Natale method (PV antrum isolation) and the generic pulmonary vein ablation (PVA), which likely includes elements of the Haissaguerre, Natale and Pappone methods. These methods are followed by the Haissaguerre (segmental PVI) and Pappone (circumferential PVI) methods at 18% and 15% respectively.

Considering just the last two years (2005 and 2006), the Natale and Haissaguerre methods vie for top spot at 26% each with the Pappone method following at 18%. Of course, this distribution may be quite different if another population group was surveyed.

TABLE 10
Popularity of procedures, %

Procedure	1998-2002	2003-2004	2005-2006	1998-2006
Focal ablation	30	7	5	9
PV ablation (PVA)	39	27	13	22
Segmental PVI	7	14	26	18
Circumferential PVI	5	16	18	15
Antrum PVI	5	23	26	22
Unspecified	16	13	12	13
Total, %	100	100	100	100

Outcome of Procedures

TABLE 11
Outcome of procedures, %

	1998-2004			2005-2006			1998-2006		
Procedure	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.
Focal ablation	21	8	71	50	0	50	28	6	66
PV ablation (PVA)	24	5	71	38	5	57	28	5	68
Segmental PVI	29	0	71	43	2	55	38	2	61
Circumferent. PVI	33	19	48	29	14	57	31	16	53
Antrum PVI	61	13	26	73	2	24	67	8	25
Unspecified	15	4	81	32	16	53	22	9	70
Average, %	31	8	61	47	6	47	**38**	**7**	**55**

The average complete success rate for 358 individual RF ablation procedures performed during the period 1998-2006 was 38% - identical to the rate observed for the 247 afibbers who underwent their initial RF procedure. The partial success rate was 7% and the failure rate 55%.

Complete success rates have improved markedly from the average 31% observed for the 1998-2004 period to 47% for the 2005-2006 period. Failure rates also declined from 61% to 47%.
By far the most successful procedure was the pulmonary vein antrum isolation procedure (Natale method) as primarily practiced at the Cleveland Clinic and the Marin General Hospital. Complete success rate for the period 1998-2006 was 67% and the failure rate was 25%. The complete success rate increased from 61% in 1998-2004 to 73% in 2005-2006.

The second most successful procedure was the segmental PVI (Haissaguerre method) as practiced in Bordeaux and several other clinics. Average complete success rate for the period 1998-2006 was 38% and an average failure rate of 61%. The circumferential PVI (Pappone method) had an average complete success rate of 31% and an average failure rate of 53% over the period 1998-2006. There was no improvement in success rate from the 1998-2004 period to the 2005-2006 period. However, the failure rate increased from 48% to 57%, perhaps indicating an influx of relatively inexperienced operators.

In interpreting these results it should be kept in mind that 63% of the pulmonary vein antrum isolation procedures were performed by Dr. Andrea Natale, a recognized world leader in RF ablation.

Adverse Events

The table below shows the incidence of adverse events that occurred during or shortly following 358 RF ablation procedures performed during the period 1998-2006. Fifty-nine percent of all procedures were not accompanied by an adverse event, while 41% were associated with one or more events.

TABLE 12
Incidence of adverse events

	1998-2004			2005-2006			1998-2006		
Events, %	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.	Comp. Succ.	Part. Succ.	Fail.
No adverse event	74	63	55	69	30	48	71	50	52
One or more	26	38	45	31	70	52	29	50	48
Total, %	100	100	100	100	100	100	100	100	100

It is clear that the risk of adverse events is substantially higher in the case of a failed ablation (48%) than in the case of a successful one (29%). This difference is statistically very significant (p=0.002). About 70% of all adverse events reported were fully resolved at the time the survey was completed.
The following table shows the distribution of events. The percentage of events relates to the number of procedures (not the total number of events). Thus, the sum of adverse events and no adverse events may not always equal 100% since some procedures were accompanied by more than one adverse event.

TABLE 13
Distribution of adverse events, %

	1998-2004			2005-2006			1998-2006			
	Comp. Part.			Comp. Part.			Comp. Part.			Total
	Succ.	Succ.	Fail.	Succ.	Succ.	Fail.	Succ.	Succ.	Fail.	Evnts
None, %	74	63	55	69	30	48	71	50	52	**59**
Hematoma	13	13	19	14	10	21	13	12	20	**17**
TIA	2	0	1	0	0	1	1	0	1	**1**
Stroke	0	0	2	0	0	0	0	0	1	**1**
PV stenosis	2	0	6	0	10	0	1	4	4	**3**
Pericarditis	0	0	3	3	10	1	1	4	3	**2**
Tamponade	0	0	2	0	0	0	0	0	2	**1**
Fistula	2	0	0	0	0	0	1	0	0	**0**
L at. tach/flutt.	2	31	12	8	20	21	5	27	15	**12**
R at. flutter	2	0	8	3	30	8	2	12	8	**6**
Minor revers.	5	0	3	7	10	1	6	4	3	**4**
Life-threaten.	0	0	1	0	0	0	0	0	1	**0**
Perm. damage	0	0	2	0	0	0	0	0	1	**1**
Ad. events, %	**26**	**44**	**59**	**34**	**90**	**55**	**30**	**62**	**57**	**47**

Over the period 1998-2006 hematoma in the groin and thigh area was the most common adverse effect at 17%.

Fortunately, this adverse event was short-lived and was completely resolved at the time the survey was submitted. The second most common adverse event was the development of post-procedural left atrial tachycardia/flutter. This complication arose in 44 of 358 procedures (12%). The left atrial tachycardia/flutter resolved on its own in about 40% of cases, but 6 (14%) ablatees underwent another ablation to deal with it. Post-procedure right atrial flutter was reported by 22 ablatees (6%) and 8 (36%) subsequently underwent an ablation to eliminate it.

In the remaining 64% the right atrial flutter was temporary and resolved itself prior to completion of the survey. NOTE: One hundred and fourteen (32%) of all ablation procedures included a right atrial flutter ablation as a precautionary measure. This approach prevented post-procedural right atrial flutter in 93% of cases.

Minor reversible events occurred during 4% of all procedures, pulmonary vein stenosis during 2.5%, and stroke and TIA accounted for 0.6% and 0.8% respectively. Tamponade (piercing of the heart wall) occurred during 3 procedures and thus accounted for 0.8% of events, pericarditis (inflammation of the heart wall) followed 8 procedures (2.1%), and one ablatee experienced a non-fatal fistula (0.3%). One respondent sustained permanent damage to the mitral valve, and another experienced a life-threatening event.

Stenosis Check

A check for pulmonary vein stenosis was carried out post-procedure in 41% of cases. Twenty-two percent were not sure if they had been checked, while the remaining 37% had not been checked. The percentage of reported stenosis checks declined from 44% in the period 1998-2004 to 37% in the period 2005-2006.

Post-Procedure Inflammation

The majority (90%) of afibbers were not aware of their level of the inflammation marker, C-reactive protein, immediately after their procedures. Only 4 patients (1%) reported levels above 5.0 mg/L (0.5 mg/dL), which is usually associated with inflammation. Fifteen ablatees (4%) reported CRP levels in the normal range (1.1 – 5.0 mg/L, and ten (3%) reported levels below 1.0 mg/L (0.1 mg/dL).

Forty-seven percent took anti-inflammatory drugs or supplements after their procedure, while 53% did not. The most popular anti-inflammatories were the following:

Fish oil	used after 20% of all procedures
Aspirin	used after 18% of all procedures
Statin drugs	used after 16% of all procedures
Prednisone	used after 3% of all procedures
Herbal anti-inflammatories*	used after 4% of all procedures

* beta-sitosterol, *Zyflamend* and boswellia

NOTE: Some afibbers used more than one anti-inflammatory

There was no indication that taking anti-inflammatories after the procedure improved the outcome.

Potassium and Vitamins

The majority (85%) of afibbers did not know their level of serum potassium after the procedure. Among the 15% who did know their level, 14% were in the normal range (3.6-5.0 mmol/L) and only 1% had a level below 3.5 mmol/L post-procedure. For these people, potassium supplementation is likely to be especially important.

Overall, 26% of ablatees supplemented with potassium after their procedure, while 51% supplemented with vitamins, antioxidants or minerals. There was no indication that doing so improved the outcome.

Ectopic Activity after Procedure(s)

TABLE 14
Ectopics after procedure

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Increased ectopic activity				
None	96	44	38	24
Less than 1 month	36	4	14	19
One month	15	7	0	4
Two months	30	10	19	10
Three months	31	16	0	8
More than 3 months	83	20	29	35
Total	291	100	100	100

Complete success was associated with a 46% incidence of continuing increased ectopic activity (PACs and PVCs) after the first, often unstable month. Failure, on the other hand, was associated with a 53% incidence of continued increased activity. This difference was not statistically significant. However, experiencing increased ectopic activity beyond the first 3 months was associated with a higher incidence of failure (35%) than of complete success (20%). This different was statistically significant (p=0.04).

Afib Episodes after Procedure(s)

TABLE 15
Episodes after procedure

	# in Group	Complete Success, %	Partial Success, %	Failure, %
Continuing afib episodes				
None	112	64	45	12
Less than 1 month	59	17	14	21
One month	16	9	5	2
Two months	19	6	14	5
Three months	12	3	0	5
More than 3 months	96	0	23	56
Total	314	100	100	100

Complete success was associated with a 9% incidence of continuing afib episodes after the first, often unstable month. Failure, on the other hand, was associated with a 66% incidence of continuing episodes after the first month. This difference was extremely significant ($p =< 0.0001$). It is also evident that experiencing episodes beyond 3 months post-procedure is a strong indicator of ultimate failure. While no successfully ablated afibber experienced episodes beyond 3 months, 56% of those ultimately unsuccessful did. These findings support the observation made by Italian researchers that patients who continue to have episodes beyond the first month post-procedure only have a 10% probability of eventual cure[1].

Warfarin Usage Post-Procedure

The percentage of ablatees who were taking warfarin after their procedure is presented in the table below. A surprising 10% were not on warfarin at all post-procedure. The practice of not using warfarin was not limited to one or two institutions, but was fairly widespread. Most (58%) of successfully ablated afibbers were on warfarin for 2 or 3 months, while most partially successful and unsuccessful ablatees (80% and 67% respectively) remained on the drug for 3 months or longer.

TABLE 16
Warfarin usage after procedure

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Warfarin usage				
None	33	7	8	12
Less than 1 month	18	2	4	7
One month	28	10	4	7
Two months	40	21	4	6
Three months	85	37	13	17
More than 3 months	141	23	67	50
Total	345	100	100	100

Post-Procedural Medication Use

TABLE 17
Antiarrhythmic/blocker use after procedure

	# in Group	Complete Succ.,%	Partial Succ.,%	Failure,%	Total,%
Antiarrhythmics/blockers					
None	91	35	16	24	28
Less than 1 month	12	2	0	5	4
One month	22	11	0	4	7
Two months	43	27	0	5	13
Three months	34	12	5	10	10
More than 3 months	128	13	79	52	39
Total	330	100	100	100	100

NOTE: This table refers to the use of antiarrhythmics/blockers immediately following the procedure(s).
Some respondents went on to discontinue drugs completely and were deemed successful if they were free of afib at the 6-month evaluation point. Others who did experience episodes were later placed on antiarrhythmics and, if the medication prevented episodes, were classified as partially successful.

A total of 28% of all ablatees were not prescribed any medication to be taken during the first few months after the procedure. Only 13% of successfully ablated afibbers continued on drugs after the first 3 months (usually beta-blockers), but 79% of partially successful and 52% of failed ablatees continued beyond 3 months.

The following table shows the type of antiarrhythmics/blockers used **IMMEDIATELY AFTER** the procedure(s).

TABLE 18
Antiarrhythmic/blocker use after procedure

	# in Group	Complete Success,%	Partial Success,%	Failure,%
Antiarrhythmics/blockers				
None	91	31	12	18
Flecainide (Tambocor)	88	24	27	20
Propafenone (Rythmol)	34	6	23	8
Disopyramide (Norpace)	8	1	0	3
Amiodarone (Cordarone)	24	2	0	9
Dofetilide (Tikosyn)	12	1	8	4
Sotalol (Betapace)	45	11	8	11
Beta-blocker	76	19	19	18
Calcium channel blocker	32	6	4	10
Total	410	100	100	100

Please note that several respondents took more than one medication. Thus, the total number in the group (410) is larger than the number of respondents (358).

The most popular post-procedure medication was flecainide, followed by beta-blockers and sotalol. A combination of flecainide and beta-blockers was also quite popular.

Recovery Time

The time it took to recover fully from a procedure is presented in the table below.

TABLE 19
Recovery time

	# in Group	Complete Succ.,%	Partial Succ.,%	Fail.,%	Aver.,%
Time to full recovery					
Less than 1 month	96	28	29	33	31
1-2 months	84	26	25	28	27
2-3 months	54	24	8	14	17
More than 3 months	75	21	38	25	24
Total	309	100	100	100	100

About 58% of all ablatees recovered fully in less than 2 months, but 24% took longer than 3 months to return to their pre-ablation level of stamina.

RF Ablation – Patient Outcome

This evaluation of final outcome of RF ablations includes 237 afibbers whose last reported procedure was a RF ablation of the left atrium for the purpose of curing atrial fibrillation. All respondents included here reported their afib status at least six months after their last procedure. The average observation period after the last ablation was 16 months with a range of six months to four years.

One hundred and thirty-four of the 237 afibbers were no longer experiencing episodes and were no longer on antiarrhythmics (complete success). Twenty-six were also afib-free, but only with the help of antiarrhythmics (partial success). The remaining 77 were still experiencing episodes with or without the use of antiarrhythmics.

Thus, the overall outcome after an average 1.5 procedures per patient was as follows:

	Objective Judgment	Subjective Judgment
Complete success	57%	65%
Partial success	11%	16%
Failure	32%	19%
TOTAL	100%	100%

The subjectively judged success rate is clearly higher than actually warranted by the actual outcome. It is likely that some afibbers considered their procedure a success even though they still experienced episodes, but generally of lesser frequency and/or shorter duration. Many also were less sensitive to former triggers adding to the feeling of success.

Continued Stroke Prevention

As shown in the table below 49% of afibbers continued a stroke prevention program after completion of their procedures.

TABLE 20
Continuing stroke prevention

	# in Group	None,%	Warfarin,%	Aspirin,%	Natural Remedies,%
Stroke prevention					
Complete success	134	69	4	10	17
Partial success	26	31	35	15	19
Failure	77	27	38	10	25
Total	237	51	19	11	20

Not too surprisingly, most (96%) of afibbers whose final procedure had been completely successful did not continue with warfarin. Seventeen percent did, however, continue with a natural stroke prevention program, and 10% continued with a daily aspirin. Seventy-one percent of afibbers whose final procedure had failed continued with a stroke prevention program with most (38%) using warfarin, but a significant 25% used a natural remedy. The most commonly used natural supplements used for stroke prevention were fish oil, nattokinase, vitamin E, and garlic.

Trigger Avoidance

While 78% of successful ablatees no longer needed to avoid previous triggers, only 19% of those having undergone an unsuccessful procedure were so lucky. Nevertheless, it would seem that any ablation, whether successful or not, does help to reduce trigger sensitivity.

TABLE 21
Trigger avoidance

	# in Group	Complete Succ.,%	Partial Succ.,%	Failure,%	Aver.,%
Trigger avoidance					
No longer necessary	131	78	46	19	55
Still necessary	37	5	12	35	16
Much less sensitive	37	8	19	28	16
Uncertain	32	9	23	18	13
Total	**237**	**100**	**100**	**100**	**100**

Post-Procedure Afib Episodes

Forty-nine paroxysmal respondents whose ablation had not been successful had kept track of their episode frequency prior to and after

their procedure(s). The median number of episodes prior to the first procedure was 25 (over a 3-month period) compared to 5 after the last procedure. This is clearly a very noticeable improvement and is statistically extremely significant ($p < 0.0001$). Seventy-three percent of the 49 respondents saw a substantial decline in their episode frequency; six percent saw no change while 21% experienced an increase. Two persistent and 2 permanent afibbers converted to paroxysmal after their procedure. The median duration of episodes decreased from 8 hours to 4 hours and this change was again statistically significant ($p= 0.002$). Most (63%) saw a decrease in their episode duration, 16% experienced no significant change and 25% saw their episode duration increase. The total afib burden (episode frequency times duration) over a 3-month period decreased from a median of 178 hours to 21 hours, again a highly significant decrease ($p < 0.0001$). Overall 65% of respondents saw a 50% or better decrease in their afib burden, but the remaining 35% saw an, often substantial, increase in the time they spent in afib.

Use of Pill-in-the-Pocket Approach

Twenty-five percent of afibbers still experiencing episodes used the on-demand approach in an attempt to shorten their duration.

Changes in Heart Rate

Changes in resting heart rate after RF ablation were quite common.

TABLE 22
Post-procedure heart rate change
Persistent and paroxysmal afibbers

	# in Group	Complete Success,%	Partial Success,%	Fail.,%	Aver.,%
Heart rate change					
Increase	119	69	46	39	56
No change	58	25	33	28	27
Decrease	36	6	21	33	17
Total	**213**	**100**	**100**	**100**	**100**

The most frequent post-procedural change was an increase in heart rate (experienced by 56%). This increase was most common among afibbers who had undergone successful procedure(s) (69%) and least common among those whose procedures had failed to cure the afib (39%). This difference was statistically significant ($p=0.04$). A decrease in heart rate was rare among successfully ablated afibbers (6%), but more common

(33%) among those whose procedure had failed. The median increase in average resting heart rate was 10 bpm for paroxysmal afibbers (1-30 bpm) who had undergone a successful ablation.

The reason for the increase in heart rate after an ablation is that a significant portion of vagal nerve endings is damaged during the RF ablation procedure. Because the vagal nerves imbedded in the myocardium serve as "speed controllers" counteracting the adrenergic influence, a reduction in the number of effective vagal nerves would be expected to lead to an increased heart rate. Thus, it is possible that a more "aggressive" ablation, as indicated by a higher heart rate after the procedure, is more likely to be successful. However, this is speculation on my part and obviously assumes that the "aggression" is directed at the right spots on the atrium walls and pulmonary vein ostia.

It is generally assumed that the increase is temporary, however, this may not always be the case. A mini-survey of 25 afibbers who had experienced a significant increase (average of 20 bpm) in post-procedure resting heart rate revealed that for 13 out of 25 respondents (52%) the heart rate was still significantly elevated a year or more after the last procedure. From personal experience I know that a substantial increase in heart rate (to 90 bpm or higher) can be very uncomfortable, so it is to be hoped that afib researchers will eventually address this problem.

Quality of Life

Although the main concern of the medical profession when it comes to lone atrial fibrillation is stroke risk, the overwhelming concern of the patient is quality of life. As all afibbers know, being in permanent afib or awaiting the next episode in a state of anxiety has a devastating effect on ones quality of life and radically changes the life of those nearest and dearest to us.

Considering quality of life improvement rather than strictly success or failure of RF ablation procedures, it becomes clear that even a failed ablation may improve life quality. The average complete success rate found in this survey (after an average 1.5 procedures) is 57%. Adding to this partial success (where afib is kept at bay with antiarrhythmics) brings the percentage of afibbers whose lives have been improved through RF ablation to 68%. Further considering that about 65% of ablatees whose procedure failed still reduced their afib burden by at least 50% brings one to the conclusion that RF ablation, whether successful or not, is likely to improve quality of life in close to 90% of those undergoing the procedure. A significant portion of the remaining 10% may however, see a worsening of their condition or may experience a serious adverse event.

Summary – RF Ablation

- The overall objectively-rated complete success rate (no afib, no drugs) for 237 afibbers after an average of 1.5 RF ablations was 57%; partial success was achieved in 11% of cases, and 32% of all afibbers who underwent one or more RF ablations continued to experience AF episodes.

- The subjective judgment of success by ablatees was somewhat more favourable with 66% feeling that the end result was total success, 15% claiming partial success, and 19% judging their procedures as a failure.

- The average objectively rated complete success rate for a single RF ablation procedure was 38%, that of partial success 7%, and that of failure 55%.

- Considering a 50% or greater reduction in afib burden (frequency x duration) as an indicator of improvement, it is estimated that close to 90% of RF ablations were ultimately successful in improving quality of life.

- Forty-one percent of 358 RF ablation procedures were accompanied by an adverse event, the most common (17%) being temporary hematoma in the thigh area. Left atrial tachycardia was also a fairly common adverse effect (12%), but resolved by itself in about 50% of cases. Stroke and TIA were rare at 0.6% and 0.8% respectively. About two-thirds of all adverse events were fully resolved at the time the survey was completed. Successful ablations were much less likely to be accompanied by an adverse event than were unsuccessful ones.

- There were no significant differences in success and adverse event rates between a first and subsequent RF ablations, perhaps indicating that the technical difficulty in performing them is pretty much the same.

- The majority (75%) of respondents experienced AF episodes at least weekly prior to their ablation.

- There was no evidence that age at diagnosis and ablation, gender, years of afib, or type of paroxysmal afib affected the

outcome to a significant degree. However, more frequent episodes were associated with a lower success rate. Underlying heart disease, mitral valve prolapse, and permanent afib showed a statistically non-significant trend towards a higher failure rate.

- The most successful procedure for the period 2005-2006 was the pulmonary vein antrum isolation procedure (Natale method) with a combined single procedure complete and partial success rate of 75%. The segmental PVI (Haissaguerre method) was the second-most successful procedure with a combined single procedure success rate of 45%.

- There was no indication that anti-inflammatories, potassium or vitamin supplementation affected the outcome of the procedure and no evidence that potassium supplementation reduced the incidence of increased post-procedure ectopic activity or episodes of AF.

- Increased ectopic activity continuing beyond 3 months post-ablation was associated with an increased incidence of failure.

- A significant majority (64%) of afibbers who had a completely successful ablation experienced no AF episodes at all after the procedure. Only 12% of those "doomed to failure" experienced no episodes at all after their procedure. No completely successful ablatees experienced episodes for more than 3 months after the procedure, while 56% of unsuccessful ablatees did so. Thus, if increased ectopic activity and AF episodes continue beyond 3 months the procedure is almost certainly a failure. On the other hand, if no AF episodes occur during the first month then the procedure is likely to be a success.

- Almost 60% of ablatees recovered fully in less than 2 months, but 24% took longer than 3 months to return to their pre-ablation level of stamina.

- Most (96%) of afibbers who had a completely successful ablation did not continue with warfarin, but 17% of them continued to use natural stroke prevention remedies such as fish oil, nattokinase, vitamin E and garlic. Ten percent took a daily aspirin for stroke prevention. In contrast, 38% of ablatees with a failed procedure continued on warfarin.

- While 78% of successful ablatees no longer needed to avoid previous triggers, only 19% of those having undergone an unsuccessful ablation were so lucky. Nevertheless, it would seem that any ablation, whether successful or not, does help to reduce trigger sensitivity.

- Even an unsuccessful ablation resulted in a significant reduction in episode frequency in 73% of cases and in 63% of cases was associated with a significant decrease in episode duration. Overall, 65% of unsuccessfully ablated patients experienced a 50% or better decrease in their afib burden while the remaining 35% saw an, often substantial, increase in the time they spent in afib.

- A post-ablation increase in heart rate was a common occurrence. This phenomenon was more prevalent among successful ablatees (69%) than among those whose ablation had failed (39%). This may indicate that a more aggressive approach (increased destruction of vagal nerve endings) is associated with a better outcome.

Performance Rating

Previous ablation/maze surveys have all arrived at the same conclusion that the most important factor in determining the outcome of a RF ablation is the skill and experience of the EP performing it. In order to provide some guidance in regard to the chance of undergoing a successful and safe ablation at a particular institution, I have developed a Performance Rating scheme. This rating takes into account the success rates and adverse event rates reported by afibbers treated at specific institutions and by specific EPs. The factors entering into the Performance Rating are as follows:

Success Score

- Completely successful ablation — score = 10
- Partially successful ablation — score = 5
- Failed ablation (continuing afib episodes) — score = 0

Adverse Events Score

- No adverse events — score = 0
- Hematoma — score = -2

- Minor reversible events score = -2
- Right atrial flutter score = -5
- Left atrial flutter score = -5
- Supraventricular tachycardia score = -5
- Moderate PV stenosis score = -5
- Pericarditis score = -5
- TIA score = -5
- Phrenic nerve damage score = -10
- Severe PV stenosis score = -10
- Tamponade score = -10
- Atrial/esophageal fistula score = -10
- Other life-threatening events score = -10
- Minor stroke score = -10
- Events causing permanent disability score = -20

The Outcome Factor adds the scores (for degree of success and adverse events) for each RF ablation and the Performance Rating then averages these outcome factors for each individual institution. For example, if a procedure is fully successful with no adverse events, than the outcome factor is +10. If a procedure is a failure and accompanied by the creation of left atrial flutter, then the outcome factor is –5. The primary performance rating does not take into account that a large number of adverse events are resolved within a few months after the procedure. To acknowledge this, an adjusted performance rating is also shown in which the effect of resolved adverse events have been ignored.

Please note that in this evaluation of 358 single RF ablation procedures a procedure is not considered a failure unless followed by another RF ablation or continued afib episodes. The subsequent occurrence of left or right atrial flutter or tachycardia is treated here as an adverse event and not as an ablation failure.

It is clear that a performance rating is not very indicative in cases where just one or two procedures have been performed. Thus, performance ratings have only been established for institutions that had reports on 6 or more procedures. Based on the Adjusted Performance Rating (combination of success and safety) the various institutions stack up as follows:

TABLE 23
Procedure performance rating
(6 or more procedures)

Rank	# of Proced.	Institution
1	10	University of Michigan
2	58	Cleveland Clinic, OH
3	26	Marin General Hospital, CA
4	7	University of Pennsylvania
5	37	Hopital Cardiologique du Haut Leveque, Bordeaux
6	11	Medical University of South Carolina (MUSC)
7	7	New York University (NYU) Medical Center
8	7	Freeman Hospital, Newcastle, UK
9	10	Royal Jubilee Hospital, Victoria, Canada
10	6	Good Samaritan Hospital, Los Angeles
11	10	University of California at San Diego
12	9	St. Paul's Hospital, Vancouver, Canada
13	6	Centinella Hospital (Pacific Rim Electrophysiology), Inglewood, CA
14	6	Hollywood Hospital, Perth, Australia
15	9	St. Barts and London Bridge, London, UK
16	6	Massachusetts General, Boston
17	7	Brigham & Women's Hospital, Boston

The first 10 institutions in the above table account for 50% of all ablation procedures performed; their performance is evaluated in detail below (ranked by complete success rate).

TABLE 24
Procedure success
Top-ranked institutions

		# of	Perform. Rate.		Success Rate,%			Adv.
Rank	Institution	Proced.	Adju.*	Prim.	Compl.	Part.	Fail.	Ev,%
1	Cleveland Clinic	58	6.7	5.2	69	5	26	40
2	Marin General	26	5.6	5.0	62	12	26	35
3	Bordeaux	37	4.3	2.7	49	0	51	41
4	MUSC	11	4.1	1.9	45	9	46	55
5	U of Pennsylvania	7	5.0	3.7	43	14	43	43
6	Freeman Hospital, UK	7	3.6	2.6	43	0	57	43
7	U of Michigan	10	7.4	7.2	40	10	50	50
8	Royal Jubilee, Canada	10	3.0	1.6	40	0	60	30
9	Good Samaritan, LA	6	2.9	2.3	33	0	67	17
10	NYU	7	3.6	2.7	29	14	57	29
	Average/Total	**179**			**54**	**6**	**40**	**39**

***resolved adverse events not included**

Please note that the adverse event rate includes all adverse events reported by patients. Over 70% of these events resolved on their own.

The electrophysiologists performing the procedures in the above 10 institutions are as follows:

Institution	Electrophysiologists
Cleveland	Drs. Andrea Natale, Walid Saliba, Robert Schweikert, Patrick Tchou
Marin General	Drs. Andrea Natale, Steven Hao
University of Pennsylvania	Drs. David Callans, Frank Marchlinski
Bordeaux	Drs. Michel Haissaguerre, Pierre Jais
MUSC	Dr. Marcus Wharton
Freeman, UK	Dr. Stephen Furniss
U Mich	Drs. Fred Morady, Frank Pelosi, Hakan Oral
Royal Jubilee	Drs. Richard Leather, Larry Sterns
Good Samaritan	Drs. Anil Bhandari, Neala Hunter
NYU	Dr. Larry Chinitz

The average procedural success and adverse event rates for the remaining 179 procedures are given below. The procedures have been grouped by the institution at which they were performed.

Group 1 contains 11 institutions not included in the top 10 for which reports of 4 to 6 procedures were available.
Group 2 contains 6 institutions for which reports of 3 ablation procedures were available
Group 3 contains 66 institutions for which reports of less than 3 procedures were available.

TABLE 25
Procedure success
Other institutions

	# in	Perform. Rating		Success Rate, %			Adverse
Institution	Group	Adj.	Prim.	Complete	Partial	Fail.	Event,%
Group 1	71	2.1	1.1	20	6	74	45
Group 2	18	1.7	0.2	22	6	72	28
Group 3	90	1.8	0.4	23	12	64	44
Total	**179**	**1.8**	**0.4**	**22**	**9**	**69**	**43**

The above statistics are indeed sobering. Undergoing a single RF ablation procedure other than at the 10 top-ranked institutions is associated with an **average** complete success rate of 22%, a partial success rate of 9%, and a failure rate of 69%. This is accompanied by an **average** adverse event rate of 43%.

Despite the overall bleak picture, there are some good performers in Groups 1 and 2, bearing in mind that the number of procedures upon which this conclusion is based is extremely limited.

TABLE 26
Good performers – Groups 1 and 2

Institution	# of Proced.	Success Rate, % Compl.	Partial	Fail.	Adverse Event Rate,%
Group 1					
Aurora Heart Inst.	4	25	50	25	25
Loyola Medical	5	40	0	60	40
Johns Hopkins	5	40	20	40	75
Group 2					
Mayo Clinic	3	67	0	33	33
Univ. of Alabama	3	33	33	33	33

Aurora Heart Institute, Milwaukee, MN	EP: Dr. Jasbir Sra
Loyola Medical Center, Maywood, IL	EP: Dr. David Wilber
Johns Hopkins Hospital, Baltimore, MD	EP: Drs. Hugh Calkins and Ronald Berger
Mayo Clinic, Rochester, MN	EP: Dr. Douglas Packer
University of Alabama, Birmingham, AL	EP: Dr. Neal Kay

Combined Procedure Success Rate

Combining the top ten with Groups 1, 2, and 3 yields the following total procedural success rates.

TABLE 27
Combined procedural success
All institutions

Institutions	Patients	Complete	Partial	Failure	Rate,%
Top 10	179	54	6	40	39
Group 1	71	20	6	75	45
Group 2	18	22	6	72	28
Group 3	90	23	12	64	44
Total	**358**	**38**	**7**	**55**	**41**

Final Success Rate

The ultimate measure of success for the individual patient is, of course, whether or not they are cured of afib irrespective of how many procedures it takes. This part of the evaluation includes 237 afibbers whose last reported procedure was a RF ablation of the left atrium for the purpose of curing AF. All respondents included here reported their final afib status at least 6 months after their last procedure. Overall final results for the 10 top-ranked institutions are presented below.

TABLE 28
Final performance rating
Top-ranked institutions

				Final Success Rate, %		
Institution	Individual Patients	# of Proc.	Repeat Rate,%	Comp. Succ.	Part. Succ.	Fail.
Bordeaux, France	22	37	37	82	0	18
Cleveland Clinic, OH	49	58	18	78	6	16
Marin General, CA	21	26	18	76	14	10
MUSC	7	11	22	71	14	14
Good Samaritan, LA	3	6	20	67	0	33
NYU	3	7	40	67	33	0
U of Pennsylvania	5	7	40	60	20	20
U of Michigan	7	10	25	57	14	29
Royal Jubilee, Canada	8	10	11	50	0	50
Freeman, Newcastle, UK	6	7	17	50	0	50
Total	**131**	**179**	**23**	**72**	**8**	**20**

NOTES:
Ranking is by highest % of patients achieving complete elimination of afib without use of antiarrhythmics.
Repeat rate is calculated as # of repeat ablation divided by # of initial procedures performed at the institutions.
First procedure on patients who came to the institution from another one is not counted as a repeat.

5 patients came to the Cleveland Clinic from other institutions for their follow-up.
4 patients came to the Bordeaux Clinic from other institutions for their follow-up.
2 patients came to Marin County from another institution for their follow-up.
1 patient came to U of Michigan from another institution for their follow-up.

The best chance of ensuring a successful outcome is by undergoing the procedure(s) at one of the top 3 institutions – Hopital Cardiologique du Haut Leveque in Bordeaux, France, the Cleveland Clinic in Ohio, and Marin General Hospital in California. The complete success rates there are 82%, 78% and 76% respectively (difference not statistically significant). The complete + partial success rates are 82%, 90% and 84% respectively – impressive indeed.

The excellent ultimate success rate in Bordeaux is, unfortunately, associated with a high repeat rate (37%). This drawback is somewhat ameliorated by the Bordeaux practice of performing most required "touch-ups" within a week or two following the initial procedure. The lowest repeat rate (11%) is associated with the Royal Jubilee Hospital in Victoria, Canada, no doubt reflecting the inordinately long waiting times within the Canadian healthcare system.

The average complete success rate in other institutions (Groups 1, 2 and 3) was 37% or about half that achieved, on average, at the 10 top-ranked institutions. The failure rate was 48% as compared to 20% at the top 10.

TABLE 29
Final procedural success
Other institutions

	Individual	Repeat	Final Success Rate, %		
Institutions	Patients	Rate, %	Compl.	Partial	Failure
Group 1	40	34	35	10	55
Group 2	9	20	44	11	44
Group 3	57	20	37	19	44
Total	**106**	**25**	**37**	**15**	**48**

Combining the results for the 237 patients and 358 procedures yields an average complete success rate of 57%, a failure rate of 32%, and an average repeat rate of 24%.

TABLE 30
Final procedural success
All institutions

	Individual	Repeat	Final Success Rate, %		
Institutions	Patients	Rate, %	Complete	Partial	Failure
Top 10	131	23	72	8	20
Group 1	40	34	35	10	55
Group 2	9	20	44	11	44
Group 3	57	20	37	19	44
Total	**237**	**24**	**57**	**11**	**32**

Comparison With Other Surveys

At least 5 surveys of PVI procedure success rates have now been published. One, the Cappato Study, published in 2005 involved 8745 patients treated at 90 different institutions around the world.[2] The outcome experience at the Cleveland Clinic, Ohio was presented for 323 patients who underwent a PVI for drug-resistant AF.[3] The University of Michigan experience (755 patients) was presented in a 2006 paper by *Oral, et al*[4], while Johns Hopkins Hospital outlined their PVI outcomes for 200 PVI procedures in a 2006 study authored by *Cheema, et al*.[5] Finally, also in 2006, a group of Danish electrophysiologists outlined their results of a study involving 100 patients who underwent a PVI using either the Haissaguerre or Pappone method.[6]

A comparison of the results of these surveys and my own current survey is presented in the tables below. Table 31 summarizes the results of initial procedures, while Table 32 summarizes final outcome, that is, outcome after repeat ablations as required.

TABLE 31
Outcome after initial procedure

Survey	Institutions	# of Proced.	Initial Success, % Comp.	Part.	Fail.	Observ., mos.
TOP-RANKED INSTITUTIONS						
Bhargava[3]	Cleveland Clinic, OH	323	71	0	29	6
Afibbers.org	Cleveland Clinic, OH	58	69	5	26	6
Afibbers.org	10 top-ranked	179	54	6	40	6
OTHER INSTITUTIONS						
Nilsson[6]	Copenhagen Univ.	100	17	0	83	3
Afibbers.org	Other	179	22	9	69	6

There are, unfortunately, only 2 studies, other than the afibbers.org survey, which have provided data for initial procedure outcome. Complete success after one ablation varies from 17% to 71% with the afibbers.org survey finding a rate of 54% for the 10 top-ranked institutions and 22% for other institutions.

TABLE 32
Outcome after final procedure

Survey	Institutions	# of Patients	Initial Success, % Comp.	Part.	Fail.	Repeat Rate,%	Observ. mos.
TOP-RANKED INSTITUTIONS							
Bhargava[3]	Cleveland, OH	323	83	0	17	12	12
Afibbers.org	Cleveland, OH	49	78	6	16	18	6
Cappato[2]	Top-rank (world)	3244	64	16	20	27	12
Oral[4]	Univ. Michigan	755	73	?	?	?	12
Afibbers.org	10 top-ranked	179	72	8	20	23	6
OTHER INSTITUTIONS							
Cappato[2]	Other (world)	5501	45	29	26	27	12
Cheema[5]	Johns Hopkins	200	41	11	48	32	12
Nilsson[6]	Copenhagen	100	44	?	?	74	12
Afibbers.org	Other	106	37	15	48	25	6

The final outcome results are somewhat better documented with complete success rates varying from 83% to 41% with the afibbers.org survey finding an average rate of 72% for the 10 top-ranked institutions and 37% for the other institutions. It is comforting to note that the success rates published by the Cleveland Clinic [3] are very close to those found in our own survey for this institution.

Conclusion

I have made every effort to ensure that the calculations and conclusions made in this survey are correct. I have observed good internal consistency in the data and am comforted by the fact that the success rates found in this 2006 LAF Ablation/Maze Survey agree well with those found in published studies. The LAF survey is based on a total of 358 procedures performed on 237 individual patients, not an overly large number, but enough to draw reasonably valid conclusions in general terms. Where the survey results become less “solid” are in the evaluation of the success rates of individual institutions. The rating of the top 3 institutions, Cleveland Clinic, Ohio, Hopital Cardiologique du Haut Leveque, Bordeaux, and Marin General Hospital, California are probably reasonably indicative since they are based on almost 100 patients and 120 procedures. A ranking based on just 4 to 6 procedures per institution is clearly not very significant and it is quite possible that a large sample would produce different results.

However, based on conversations with hundreds of afibbers, perusal of hundreds of articles relating to RF ablation, and my own instinctual feeling, I have no hesitation in recommending the 10 top-ranked

institutions presented in this survey. There may well be other institutions and individual EPs that deserve top ranking, but I have no evidence that this is indeed the case.

To summarize, the inescapable conclusion of this survey is that RF ablation for atrial fibrillation is still an emerging technology and that a half decent chance of success can only be expected in top-rated institutions. To go anywhere else, at this point in time, will no doubt lead to disappointment and perhaps serious adverse effects. That said, it is also clear that most, probably as many as 90%, RF ablations result in a significant improvement in quality of life whether they are completely successful or not. This also means that 10% of all afibbers embarking on the ablation path can expect no improvement and in a significant proportion, a worsening of afib or a major adverse event.

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Outcome of Other Procedures

Evaluation of Background Data

Seventy-five afibbers responded to this part of the survey and provided details of a total of 86 procedures. Most respondents (78%) had a surgical procedure or a flutter, AV-node, or cryoablation as their first procedure with the remaining 22% having had an unsuccessful RF PVI procedure before undergoing one of the above-mentioned procedures. Fourteen respondents (19%) had a second procedure, 12% had a third, and 7% had a fourth or fifth procedure.

The procedures were distributed as shown in the following table.

	Number of Procedures				
Procedure	1st	2nd	3rd	Further	Total
Cryoablation	4	2	0	0	6
Maze procedure	9	1	2	1	13
Mini-maze procedure	19	1	2	1	23
Right atrial flutter	18	5	2	1	26
Left atrial flutter	2	3	2	1	8
AV node + pacemaker	6	2	1	1	10
Total	**58**	**14**	**9**	**5**	**86**

Demographics	Male	Female	Total
Gender distribution	80%	20%	100%
Average (median) age*	59	60	59
Age range (present)	42-72	45-79	42-79
AF confirmed by diagnosis	90%	87%	89%
Underlying heart disease	19%	20%	19%
Mitral valve prolapse	9%	13%	10%
Mitral valve regurgitation	10%	7%	10%
Median age at diagnosis	49	49	49
Age range (at diagnosis)	20-68	14-73	14-73
Median age at last procedure	58	59	58
Age range (last procedure)	39-71	43-74	39-74

* at time of completing questionnaire

There are no significant differences between males and females as far as demographic variables are concerned. However, the incidence of underlying heart disease in this group of 75 afibbers is twice as high as the incidence among the 335 afibbers discussed in Part 1 of the survey.

A total of 61 respondents had provided detailed information regarding their type of AF (adrenergic, mixed, vagal). The majority of respondents (79%) had paroxysmal afib. Mixed (random) AF was the most common type of paroxysmal AF at 63% followed by vagal at 28%, and adrenergic at 9%. These percentages are similar to those found in the overall group covered in Part 1.

Most paroxysmal afibbers (82%) experienced episodes at least once a week and 31% had episodes every day. Only 10% of those seeking a cure through catheterization or surgical procedures had episodes less frequent than once a month. This indicates that most afibbers only opt for a procedure when the frequency becomes intolerable or permanent AF becomes a reality.

The median duration of paroxysmal episodes was 10 hours with a range from 1 to 60 hours.

The majority of respondents (93%) were taking one or more drugs on a continuous basis to reduce their episode frequency and duration, or ameliorate the effects of their permanent afib. The most popular drug was amiodarone used by 23% of respondents, sotalol used by 17%, and beta-blockers by 14%.

Catheterization Procedures

Right Atrial Flutter Ablation

Twenty-six respondents had undergone a right atrial flutter ablation either as an initial procedure (18 respondents) or as a follow-up procedure after a PVI, mini-maze or unsuccessful right atrial flutter ablation.

Atrial flutter and AF are similar in that they both involve abnormal, sustained, rapid contractions of the heart's upper chambers (atria). In atrial flutter the atria contract 220 to 350 times a minute in an orderly rhythm. In AF the rate of contraction may be as high as 500 beats/minute and the rhythm is totally chaotic. The two arrhythmias can both occur as a result of an enlarged atrium or in the aftermath of open-heart surgery, but the mechanism underlying them is quite different.

Nevertheless, they can coexist in the same patient and one may convert to the other.

There are two major types of atrial flutter – common or type 1 and atypical or type 2 flutter. Type 1 flutter is by far the most common (65-70% of all cases) and is characterized by a specific conduction abnormality in the lower right atrium. Type 2 or atypical flutter, on the other hand, has no easily discernible origin and is therefore harder to deal with.

Because the location of the origin of atrial flutter, at least in the common type, is so well known and consistent from patient to patient radio frequency catheter ablation can be used with considerable success to permanently eradicate atrial flutter. Unfortunately, this procedure is unlikely to cure AF, which may often coexist with atrial flutter. There is also some evidence that atrial flutter patients who have a successful ablation increase their risk of later developing AF by 10-22%. So undergoing RF ablation for atrial flutter may not remove the necessity of dealing with AF.

Because of the close connection between AF and atrial flutter, it was quite common, in the early days of ablation, to perform an atrial flutter ablation in the hope that it would cure the AF. The atrial flutter ablation involves only the right atrium so there is no need to pierce the septum to the left atrium as is done in a PVI.

After the 1998 discovery that 80-90% of paroxysmal episodes originate in the left atrium near the pulmonary veins, the use of the right atrial flutter ablation in an attempt to cure AF became less common, but the procedure is still used as a first attempt in patients with a combination of AF and flutter. It is, of course, also used in patients suffering from right atrial flutter only.

Only one respondent out of the 18 first procedures reported that the procedure had cured their afib; thus, in 94% of cases the right atrial flutter ablation was unsuccessful in eliminating afib. It did, however, eliminate the flutter component in 3 patients who experienced both flutter and afib. The procedure was also successful in eliminating flutter in the 3 patients who developed the condition after a PVI or mini-maze.

The majority (65%) experienced no adverse events relating to their procedure, but 11% did experience hematoma in the thigh/groin area, and 11% reported the development of post-procedural left atrial flutter or tachycardia.

A significant increase in resting heart rate post-procedure was reported by only one respondent.

Thirteen (72%) of the 18 respondents who had a right atrial flutter ablation as their first procedure went on to undergo a radiofrequency PVI as their next procedure. It is interesting that only one of the 18 right atrial flutter procedures was performed at a top-ranked institution.

Conclusion – Right atrial flutter ablations are generally successful in eliminating right atrial flutter, but only very rarely (6% of cases) do they cure AF as well.

Left Atrial Flutter Ablation

Left atrial flutter is considerably less common than right atrial flutter, but can occur as a side effect of a PVI procedure or mini-maze. Post-procedural left atrial flutter may disappear on its own over a 6-month period or so, but some cases require a repeat ablation to fix the flutter.

Two respondents had left atrial flutter as their primary condition and one was successfully ablated for this, while at the same time eliminating afib.

Six respondents developed left atrial flutter after their PVI or mini-maze and 5 were successfully ablated for the condition. Most (63%) experienced no post-procedural adverse effects, but 2 respondents experienced hematoma. Two also saw a significant increase in resting heart rate after the procedure.

Conclusion – Left atrial flutter can occur as a sequel to a PVI or mini-maze. In most cases it disappears on its own, but in some cases a repeat ablation is necessary to correct the flutter. This procedure (based on a very small sample size) is usually successful.

Cryoablation

The cryoablation procedure is similar to the standard RF ablation procedure except that the ablation catheter is nitrogen-cooled rather than electrically heated. The advantage of cryoablation is that it reduces procedure stroke risk and does not create pulmonary vein stenosis even if the ablation is done inside the pulmonary veins.

Six afibbers, all male, had undergone cryoablation – 4 as a first procedure and 2 as a second procedure, one following a failed cryoablation attempt and the other following a RF ablation. Only one of the 4 original procedures was successful, while both the follow-up procedures resulted in elimination of AF. Thus, based on this very small sample, the procedural success rate of cryoablation PVIs is 50%. Three of the 6

procedures were not accompanied by any adverse effects, but 2 patients reported hematomas and 1 reported the development of both left and right atrial flutter. No respondents reported any significant change in resting heart rate after the procedure.

Two of the successful procedures were performed by Drs. Rodriguez and Timmermanns in Maastricht, The Netherlands and one by Dr. Gregory Feld at the University of California at San Diego.

Conclusion – It is clearly not possible to conclude anything definitive about the effectiveness of cryoablation based on a sample of six. However, it does appear that post-procedural heart rate elevation is not a problem with cryoablation.

AV Node Ablation + Pacemaker Implantation

Palpitations, elevated heart rate, and other major symptoms of an atrial fibrillation episode are associated with rapid and irregular contractions of the left ventricle rather than with the actual "quivering" of the left atrium. So, although the root cause of AF is found in the left atrium, its effects can, to a large extent, be eliminated by isolating the AV node (the ventricular beat controller) from impulses originating in the left atrium and feeding the ventricles their "marching orders" from an implanted pacemaker. AV node ablation + pacemaker installation is a relatively simple procedure and is therefore mostly successful. It does also provide substantial symptom relief allowing afibbers to live a fairly normal life. Nevertheless, the procedure is considered a last resort for the following reasons:

- It does nothing to stop the fibrillation in the atrium and may, in fact, hasten the progression to permanent AF.
- It does not reduce stroke risk as do PVIs and maze procedures. Thus, the patient must continue on warfarin for life.
- It makes the patient dependent on the pacemaker. If it or the leads malfunction, or the battery runs out the patient may die.
- It does little to prevent the fatigue and reduced exercise capacity felt by some afibbers during an episode.

Ten afibbers (30% female) had undergone the AV node ablation + pacemaker implantation. Six had it as their first procedure and the other 4 after failed maze or PVI procedures. Three out of the 10 respondents (30%) had underlying heart disease, a proportion substantially higher than the 10% observed in the overall group.

The members of the AV node ablation group also tended to have been diagnosed later than the overall group (age 56 vs. 48 years) and had their last procedure later in life (age 62 vs. 56 years). Forty percent of the group was on amiodarone vs. only 11% in the overall group.

Eight of the 10 patients felt that their procedure had been successful, even though it gave symptomatic relief only. The remaining 2 were not satisfied with the outcome and 1 went on to have a circumferential PVI (partially successful), while the other underwent a successful maze procedure. It is worth noting that none of the AV node ablation procedures were performed at top-ranked institutions.

None of the patients reported adverse events. The pacemaker determined the resting heart rate (60-80 bpm).

Conclusion – Based on this small sample of 10 respondents, it is clear that AV node ablation + pacemaker installation is usually a successful procedure and provides significant symptomatic relief even though it does not cure AF. Nevertheless, it is still the procedure of last resort.

Surgical Procedures

Maze Procedure

Thirteen respondents reported having undergone a full maze procedure – 9 as their initial procedure, 3 after failed PVIs, and 1 after an unsatisfactory AV node ablation + pacemaker implantation. As shown in the table below the maze group differed significantly from the total group of 335 afibbers in several respects.

Variable	Total Group	Maze Group
No. in group	335	13
Age at diagnosis, yrs.	48	41
Underlying heart disease, %	10	38
Permanent AF, %	19	45
Paroxysmal with daily episodes, %	22	67
Amiodarone usage, %	11	33

It is clear from the above comparison that respondents undergoing the maze procedure had a higher incidence of underlying heart disease and permanent afib than did the total group. This makes sense since the full

maze procedure really would be "overkill" for a true lone afibber (no underlying heart disease) with paroxysmal AF.

Three out of the 13 procedures were cryo-maze. In other words, the maze lesions were applied with a nitrogen-cooled catheter rather than with RF energy or the cut-and-sew approach. Only one of these procedures was successful. It is, of course, problematical, perhaps even unwise, to pronounce on success rates with only 13 procedures in the sample. Nevertheless, as with other procedures, there would appear to be a definite trend for procedures performed by top-ranked cardiac surgeons to be more successful than those performed by less prominent ones.

	# of	Success Rate, %			Adv.Event
Surgeon	Procedures	Complete	Partial	Failure	Rate,%
Top-ranked	6	67	17	17	40
Other	7	14	14	72	71
Total	13	38	15	46	58

It is, of course, open to argument who is and who is not "top-ranked", but I do believe that the surgeons in the above group (Drs. Damiano, Geiss, Gillinov and McCarthy) would all fall in this category.

The relatively low complete success rate for even top-ranked surgeons is unexpected. The success rate for the full maze procedure is often quoted at 90% or better. However, a recent report issued by the Washington School of Medicine, Barnes-Jewish Hospital (Dr. Damiano's "home base") arrived at a complete success rate of 67% and a partial success rate of 24% for an overall success rate of 91%.[1]

It would thus seem that success rates for the maze procedure include patients who are afib-free, but only with the help of antiarrhythmics (at the 12-month check-up). Using this measure the success rate of top-ranked surgeons in our survey was 84%. An overall average success rate of 84% was also observed in a study of 3832 patients who had undergone a Cox-Maze III procedure.[2] Thus, while lower than expected, the success rate for top-ranked surgeons found in our survey is not out of line with published studies.

Our results, albeit based on a very small sample, lead to the conclusion that, just as in the case of conventional PVIs, the choice of surgeon or EP is the all-important variable with the type of procedure playing a lesser role in the final outcome.

Seven out of 12 (58%) of patients undergoing the maze procedure experienced one or more adverse events, some of them quite serious. Two suffered a transient ischemic attack (TIA, mini-stroke), one reported excessive fluid retention, and one pericarditis. This rate of serious adverse events is higher than experienced in any other procedure.

The majority (82%) of the 12 patients for whom data was available continued on warfarin for 3 months or more, and 42% were prescribed amiodarone after the procedure. Five patients (42%) recovered fully in less than 3 months, but the remaining 7 took more than 3 months to do so. Half the respondents reported an increase in resting heart rate of 10 bpm or more and only one reported a decrease. The increase applied whether or not the procedure was successful. One of the unsuccessful maze patients went on to undergo an AV node ablation + pacemaker implantation, while the others had no follow-up procedures and continued to experience afib episodes.

Conclusion – Unless performed by a top-ranked cardiac surgeon the full maze procedure is clearly not as successful as generally believed and may have significant adverse effects. Thus, there would seem to be little reason for a paroxysmal afibber with no heart disease to select this highly invasive and difficult procedure over a standard PVI or mini-maze procedure.

Mini-Maze Procedure

Twenty-three respondents reported undergoing a mini-maze procedure, 19 as their initial procedure and 4 after one or two failed radiofrequency PVIs. As shown in the table below there were no significant differences in 5 key variables between the total group of survey respondents and the mini-maze group except for a somewhat greater incidence of underlying heart disease.

Variable	Total Group	Mini-Maze Group
No. in group	335	23
Age at diagnosis, yrs.	48	49
Underlying heart disease, %	10	23
Permanent AF, %	19	18
Paroxysmal with daily episodes, %	22	24
Amiodarone usage, %	11	13

Two of the mini-maze procedures used microwave energy to create the lesions; both were successful. One of the procedures was performed by

Dr. Adam Saltman at the University of Massachusetts; the other was done at Good Samaritan Medical Center in Phoenix, AZ.

One mini-maze procedure used high intensity focused ultrasound (HIFU) for lesion creation and was unsuccessful.

Of the remaining 20 procedures, 12 were carried out by 5 top-ranked surgeons.

Dr. Randall Wolf	University of Cincinnati Hospital	8 procedures
Dr. Dale Geiss	OSF, St. Francis Medical, Peoria, IL	1 procedure
Dr. James Cox	Ohio State University Hospital	1 procedure
Dr. Adam Saltman	University of Massachusetts	1 procedure
Dr. Michael Mack	Medical City, Dallas, TX	1 procedure

RF-powered catheters or clamps were used for lesion creation in all 20 procedures. The outcome results are presented below.

	# of	Success Rate, %			Adv.Event
Surgeon	Procedures	Complete	Partial	Failure	Rate,%
Top-ranked	12	75	0	25	50
Other	8	25	12	63	38
Total	20	55	5	40	45

NOTE: Two of the successful procedures involved the full maze set of lesions

It is clear that the mini-maze is a highly successful procedure if performed by a top-ranked cardiac surgeon. It is, like the conventional RF PVI, far less successful if performed by less skilled operators. The incidence of adverse events tended to be slightly higher than for the conventional PVI and were generally more serious as shown in the table below.

Adverse Event	Patients Involved,%
Left atrial tachycardia/flutter	17
Right atrial flutter	13
Pneumonia	9
Tamponade	4
Serious hemorrhage	4
Subcutaneous nerve pain	4

For comparison, outcome results for a single radiofrequency PVI are presented in the table below.

Outcome of Single RF PVI

	# of	Success Rate, %			Adv. Event
EP	Proced.	Compl.	Partial	Failure	Rate,%
Top 3*	121	61	5	34	39
Top 10	179	54	6	40	39
Other	179	22	9	69	43
Total	358	38	7	55	41

* Bordeaux, Cleveland Clinic, Marin General

It is evident that a single mini-maze procedure performed by a top-ranked cardiac surgeon is likely to be more successful than a single RF PVI performed even by the very best EP. The fact that the success rates for other than top-ranked surgeons and EPs are equally poor for conventional PVIs and mini-mazes is perhaps the best example yet of the crucial importance of selecting the most skilled doctor to perform the procedure, and equally, of the relative lack of importance of the procedure chosen.

The standard RF PVI can be repeated, whereas I have not seen any examples of full maze and mini-maze patients being given the option of a second procedure if the initial one fails. Thus, it is of interest to compare the final outcomes of RF PVIs after repeat ablations.

Final Outcome of Multiple PVIs

	# of	Success Rate,%		
EP	Patients	Complete	Partial	Failure
Top 3*	92	78	7	15
Top 10	131	72	8	20
Other	106	37	15	48
Total	237	57	11	32

* Bordeaux, Cleveland Clinic, Marin General

The success rate for the top three institutions after multiple PVIs is very close (difference not statistically significant) to that obtained by top cardiac surgeons performing the mini-maze procedure. Overall, the final outcome for the conventional PVI and the mini-maze is not significantly different when the final outcome for all patients (not just those treated by top-ranked surgeons or EPs) is considered.

Thirty-five percent of respondents recovered fully in less than 2 months, but 30% took 3 months or longer to return to their pre-procedure level of stamina.

Only 9% of respondents had been checked for pulmonary vein stenosis perhaps indicating that this possible complication is not a concern for the mini-maze procedure.

Patients with a successful outcome experienced afib episodes for less than a month (or not at all) after the procedure, while those with an unsuccessful outcome reported episodes for more than a month post-procedure. Twenty-six percent of patients did not take warfarin after the procedure, but 56% took it for 3 months or longer post-procedure. Eighty-three percent of all patients were prescribed antiarrhythmics after with amiodarone and flecainide being the most popular.

Four of the unsuccessful and the one partially successful procedure respondents went on to undergo further procedures. One had a successful AV node + pacemaker implantation, one had two conventional RF PVIs which finally resulted in a cure. The remaining two had one conventional RF PVI each with the outcome being uncertain at this time (less than 6 months since procedure).

Fourteen kept track of their resting heart rate before and after the procedure. About half (57%) experienced a significant increase post-procedure, 21% observed no change, and 22% observed a decrease. There was no correlation between success and heart rate increase.

Conclusion – Based on this survey it would appear that a mini-maze procedure performed by a top-ranked cardiac surgeon provides the best chance of being cured of AF with one single procedure. However, the incidence and severity of adverse events would seem to be higher than for catheterization procedures. It would also seem (based on the experience of just one respondent so far) that it might be possible to get a second chance if the procedure fails by following up with a conventional catheter-based PVI.

Summary – Other Procedures

A total of 86 procedures, other than the conventional RF PVI, was performed in order to eliminate AF or flutter arising from a PVI procedure. The following observations were made:

- Right atrial flutter ablations are generally successful in eliminating right atrial flutter, but only very rarely (6% of cases) do they cure AF as well.

- Left atrial flutter or tachycardia occurs fairly frequently as a sequel to a RF PVI or mini-maze. In most cases it resolves on its own, but in some cases a repeat ablation is necessary to correct it. This procedure (based on a very small sample size) is usually successful.

- There were only 6 responses from afibbers who had undergone cryoablation, so it is not possible to draw conclusions as to the effectiveness and safety of this procedure. However, it does appear that post-procedural heart rate elevation is not a problem with cryoablation.

- Based on a small sample of 10 respondents it would appear that AV node ablation + pacemaker installation is usually a successful procedure and provides significant symptomatic relief even though it does not eliminate the fibrillation of the atria.

- Unless performed by a top-ranked cardiac surgeon the full maze procedure is less successful than generally believed and may have significant adverse effects. Based on the input from just 13 respondents, there would seem to be no reason for a paroxysmal afibber with no underlying heart disease to select this procedure over a conventional RF PVI or mini-maze procedure.

- A mini-maze procedure performed by a top-ranked cardiac surgeon would appear (based on 23 responses) to provide the best chance of being cured of AF with a single procedure. It would also seem (based on the experience of just one respondent so far) that it might be possible to get a second chance if the procedure fails by following up with a conventional, catheter-based PVI.

References

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Acknowledgement

This concludes the evaluation of the 2006 ablation/maze survey. This survey obviously would not have been possible without the wholehearted (pun intended) cooperation of 335 afibbers who have undergone an ablation or maze procedure. On behalf of our fellow afibbers and myself, I would like to extend a sincere thank you to all respondents.

Appendix A

Glossary of Medical Terms

Ablation
A procedure for destroying heart tissue that is creating abnormal electrical impulses.

Accessory pathway
A collection of muscle fibres that bypass the normal pathway for electrical impulses going from the atria to the ventricles through the atrioventricular (AV) node.

ACE inhibitor
A pharmaceutical drug that inhibits the enzyme which converts angiotensin I to angiotensin II.

Acetylcholine
The neurotransmitter released at parasympathetic (vagus) nerve endings.

Acidosis
A condition in which the blood is excessively acidic (pH below 7.38). It is caused by an imbalance in the bicarbonate-carbonic acid buffer system that keeps the pH of blood within a very narrow range.

Acute
Of rapid onset, severe symptoms and short duration.

Adenoma
A benign tumour of epithelial origin.

Adrenaline
See Epinephrine.

Adrenergic
Pertaining to the sympathetic branch of the autonomic nervous system.

Adrenergic LAF
Lone atrial fibrillation triggered by excessive sympathetic stimulation.

Adrenergic tone
The strength or vigour of the sympathetic branch of the autonomic nervous system.

ADP (adenosine diphosphate)
A compound involved in energy transfer within cells. It consists of adenine, ribose and two phosphate groups.

Afferent
Pertaining to nerves or neurons that carry impulses (information) from an organ to the brain or spinal cord (See also efferent).

Alkalosis
A condition in which the blood is excessively alkaline (pH above 7.44). It is caused by an imbalance in the bicarbonate-carbonic acid buffer system that keeps the pH of blood within a very narrow range.

Aneurysm
A bulge formed by dilation of the wall of the heart or blood vessel.

Angina pectoris
Pain in the center of the chest, which is induced by exercise and relieved by rest. Angina occurs when the demand for blood exceeds the supply and is usually caused by atherosclerosis of the coronary arteries.

Antiarrhythmic
Pharmaceutical drug designed to prevent abnormal heart rhythms or to convert abnormal rhythms to normal sinus rhythm.

Anticoagulant
Pharmaceutical drug designed to prevent blood clotting.

APC [activated protein-C resistance]
A condition caused by the presence of a mutation of blood coagulation factor V (factor V Leiden). APC is associated with an increased risk of venous thromboembolism.

Apoptosis
Self-destruction (suicide) of individual cells to avoid a threat to the survival of the organism as a whole.

Arrhythmia
An abnormal heart rhythm.

Atherosclerosis
The development of fatty plaque and scar tissue on the inner wall of the arteries – eventually leading to obstruction of blood flow and an increased risk of thrombosis.

Artery
A blood vessel that carries blood away from the heart.

Atria
The two upper chambers of the heart. The right atrium receives returning blood from the body and the left atrium receives oxygenated blood from the lungs.

Atrial appendages
Small pouches connected to the right and left atria. The left atrial appendage (LAA) is associated with the generation of blood clots during atrial fibrillation.

Atrial fibrillation
A chaotic movement of electrical impulses across the atria leading to a loss of synchrony between the atria and the ventricles.

Atrial flutter
An abnormal, sustained, rapid contraction of the atria. The rhythm is rapid, but regular as opposed to atrial fibrillation where it is rapid and irregular.

Atrial natriuretic peptide [ANP]
A hormone formed in the atria. ANP is involved in regulating blood pressure and salt and water balance in body fluids.

Atrial refractory period [ARP]
See Refractory period

Atrioventricular (AV) node
A set of specialized heart cells that conducts the normal electrical impulses from the atria to the ventricles.

Auscultation
The act of listening for sounds in the body to ascertain the functioning of the heart, lungs, abdomen and other organs (usually done with a stethoscope).

Autonomic nervous system [ANS]
The part of the central nervous system that is not under conscious control (involuntary). It controls the body's internal organs including the heart and digestive system and is responsible for regulating blood pressure.

AV node ablation
Full or partial destruction (by ablation) of the AV node's ability to conduct signals between the atria and ventricles. A permanent pacemaker is required after AV node ablation.

Baroreceptors
Specialized muscle cells located in the walls of the heart and major arteries. They "measure" blood pressure by stretching or relaxing as blood flows past them.

Beta-blocker
A pharmaceutical drug which blocks the receptor sites for the neurotransmitters (catecholamines) used by the sympathetic (adrenergic) branch of the autonomous nervous system.

Bigeminy
An abnormal heart rhythm in which a normal heartbeat (originating from the SA node) is followed by an ectopic beat (originating outside the SA node) in rapid succession.

Biopsy
The removal of a small piece of living tissue from the body for microscopic examination. Biopsy is often carried out with a special hollow needle (needle biopsy) to minimize invasiveness and discomfort.

BMI [body mass index]
Equals a person's weight (in kilograms) divided by height in meters squared (BMI= kg/m^2). A BMI between 18.5 and 24.9 is ideal; above 25 is overweight and above 30 is obese.

Bradycardia
An abnormally slow heart beat.

Brain natriuretic peptide [BNP]
A hormone released almost exclusively from the ventricular myocardium. Elevated levels may indicate heart failure.

Bundle of His
A small bundle of specialized cardiac muscle fibres connecting the AV node with the upper part of the ventricles.

Calcium-channel blocker
A pharmaceutical drug that inhibits the flow of calcium ions through or across cell membranes. It is used in the treatment of stroke and certain heart conditions.

Carcinoma
A malignant tumour of epithelial origin.

Cardiogenic
Originating in the heart

Cardiogenic emboli
Blood clots originating in the heart

Cardioversion
The conversion of an irregular heart rhythm to normal sinus rhythm. Cardioversion can be done with drugs or through an electric shock administered to the chest area.

Carotid artery
The artery that carries blood from the heart to the brain. It is situated in the front of the neck.

Catecholamines
A group of chemical compounds (amines) derived from tyramine and tyrosine. The group includes epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine.

Catheter
A tube designed to be inserted into a narrow opening or hollow organ such as the urinary bladder or a vein. The catheter is used to drain fluids or to allow the insertion of special instruments used for imaging or ablation.

Catheter ablation
Destruction of tissue by the application of electrical current, usually at radio frequencies, via a catheter threaded through a vein to reach the area to be ablated (AV node, pulmonary veins, “hot spots” in the atria).

Cerebrovascular event
See Stroke.

Chronic
Persisting over a long period of time.

Circumferential pulmonary vein isolation [CPVI]
An ablation procedure involving the creation of two rings of lesions in the left atrium; one completely enclosing the left pulmonary veins and another completely enclosing the right pulmonary veins; the two rings are usually joined by a linear lesion. Also known as the Pappone method.

Coagulation (of blood)
Process whereby blood is converted from a liquid to a solid state.

Comorbidity
A disease condition accompanied by one or more unrelated disease conditions.

Congestive heart failure [CHF]
Failure of the heart to pump sufficiently strongly to prevent the accumulation of fluid in the lungs.

Coronary arteries
The arteries that supply the heart itself with oxygenated blood.

Cortex
The outer part of the adrenal gland. Aldosterone, cortisol and DHEA (dehydroepiandrosterone) are synthesized here.

Couplet
An abnormal heart rhythm involving two ectopic beats in a row.

Deep vein thrombosis [DVT]
A condition where a blood clot is formed in a deep vein, usually in the legs.

Depolarization
The sudden surge of ions across heart cell membranes that initiates the contraction of the heart.

Diastolic
Pertaining to the time period between fillings of the ventricles. The diastolic pressure is the lower of the two readings reported when measuring blood pressure.

Diuretic
An agent that increases the excretion of urine.

Docosahexaenoic acid [DHA]
A main component of fish oils.

Echocardiogram
An ultrasound picture of the heart as it beats.

Ectopic beat
A heart beat that is initiated at a location other than the sinoatrial node. The junction between the left atrium and the pulmonary veins is a primary spawning ground for ectopic beats.

Edema
Swelling caused by an abnormal accumulation of fluid in body tissues.

Efferent
Pertaining to nerves or neurons that carry impulses (instructions for action) from the brain or spinal cord to a target organ or muscle.

Ejection fraction
The proportion of the blood volume in the left ventricle that is actually pumped out in each heartbeat. The proportion for a healthy heart is 50-60 per cent. A value of 40 per cent or below indicates ventricular dysfunction.

Electrocardiogram [ECG]
A recording of the electrical activity of the heart during contraction.

Electrolytes
Chemical substances that dissociate into two or more ions when dissolved in water.

Embolism
A condition in which a blood clot becomes lodged in an artery and obstructs the flow of blood [embolic].

Endarterectomy
Surgical removal of the inner lining of an artery that is clogged with atherosclerotic build-up.

Endogenous
Originating from within an organism, cell or tissue.

Endothelium
The single layer of cells that line the heart, blood vessels and lymphatic vessels [endothelial].

Enzyme
A protein-based substance (catalyst) that speeds up the rate of a biological reaction without being consumed in the process.

Epidemiology
Dealing with the study of the causes, distribution and control of diseases in populations [epidemiologic].

Eicosapentaenoic acid [EPA]
A main component of fish oils

Epithelium
Membranous tissue that covers most internal and external surfaces of the body and its organs [epithelial].

Exogenous
Derived or developed from outside the body, originating externally.

Epinephrine
A hormone secreted by the medulla of the adrenal gland. Also known as adrenaline.

Factor V Leiden
A mutation in blood coagulation factor V that results in an increased tendency to blood clotting – especially deep vein thrombosis.

Fibrillation
Rapid and chaotic beating of the heart.

Fibrinolysis
The process by which blood clots are removed from the circulation. It involves digestion of insoluble fibrin by the endogenous enzyme plasmin [fibrinolytic].

Focal Ablation
The original radio frequency ablation procedure in which specific active foci of aberrant impulses are located and ablated.

Framingham Heart Study
A large epidemiologic study begun in 1948 with the purpose of discovering the causes of heart disease and stroke. The study now involves thousands of men and women and their offspring from the town of Framingham in Massachusetts.

Gastrointestinal
Relating to the stomach and intestines [gastrointestinal tract].

Glucose tolerance test
A test used in the diagnosis of diabetes and impaired glucose tolerance. It measures how well the body deals with sugar (glucose).

Glycemic index
A measure of how much and how quickly glucose is released and absorbed from a carbohydrate food. Pure glucose has a value of 100.

Heart failure
See Congestive heart failure.

Heart rate variability [HRV]
A measure of the beat- to-beat variability in heart rate.

Hematoma
A localized swelling of blood resulting from a break in a blood vessel.

Hemorrhagic stroke
See Stroke

Holter monitor
A portable device for measuring heart rhythm over a 24-hour period.

Homocysteine
A sulphur-containing amino acid used by the body in cellular metabolism and the manufacture of proteins.

Hyperhomocysteinemia
An elevated blood level of homocysteine.

Hyperlipidemia
An excess of fats or lipids in the blood.

Hypertension
A blood pressure that is persistently above the upper limit of the reference range (140/90).

Hyperthyroidism
An overactive thyroid gland. The condition is characterized by increased metabolic rate, high blood pressure and a rapid heartbeat.

Hypocalcemia
An abnormally low blood level of calcium.

Hypoglycemia
A lack of glucose in the blood stream. The condition can cause sweating, mental confusion, atrial fibrillation and muscle weakness.

Hypokalemia
An abnormally low blood level of potassium.

Hypomagnesemia
An abnormally low blood level of magnesium.

Hyponatremia
An abnormally low blood level of sodium

Hypotension
An abnormally low blood pressure.

Hypothyroidism
An underactive thyroid gland. The condition is characterized by fatigue, hair loss, feeling cold, constipation and skin pallor.

ICD
Implantable cardioverter-defibrillator.

Idiopathic
Of no known cause.

Incidence
The extent or frequency of occurrence.

Infarction
Localized cell death (necrosis) resulting from obstruction of the blood supply.

INR
International Normalized Ratio. A measure of the blood's tendency to coagulate (form clots) when on warfarin (Coumadin). A normal INR is 1.0. Warfarin dose is usually adjusted to give an INR between 2.0 and 3.0.

Intermittent claudication
Muscle pain, usually in the calf muscles, that is brought on by exercise and relieved by rest. It is usually caused by atherosclerosis of the arteries feeding the affected limb.

Intracardiac Echocardiography [ICE]
An ultrasound technique for visualizing the inside of heart chambers.

Intracellular
Situated or occurring inside a cell.

Intracranial
Within the head.

Ion
An electrically charged atom or molecule.

Ion channel
A pore in a cell's membrane that provides a channel for ions to cross the membrane.

Ischemia
Inadequate blood flow to the heart or other body parts [ischemic].

Ischemic stroke
See Stroke

Left atrial appendage
See Atrial appendages.

Left ventricular dysfunction
Inadequate pumping capacity of the left ventricle. Characterized by a left ventricular ejection fraction below 40 per cent.

Macrophages
Large scavenger cells found in connective tissue and in many major organs and tissues including the liver, lymph nodes, spleen, bone marrow and central nervous system.

Mast cells
Large cells in connective tissue that release heparin, histamine and serotonin in response to inflammation or allergens.

Maze procedure
A surgical procedure that involves the creation of a pattern of scar tissue to contain and channel the heart's electrical impulses and thereby prevent atrial fibrillation.

Medulla
The inner part of the adrenal gland. Epinephrine and norepinephrine are synthesized here.

Mitral stenosis
A narrowing of the opening of the mitral valve.

Mitral valve
A valve that allows blood to flow between the left atrium and the left ventricle while preventing back flow.

Mitral valve prolapse [MVP]
A usually benign abnormality of the mitral valve resulting in regurgitation (back flow) of blood from the left ventricle to the left atrium.

Monocyte
A variety of white blood cells whose purpose is to ingest foreign particles such as bacteria and tissue debris.

Mortality
Incidence of death in a given period.

Myocardial infarction [heart attack]
Destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle.

Myocarditis
An acute or chronic inflammation of the heart muscle.

Myocardium
The middle of the three layers that form the wall of the heart. It is composed of muscle fibres.

Myocyte
A muscle cell.

Myxoma
Benign gelatinous tumour of connective tissue. Atrial myxoma most commonly involves a tumour in the left atrium.

Necrosis
Death of cells through injury, disease or obstruction of blood supply.

Neutropenia
Decrease in the number of neutrophils (a type of white blood cell) resulting in an increased susceptibility to infection.

Nitric oxide [NO]
A colourless gas produced in cellular metabolism. It is involved in oxygen transport to tissues, the transmission of nerve impulses and the relaxation of blood vessel walls.

Non-valvular atrial fibrillation
Atrial fibrillation that is not caused by malfunctioning or damaged heart valves.

Norepinephrine
The neurotransmitter released at sympathetic (adrenergic) nerve endings. Also known as noradrenaline.

Normal sinus rhythm [NSR]
The normal rhythm of the heart when beats are initiated only at the sinoatrial node.

Ostial PVI
A pulmonary vein isolation procedure where the ablation lesions are placed in the left atrium around the openings of the pulmonary veins rather than inside the pulmonary veins. The ostial procedure eliminates or sharply reduces the risk of pulmonary vein stenosis.

On-demand-approach
A method of self-terminating atrial fibrillation episodes. It involves taking propafenone or flecainide immediately following the start of the episode. Also known as the pill-in-the-pocket approach.

Oxidative stress
A condition that occurs when the body's natural antioxidant defences are overwhelmed by reactive oxygen species and other free radicals.

Pacemaker
An implanted device meant to provide small electric shocks to the heart to initiate heartbeats (contractions) at a predetermined rate.

Palpitation
A sensation of a rapid, irregular heart beat.

Parasympathetic
Pertaining to the parasympathetic branch of the autonomic nervous system.

Paroxysmal
Occurring at intervals (intermittent).

Peripheral arterial disease [PAD]
Atherosclerosis in arteries other than the coronary arteries. Intermittent claudication may occur if the atherosclerotic deposits are blocking the arteries feeding the legs.

Permanent LAF
Continuous lone atrial fibrillation that does not respond to cardioversion.

Persistent LAF
Lone atrial fibrillation episodes lasting more than seven days, but amenable to cardioversion.

Pheochromocytoma
A tumour of the adrenal gland that produces epinephrine and norepinephrine.

Platelet
Blood cell involved in the initiation of blood clotting [thrombocyte].

Platelet inhibitor
A drug that prevents the aggregation of platelets.

Plaque
A build-up of cholesterol and fatty substances on the inner lining of arteries.

Postprandial
Occurring after a meal, especially dinner.

Premature atrial complex [PAC]
A premature heart beat originating in the atrium other than at the sinoatrial node.

Premature ventricular complex [PVC]
A premature heart beat originating below the atrioventricular node, often in the ventricular muscle itself.

Prevalence
The total number of cases of a disease in a given population at a specific time.

Proarrhythmic
Capable of inducing arrhythmia.

Prophylaxis
Action taken to prevent disease [prophylactic].

Prostaglandin
A hormonelike compound synthesized in the body from 20-carbon unsaturated fatty acids, notably arachidonic acid. Prostaglandins are involved in a wide range of physiological functions including control of blood pressure, contraction of smooth muscle and modulation of inflammation.

Prothrombin time
A measure of the blood's tendency to clot when medicated with warfarin. See INR.

PUFA
Polyunsaturated fatty acid.

Pulmonary embolism
A blood clot lodged in the pulmonary artery.

Pulmonary vein ablation [PVA]
Ablation of sources of ectopic heartbeats located at the junction of the left atrium and the pulmonary veins.

Pulmonary vein isolation [PVI]
Isolation of the pulmonary veins from the left atrium by ablating (generating lesions) a ring around each pulmonary vein.

Pulmonary veins
The veins draining oxygenated blood from the lungs to the left atrium.

Purkinje fibres
A group of specialized heart cells that conduct electrical impulses in the ventricles.

QT Interval
The duration of the activation and recovery of the ventricular myocardium. A prolonged QT interval is associated with ventricular arrhythmias.

Refractory period
The rest period following a contraction of the heart muscle. The cell does not respond to stimulation during this period.

Reperfusion
The restoration of blood flow to an organ or tissue that has had its blood supply cut off due to a stroke or heart attack. Reperfusion is associated with increased free radical activity.

Rheumatic heart disease
Heart disease caused by rheumatic fever.

Run
An abnormal heart rhythm characterized by four or more ectopic beats in a row.

Sinoatrial (sinus) node
The specialized (pacemaker) tissue that initiates a heart beat. It is located near the top of the right atrium.

Sinus rhythm
See Normal sinus rhythm.

Stasis
Stagnation or cessation of flow; for example, of blood or lymph fluid.

Stenosis
A constriction or narrowing of a duct or passage; for example, pulmonary vein stenosis.

Stroke
An event that damages nerve cells in the brain. It is caused by an interruption of the oxygen supply to the brain due to a blood clot (ischemic stroke) or a burst blood vessel (hemorrhagic stroke).

Subcutaneous
Beneath the skin.

Supraventricular
Located above the ventricles, that is in the atria or atrioventricular node.

Supraventricular tachycardia [SVT]
A rapid, but regular heart rate caused by a fault in the conduction system around the atrioventricular node.

Suture
The closure of a wound or incision with material such as silk or catgut. The term is also used to describe the material used in closing the wound or incision.

Sympathetic
Pertaining to the sympathetic branch of the autonomic nervous system.

Systemic
Relating to or affecting the body as a whole.

Systolic
Pertaining to the time at which the ventricles contract. The systolic pressure is the higher of the two readings reported when measuring blood pressure.

T-cells
A specialized kind of white blood cells (lymphocytes) that help identify foreign cells and antigens so that killer cells can dispose of them.

Tachycardia
A rapid, but regular heart beat usually in excess of 100 bpm.

Tamponade
Compression of the heart caused by the build-up of fluid or blood in the space between the sac (pericardium) surrounding the heart and the heart muscle (myocardium) itself.

Thallium stress test
A test used to assess the blood flow through the coronary arteries before and after exercise.

Thrombosis
A condition in which blood changes from a liquid to a solid state, i.e. forms a clot [thrombotic].

Thrombus
A blood clot.

Thrombolysis
The dissolution of a blood clot by the infusion of an enzyme, such as streptokinase, into the blood [thrombolytic].

Thyrotoxicosis
A serious condition resulting from an excess of thyroid hormones.

Transesophageal
Through or across the esophagus. The term is often applied to a special form of echocardiography used to check for blood clots in the left atrial appendage.

Torsade de Pointes
A distinctive form of ventricular tachycardia associated with a prolonged QT interval.

Transient ischemic attacks (TIAs)
A sudden, temporary loss of neurological function caused by blockage of small arteries supplying blood to the brain (mini-stroke).

Transthoracic
Through or across the chest. The term applies to the standard form of echocardiography.

Tricuspid valve
A valve that allows blood to pass between the right atrium and the right ventricle.

Trigeminy
An abnormal heart rhythm in which every third beat is ectopic (originating outside the SA node).

Triplet
An abnormal heart rhythm involving three ectopic beats in a row.

Vagal
Pertaining to the parasympathetic branch of the autonomic nervous system.

Vagal LAF
Lone atrial fibrillation triggered by excessive parasympathetic stimulation.

Vagal tone
The strength or vigour of the parasympathetic branch of the autonomic nervous system.

Vasodilatation
An increase in the diameter of blood vessels, especially arteries. It is brought about by a relaxation of vessel walls mediated, for example, by nitric oxide.

Vagus nerve
The tenth cranial nerve originating in the brain stem. It enervates the heart, gastrointestinal tract and larynx (voice box).

Valsalva manoeuvre
A manoeuvre that increases vagal tone. It is performed by attempting to forcibly exhale while keeping the mouth and nose closed for about 15-30 seconds. It may sometimes help to abort an episode of supraventricular tachycardia or adrenergic LAF.

Vein
A blood vessel that carries blood towards the heart.

Vena cava
The large vein(s) that returns blood from the body to the heart (right atrium).

Ventricles
The two lower chambers of the heart.

Ventricular fibrillation
An often-fatal cardiac arrhythmia characterized by rapid, irregular fibrillation of the ventricles. Ventricular fibrillation is the main cause of sudden cardiac death (cardiac arrest).

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