



# CANADIAN HEART RESEARCH CENTRE



Excellence in Cardiovascular Research and Education

## EVIDENCE BASED ARRHYTHMIA MANAGEMENT UPDATE: AN UPDATE FOR THE CLINICIAN

FRIDAY, APRIL 30, 2004  
FAIRMONT ROYAL YORK HOTEL  
TORONTO, ONTARIO



CANADIAN  
HEART  
RESEARCH  
CENTRE

*A Not-For-Profit Academic Research Organization.*



# CANADIAN HEART RESEARCH CENTRE



2004

**Excellence in Cardiovascular Research and Education**

## ***An Academic Research Organization***

*The Canadian Heart Research Centre is a federally incorporated not-for-profit academic clinical research organization dedicated to the conduct of clinical trials and education in the treatment and prevention of cardiovascular disease in Canada.*

*The Canadian Heart Research Centre is a multi-faceted organization that has an intimate understanding of the needs of physicians and industry. Growing rapidly, with an emphasis on information technology and operations infrastructure, the Canadian Heart Research Centre is now on the leading edge of cardiovascular research and education.*

*As an academic research organization, Canadian Heart Research Centre is engaged in a full scope of activities from establishing new therapies in clinical trials to professional development through physician education and patient management oriented registries.*



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University of Toronto  
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Faculty of Health Sciences  
McMaster University  
Hamilton, Ontario

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McMaster University, Hamilton

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Department of Medicine  
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**Gail Karabin**

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Continuing Medical Education  
Associate - Medical

Dear Colleague:

On behalf of the faculty and sponsors of the Arrhythmia Management Update (AMU), we welcome you to the Fairmont Royal York Hotel in Toronto.

We are pleased to inform you that this program meets the accreditation criteria of the College of Family Physicians of Canada. This education event is approved as an Accredited Group learning Activity under Section 1 of the Framework of CPD options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

With the support of six unrestricted educational grants from our industry partners, as well as the organizational support from the Canadian Heart Research Centre, this program promises to be strong. The curriculum and faculty have been set to ensure an interactive and stimulating program for all participants.

The AMU program consists of structured lectures lead by an excellent Canadian and international faculty. AMU has been designed to review established best practices and recent clinical advances in the management of cardiac arrhythmias. A major goal of the planning group is to focus on the practical application of this knowledge in the real world management of patients with cardiac arrhythmias in Canada.

We are certainly very pleased to offer this program and we look forward to your participation. If you need to contact us for any reason, please see us at our registration desk.

Once again, welcome and thank you for your participation in what promises to be a great scientific event.

Yours very truly,



John Axler, MD



Stuart Connolly, MD



Paul Dorian, MD

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# Hypertension and Anti-hypertensive Therapy: What does this have to do with Atrial Fibrillation?

**JEFF HEALEY, MD**

## Biography

Cardiologist/Electrophysiologist at McMaster University.

Trained (Cardiology/EP) at the University of Ottawa Heart Institute.

Current research into the role of electrical and mechanical remodeling in the development of clinical atrial fibrillation, and the role of the renin-angiotensin-aldosterone system.

## **JEFF HEALEY, MD**

### **Abstract**

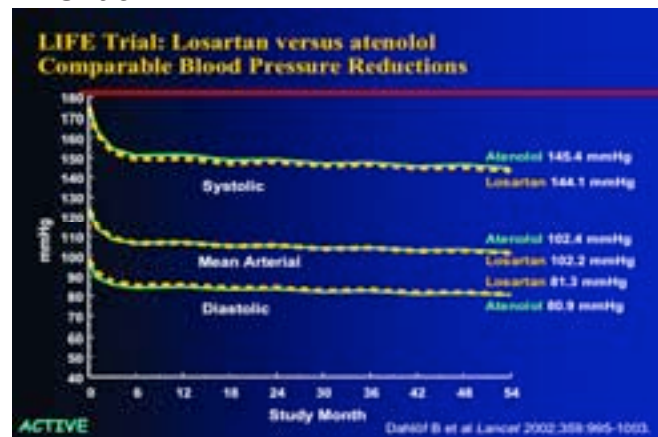
Atrial Fibrillation and hypertension are two prevalent, and often co-existent conditions in the North American population. Their incidence increases with advancing age, and they are responsible for considerable morbidity and mortality. Although the relationship between the two conditions has long been appreciated, the treatment of hypertension is not currently a focus in the clinical management of atrial fibrillation. Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement and slowing of atrial conduction velocity. These changes in cardiac structure and physiology favor the development of atrial fibrillation and increase the risk of thrombo-embolic complications. Conventional therapy of atrial fibrillation has focused on interventions to control heart rate and rhythm, and the prevention of stroke through the use of anticoagulant medications. In patients with atrial fibrillation, aggressive treatment of hypertension may reverse the structural changes in the heart, reduce thrombo-embolic complications and retard or prevent the occurrence of atrial fibrillation. Specific pharmacotherapy could potentially play a major role in the primary and secondary prevention of atrial fibrillation and its complications.

Slide 1

## Atrial Fibrillation: A Complication of Hypertension

1. Epidemiology
2. Process of Cardiac Remodelling
3. Role of the RAAS
4. Local Research Initiatives

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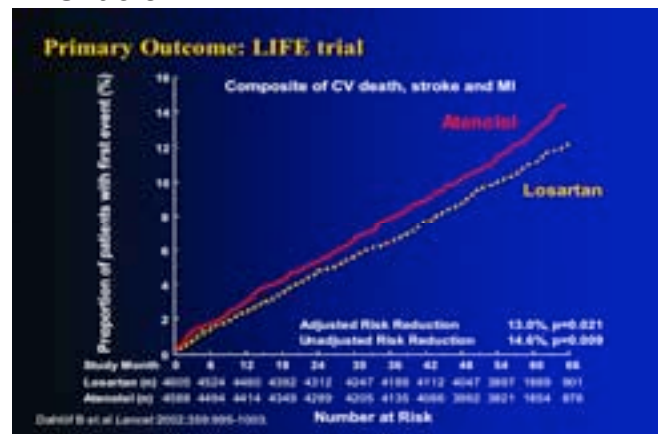
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### The Framingham Study: Factors Associated with AF

Factor	Prevalence in Men (%)	Risk Ratio for AF
Stroke	2.4	4.2
Coronary Attacks	8.6	2.0
Cardiac Failure	0.8	17.5
Rheumatic Heart Dis.	1.2	8.3
Hypertensive Heart	28.3	2.1

N Engl J Med 1982;306:1018-22

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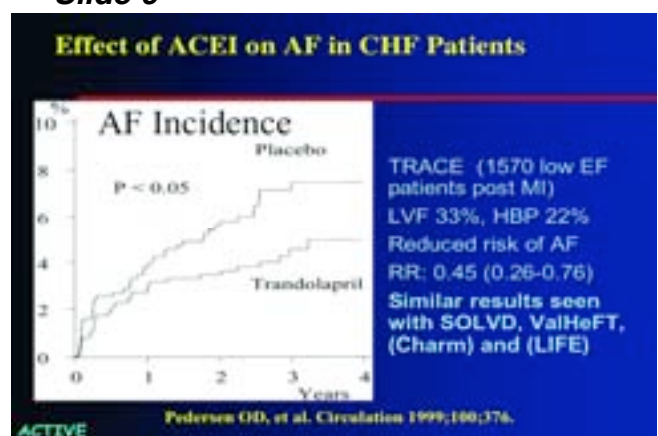
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### SPAF III: Randomized Trial of Anti-thrombotic Therapy in AF

Patient Characteristics	Adjusted warfarin	Mini-dose warfarin + ASA
Patients (n)	523	521
Age (years)	71	73
Mean BP Systolic (mmHg)	140	136
Mean BP Diastolic (mmHg)	78	79
Stroke or Thromboembolism (%)	57	59
Diabetes (%)	20	17
Prior MI (%)	20	19
Prior thromboembolism (%)	36	40

Lancet 1996

Slide 6





# Drug Treatment of Atrial Fibrillation Post-AFFIRM, RACE and PIAF: Rate Control vs Rhythm Control

**STEFAN HOHNSLOSER**, M.D., F.A.C.C, F.E.S.C.

## Biography

**Born** June 2, 1954, Pforzheim, Germany

### Education

1960 - 1964	Elementary School, Pforzheim, Germany
1964 - 1973	High School: Reuchlin Gymnasium, Pforzheim, Germany
1973 - 1980	Medical School, University of Freiburg, Germany
6/1980 - 4/1982	Research Assistant, Department of Physiology, University of Freiburg
5/1982 - 6/1984	Research Assistant, Department of Internal Medicine, University Hospital Freiburg
1982 -	Involvement in clinical trials in cardiology
7/1984 - 12/1985	Research Assistant, Harvard School of Public Health, and Brigham and Women's Hospital, Boston, USA
2/1986 - 12/1987	Research Assistant, Department of Cardiology, University Hospital, Freiburg i. B.
1/1988 - 12/1990	Assistant Professor of Cardiology, University Hospital, Freiburg
1/1991 - 4/1995	Associate Professor of Cardiology, University Hospital, Freiburg
5/1995 -	Professor of Medicine and Cardiology, J. W. Goethe University, Frankfurt
1/2002	Director, Department of Clinical Electrophysiology, J. W. Goethe University, Frankfurt

### Memberships

- Fellow of the American College of Cardiology
- Fellow of the European Society of Cardiology
- Fellow of the North American Society of Pacing and Electrophysiology
- German Society of Cardiology

### Research Interest

- Sudden cardiac death
- Risk stratification for sudden death
- Device therapy of life-threatening arrhythmias
- Pharmacological/nonpharmacological therapy of atrial fibrillation

### Reviewer for

- New England Journal of Medicine
- Circulation
- Journal of the American College of Cardiology
- Journal of Cardiovascular Electrophysiology
- American Journal of Physiology
- American Journal of Cardiology

### Reviewer for

- European Heart Journal
- American Heart Journal
- Pace
- Zeitschrift für Kardiologie
- Journal of Electrocardiography

### Editorial Board Membership

- Circulation
- Journal of Cardiovascular Electrophysiology
- Europace
- Journal of Cardiovascular Pharmacology and Therapeutics

### Publications

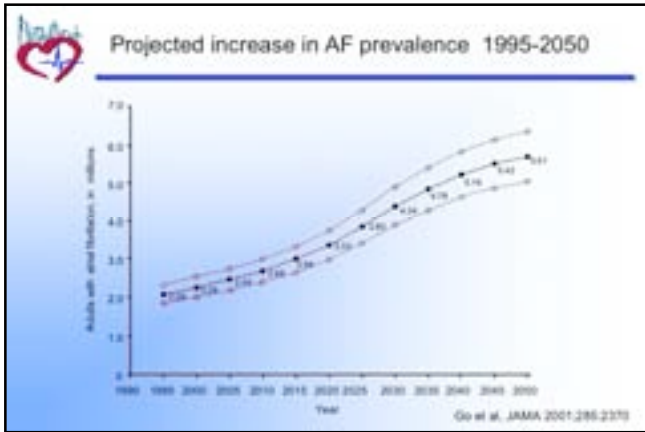
- Author on 213 articles in peer-reviewed journals
- Author on 328 published abstracts presented at national/international meetings
- Author on 23 invited review articles
- Author on 40 book chapters

**STEFAN HOHNSLOSER, M.D., F.A.C.C, F.E.S.C.**

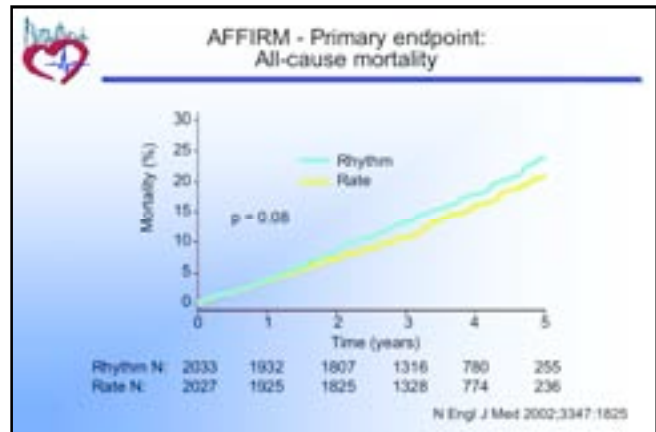
## Abstract

Pharmacological treatment remains the mainstay of therapy in patients with atrial fibrillation (AF). Initial therapy of AF is often directed toward the maintenance of sinus rhythm by means of cardioversion and the use of antiarrhythmic drugs. Heart rate control is often only pursued when rhythm control fails. There are 4 randomized controlled trials which have carefully evaluated the yield of these two treatment strategies as the initial approach to patients with paroxysmal or persistent AF. In essence, all 4 trials demonstrated that an initial strategy of rate control is equally effective compared to the rhythm control approach in terms of clinically important outcome measures including mortality, stroke prevention, or quality of life. Accordingly, rate control should be considered a primary approach to therapy in patients with AF. The 4 randomized trials clearly demonstrate that continuous anticoagulation is mandatory in all patients with AF and risk factors for stroke, irrespective of the initial therapeutic approach of rhythm or rate control.

Slide 1



Slide 4



Slide 2

Rhythm or rate control in AF

Trial	Total	Patients Rhythm control	Rate control	Primary endpoint
PIAF	252	127	125	Improvement in AF-related symptoms
STAF	200	100	100	Composite of total mortality, cardiac resuscitation, CV event, systemic thromboembolism
AFFIRM	4060	2033	2027	Total mortality
RACE	522	266	256	Composite of CV death, CHF hosp., thromboembolic events, severe bleeding, PM insertion, severe adverse events
<b>Total</b>	<b>5034</b>	<b>2526</b>	<b>2508</b>	

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Slide 3

Rhythm or rate control in AF

Patient characteristics

	Age (years)	% male	% Hx hypertension	Lone AF
PIAF	61 ± 10	74 %	49 %	15 %
STAF	66 ± 9	64 %	62 %	10 %
AFFIRM	70 ± 9	61 %	51 %	13 %
RACE	68 ± 9	63 %	49 %	21 %

Slide 6

Management of newly detected atrial fibrillation

A clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians

Recommendation 1: Rate control with chronic anticoagulation is the recommended strategy for the majority of patients with atrial fibrillation. Rhythm control has not been shown to be superior to rate control (with chronic anticoagulation) in reducing morbidity and mortality and may be inferior in some patient subgroups to rate control. Rhythm control is appropriate when based on other special considerations, such as patient symptoms, exercise tolerance, and patient preference. Grade 2A

Ann Intern Med 2003;139:1009-17

# Is RV Pacing for Bradycardia Deleterious? Reassessment Post-DAVID

## **CARLOS MORILLO, MD**

### Biography

Dr. Carlos Morillo was born in Colombia in 1958. He received his training in Internal Medicine and Cardiology in Colombia and in Canada at the University of Western Ontario where he pursued further Cardiology and electrophysiology training. He also did training in Autonomic physiology at the Medical College of Virginia. He joined the Faculty at McMaster University in 2002 as a Professor in the Department of Medicine. His major research interests have been in the area of autonomic modulation of inappropriate sinus tachycardia and postural orthostatic tachycardia, as well as mechanisms, diagnosis, and therapy of patients with recurrent syncope and orthostatic intolerance. He developed with Dr. George Klein, the rapid atrial pacing model of atrial fibrillation and reported the first successful ablation of atrial fibrillation in an experimental model. He has also described the role of early cardioneuropathy in the development and progression of Chagas cardiomyopathy and is currently leading a large trial of antitrypanosomal therapy in several countries in South America. His interests also include clinical trials in arrhythmias and syncope. He is the past president of the Latin American Society of Pacing and Electrophysiology and was a member of the Board of Governors of the American Autonomic Society. He has been a member of various committees in Canada, USA and Colombia, and is a member of the Editorial Board of EUROPACE and Clinical Autonomic Research journals. He has received numerous awards and distinctions for research including the Heart and Stroke Foundation of Canada Research Fellowship award and the Charles Pfizer Research Award

## CARLOS MORILLO, MD

### Abstract

Recent studies suggest that right apical ventricular pacing may be deleterious by inducing ventricular dyssynchrony. Right apical ventricular pacing prolongs QRS duration and promotes impaired contractility that may precipitate heart failure and atrial fibrillation. Recent evidence suggests that right ventricular apical pacing increases atrial size and reduces left ventricular ejection fraction. These findings have been reported in patients with sinus node dysfunction and a bradycardic indication for pacing. The mechanisms that promote AF and HF in right ventricular paced individuals appear to be related to the increased intraventricular conduction delay and increased atrial stretching and dilatation induced by pacing. However, increased heart rate, altered AV conduction times and filling times related with atrial pacing may have also been potentially involved. The DAVID Trial randomized patients with a Class I indication for ICD's to and ICD programmed in the DDDR pacing mode (lower rate:70 bpm) compared to VVI backup pacing (40 bpm). The primary outcome was Death or CHF hospitalization and IV diuretics and IV inotropic medication for < 24hrs. The main finding of the DAVID trial was that DDDR pacing was associated with a 68.5% increase in the composite primary outcome of death and heart failure. These findings were surprising given the fact that DDDR pacing was viewed as a more physiologic pacing mode. DAVID II will test the hypothesis whether AAIR at 70 bpm will reduce heart failure and atrial fibrillation in patients with standard ICD indications. These effects may be particularly exaggerated in patients with baseline LV dysfunction and narrow QRS duration (< 120ms) and that are paced >40% of the time. Alternative pacing sites such as the RV outflow tract and the LV lateral wall may be the answer for the prevention of the deleterious effects of RV apical pacing. Above all the most important lesson is that unnecessary pacing is indeed deleterious.

Slide 1

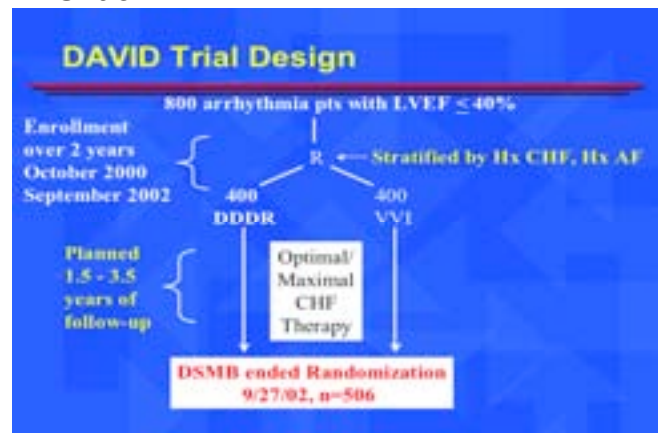
**Is RV Pacing for Bradycardia Deleterious?  
Reassessment post-DAVID**




**Evidenced Based Arrhythmia  
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Toronto  
April 30, 2004**

Carlos A. Morillo, MD, FRCP(C)  
Arrhythmia Service, McMaster University,  
Hamilton, ON

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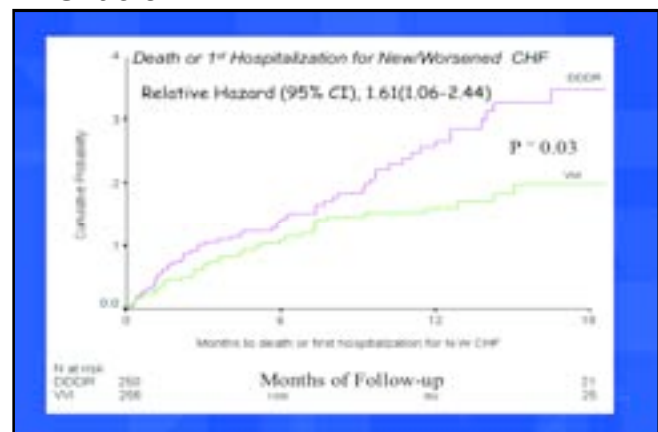
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## Hypothesis

DDDR pacing .....

- 1) . . . improves prognosis of patients treated with ICDs.
- 2) . . . Improves the Quality of life of patients treated with ICDs.
- 3) . . . Reduces the cost of treating patients with ICDs.

Slide 5



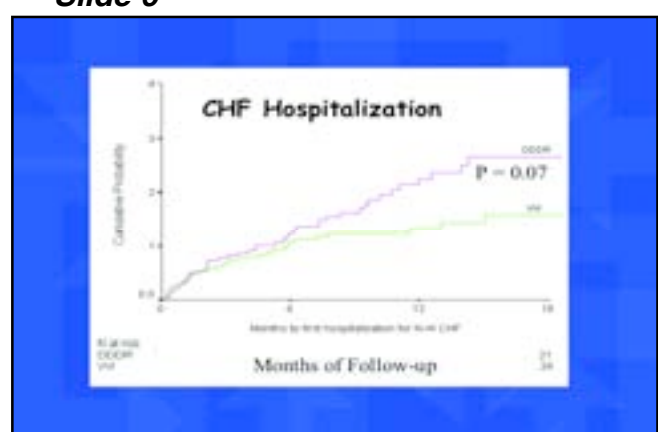
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## Rationale

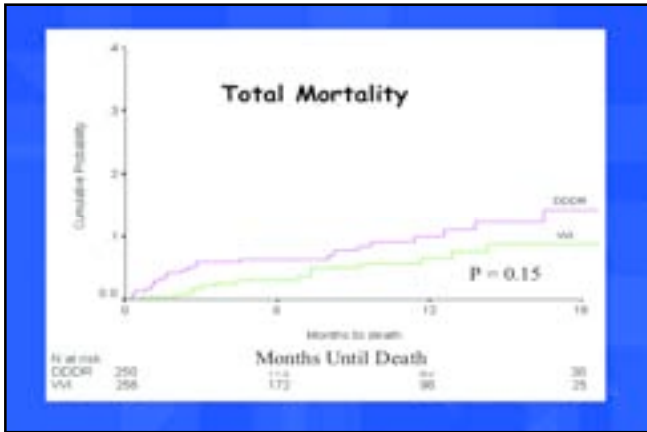
Right Apical Ventricular Pacing

- 1) Increases QRS duration
- 2) Ventricular dyssynchrony
- 3) Deteriorates LV Function and may precipitate HF & AFib

Slide 6



Slide 7

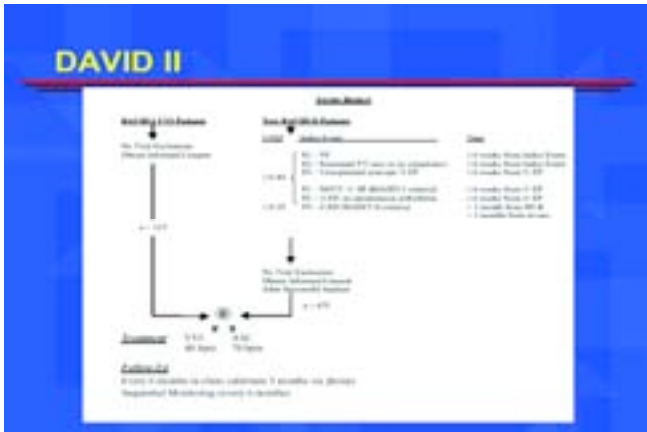


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Conclusions

- DDDR pacing increases the combined endpoint of Heart Failure Hospitalization and death in comparison to ventricular backup pacing.
- No benefit and significant detriment is associated with DDDR pacing in ICD therapy indicated patient.
- RV pacing without a bradycardic indication may lead to iatrogenic ventricular dyssynchrony
- Unnecessary therapy is usually detrimental!

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Slide 9

**Implications**

- Since DDDR pacing
  - Increases heart rate
  - Alters AV interval
  - Alters ventricular activation
- AND
- Percent RV pacing correlates with poor outcomes
- The implication is that ventricular dyssynchrony caused by RV pacing produces this adverse outcome and should be avoided in ICD indicated patients without indications for antibradycardia pacemaker support.

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# Anticoagulants, Direct Thrombin Inhibitors and Antiplatelet Agents, and Prevention of Stroke in Atrial Fibrillation

**STUART J. CONNOLLY, MD**

## Biography

Dr. Stuart Connolly was born in Montreal, Canada in 1949. He received his cardiology training at the University of Toronto and received post graduate training in electrophysiology at Stanford University.

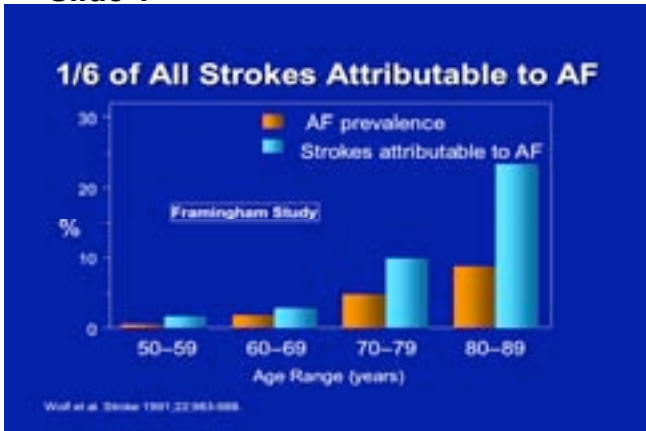
In 1983 he joined the faculty at McMaster University where he is now a Professor and is the Director of the Arrhythmia Service and the Electrophysiology Lab. His main research interests have been in the area of randomized clinical trials and he has been involved in the design and implementation of a number of studies related to the management of patients with cardiac arrhythmia. Among the studies of which he was the principal investigator are the Canadian Atrial Fibrillation Anticoagulation (CAFA) Study, The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), the Canadian Implantable Defibrillator Study (CIDS), The Canadian Trial of Physiologic Pacing (CTOPP) and two Vasovagal Pacemaker Studies (VPS –1 and VPS-2). Dr. Connolly is principal investigator of the Atrial Fibrillation Clopidogrel Trial With Irbesartan For Prevention Of Vascular Events (ACTIVE)

# STUART J. CONNOLLY

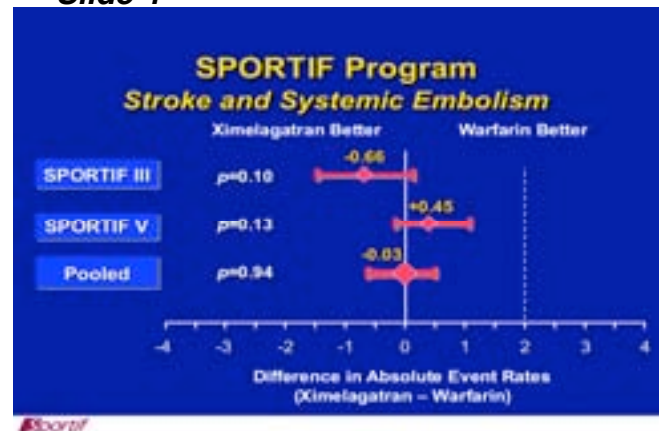
## Abstract

Atrial fibrillation is the most common significant cardiac arrhythmia and it is present in about 1% of the population of western countries. In the elderly atrial fibrillation is a significant factor contributing to the overall burden of stroke which is one of the major causes of death and disability in our culture. In the 1990s it was established that warfarin and aspirin are effective for reducing the risk of stroke in atrial fibrillation. Warfarin is about twice as effective as aspirin reducing the risk of stroke by about two-thirds. However, warfarin therapy is limited by the difficulties of administering this treatment over time. Warfarin has a narrow therapeutic window and marked inter-patient and intra-patient variability in treatment effect. This leads to a significant risk of hemorrhage as well as major lifestyle alterations. Better therapies are required and several new initiatives appear promising. Ximelagatran is a direct thrombin inhibitor which has been developed for a variety of thrombosis indications including atrial fibrillation, and large randomized trials in patients with atrial fibrillation have been completed. These trials were designed as non-inferiority trials compared to warfarin and they have been meta-analysed. Ximelagatran is equivalent to warfarin in efficacy and may confer a somewhat reduced risk of hemorrhage. Ximelagatran will soon be released for general use in many countries. Initial use of the drug will require some monitoring of liver function tests because of increased AST in about 6% of patients. The combination of aspirin and clopidogrel has been shown to reduce vascular events in acute coronary syndrome and in patients receiving coronary artery interventions. The ACTIVE trial is evaluating this combination of antiplatelet drugs in atrial fibrillation. This trial includes a non-inferiority trial against warfarin and a superiority trial against aspirin alone. Results will be available in 2007. There are several other initiatives that are in early stages of development. The most promising of these are evaluating both the oral and the intravenous forms of Factor 10A inhibitors. There is also a considerable interest in mechanical occlusion of the left atrial appendage either surgically or by endo-vascular procedure.

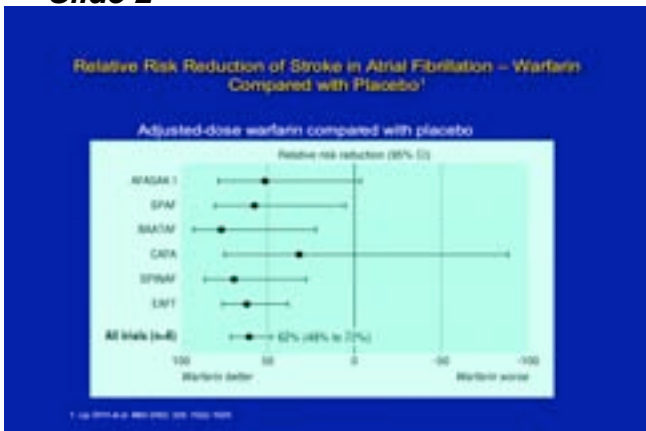
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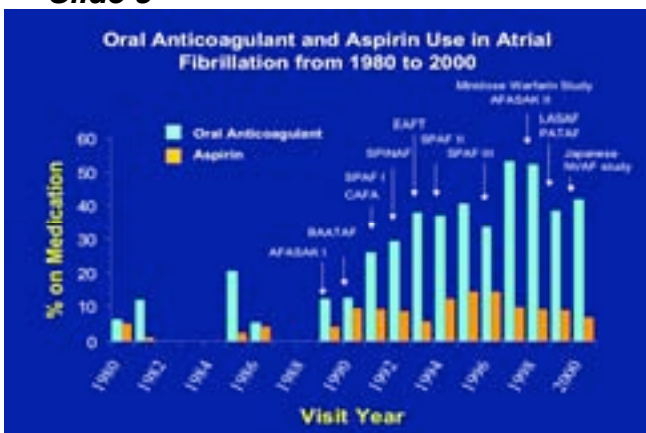
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Slide 3



# Prophylactic ICD Therapy for Everyone With LV Dysfunction? DINAMIT, DEFINITE, and SCD-HeFT Analyzed

**PAUL DORIAN**, MD, MSc, FRCPC

## Biography

Dr. Paul Dorian is currently the Director of the Cardiac Electrophysiology Program at St. Michael's Hospital in Toronto, Canada. He is Professor of Medicine in the Division of Cardiology and in the Division of Clinical Pharmacology at the University of Toronto.

Dr. Dorian received his medical degree from McGill University in Montreal in 1976. He continued training in Internal Medicine and Cardiology at the University of Toronto, and received certification by the Royal College of Physicians and Surgeons of Canada in Internal Medicine in 1983 and certification in Cardiology in 1984. He completed training in Clinical Pharmacology at the University of Toronto in 1982, and received an MSc in Pharmacology from the University of Toronto in 1982. From 1983 to 1985, he completed a Fellowship in Cardiac Electrophysiology at Stanford University Medical Centre in California.

His research interests include factors related to the induction and maintenance of ventricular fibrillation, defibrillation, and antiarrhythmic drug effects on ventricular fibrillation and defibrillation. His other interests also include quality of life in patients with cardiac arrhythmias, and the clinical pharmacology of antiarrhythmic drugs.

He has recently completed a clinical trial in out of hospital cardiac arrest and continues collaborative trials in prehospital care.

## Abstract

The “landscape” regarding prophylactic implanted cardioverter defibrillators is changing rapidly, given recent landmark clinical trials.

The secure knowledge from randomized trials of implanted cardioverter defibrillators versus best medical therapy as “secondary prophylaxis” of sudden and all cause death has firmly established that defibrillators are effective at preventing arrhythmic death, and reducing mortality in patients at high risk of lethal ventricular arrhythmias.

Subsequent studies of “primary prophylaxis” (i.e. in patients who have never had life threatening ventricular arrhythmias) have strongly suggested that, in appropriately selected patients, defibrillators can reduce all cause mortality by a clinically meaningful amount. Recent, presented but as yet unpublished, clinical trials have deepened our understanding of the presence and magnitude of benefit from ICD’s, and a better understanding of the patient subsets who will benefit from ICD’s.

In order from most highly selected to least selected patient populations:

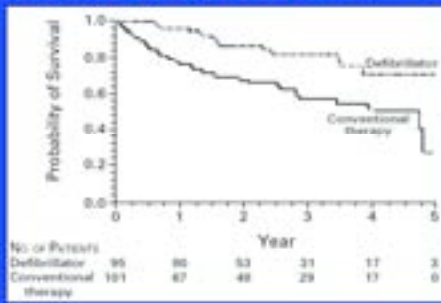
- 1) The COMPANION study compared patients receiving an implanted defibrillator with cardiac resynchronization, to receiving cardiac resynchronization (bi-ventricular pacing) alone, to optimal pharmacological therapy without devices. Patients had to have heart failure, recent hospitalization for CHF, prolonged QRS duration, and poor LV function. There was a significant clinical and mortality benefit in the group receiving the defibrillator plus resynchronization versus pharmacological therapy alone. The absolute mortality benefit was 7% at 1 year.
- 2) The DEFINITE study compared prophylactic ICD’s versus optimal pharmacological therapy in patients with idiopathic dilated cardiomyopathy, nonsustained arrhythmias on Holter monitoring, and LVEF <35%. There was a marginally significant (p=0.06) absolute mortality reduction of about 5% at two years in the ICD group.
- 3) The DINAMIT study compared prophylactic ICD to optimal drug therapy in survivors of acute myocardial infarction, within 40 days of the MI, with EF <35% and depressed heart rate variability (a risk marker for sudden and all cause death). The ICD did not alter mortality (hazard ratio = 1.08 ICD versus control), although there was a significant reduction in sudden, presumably arrhythmic death, offset by an increase in non-sudden cardiac death in the ICD group.
- 4) The SCD-HeFT study, the largest trial, was a three arm study comparing an ICD, or drug therapy with amiodarone, or matching placebo (1:1:1 randomization), in over 2000 patients. The only inclusion criterion was an ejection fraction of 35% and class II or higher NYHA symptoms of heart failure. Half of patients had coronary disease and the other half dilated cardiomyopathy. There was no difference in mortality between amiodarone and placebo. This study convincingly showed that amiodarone is not useful as primary prophylaxis in patients with chronic LV dysfunction. The implanted defibrillator reduced all cause mortality by 23%, an absolute mortality reduction of 7.5% at 5 years.

Taken together, these studies establish without any doubt that implanted defibrillators reduce all cause death in patients with poor ventricular function and symptoms of heart failure. The magnitude of benefit is likely to be variable however, ranging from as low as 1.5% per year to as high as 5% per year absolute mortality reduction depending on patient subsets.

Substudy analyses are to be performed with great caution. However, it appears that patients with poorer LV function (e.g. EF<30%), prolonged QRS duration (e.g. QRS >120 msec), may derive greater benefit. It is very clear that patients should not receive defibrillators very early after MI, and the time that should elapse between an MI and a decision to implant an ICD is open to question. Finally, most of these trials enrolled relatively young patients, between 55 and 65 years of age, and extrapolating study results to the frail elderly that have the highest incidence of heart failure is to be done cautiously. At a minimum, these recent study results confirm previous studies, and consensus guideline recommendations, to strongly consider ICD implantation in patients with coronary or non-coronary cardiomyopathy, ejection fraction <30%, and symptoms of heart failure.

Slide 1

MADIT II: Previous MI, EF < 30%

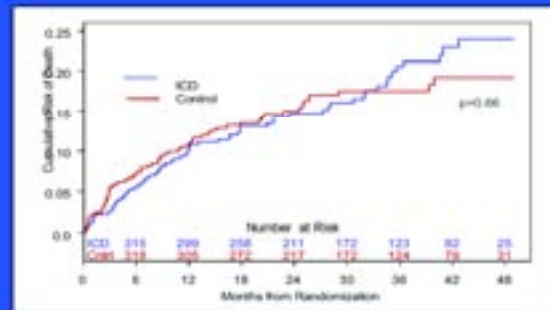


No. of Patients	Defibrillator	Conventional therapy
0	95	101
1	86	87
2	63	48
3	31	29
4	17	17
5	3	0

Moss et al., N Engl J Med 1996;1933

Slide 4

DINAMIT All-Cause Mortality



Slide 2

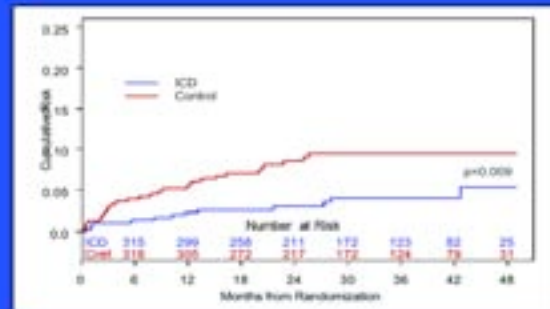
DINAMIT

DINAMIT Defibrillator IN Acute Myocardial Infarction Trial

ST. JUDE MEDICAL

Slide 5

DINAMIT Arrhythmic Death



Slide 3

DINAMIT

Study Criteria

Open label, Multicentre:

Randomize patients early post MI to ICD or no ICD

Inclusions:

- Acute MI (day 6-40)
- EF ≤ 35%
- Depressed HRV
- Age 18-80yrs

Exclusions:

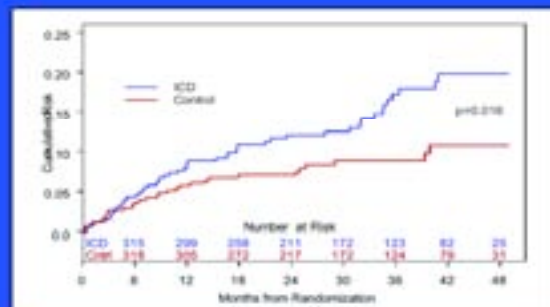
- NYHA IV, life expectancy < 2yrs
- CABG or 3v-PCI since MI
- Sustained VT/VF > 48hr post MI

PRIMARY Outcome: All-Cause MORTALITY

SECONDARY Outcomes: Arrhythmic Death, QOL

Slide 6

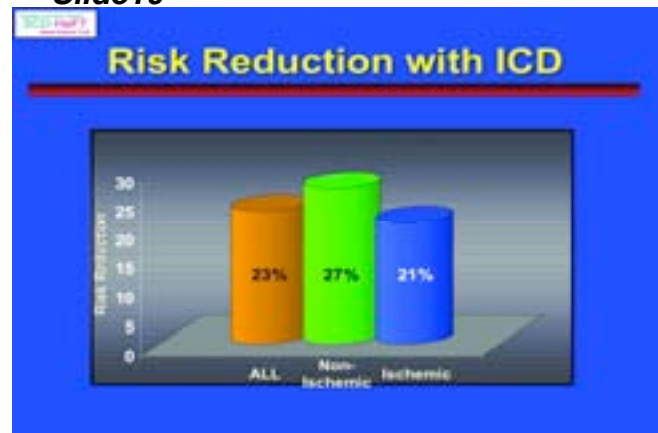
DINAMIT Non-Arrhythmic Death



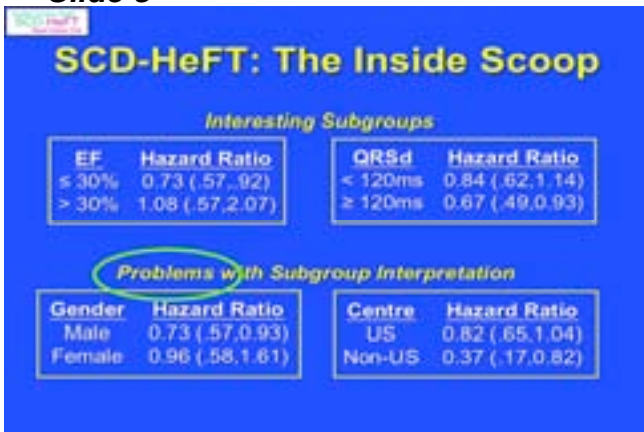
Slide 7



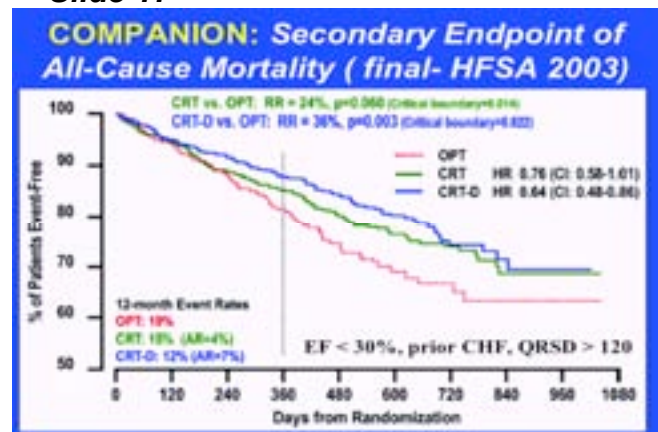
Slide 10



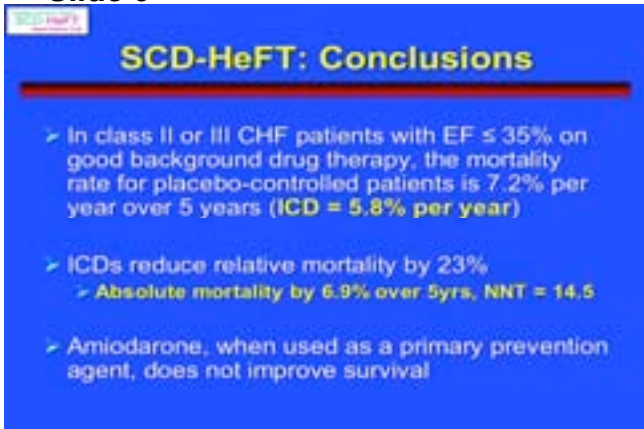
Slide 8



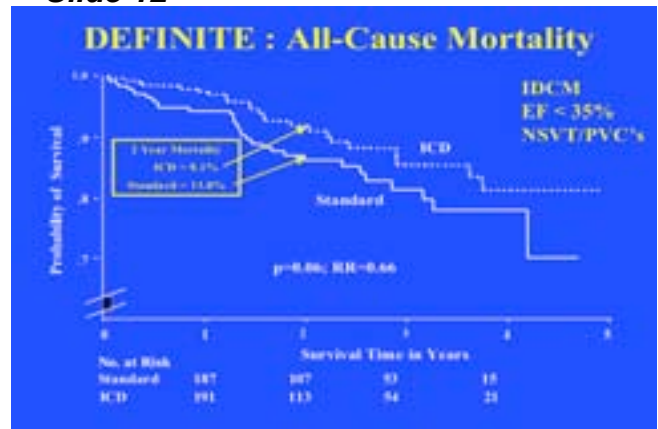
Slide 11



Slide 9



Slide 12



# Prevention of Cardiac Sudden Death with Omega-3 Fatty Acids: It's Not a Fishy Story

## **ALEXANDER LEAF, MD**

### Biography

Graduation Medical School - MD University of Michigan, Ann Arbor, 1943.

Internship, Mass General Hospital; Boston, 1944

Residency, Mayo Foundation, Rochester, Minnesota, 1944-1946

USA Army Medical Corp, 1946-1947

#### **Research Fellowships:**

Research Fellow in Medicine, University of Michigan Medical School, 1947-1949

Research Fellow in Medicine, Mass General Hospital and Harvard Medical School. 1941-1951

Research, Zoophysiology Lab, University of Copenhagen, Denmark, 1954, Sept-Dec.

Research Department of Biochemistry, University of Oxford, England, 1955-1956

#### **Academic appointments:**

1949-1951 Research Fellow in Medicine, MGH and Harvard Medical School

1951 - 1981 Promoted through the ranks to Jackson Professor of Clinical Medicine, HMS and Chief of Medical Service, MGH.

the latter from 1966-1981

1980 - 1990 Ridley Watts Professor of Preventive Medicine, Harvard Medical School and Chairman of that Department.

1990 - Jackson Professor of Clinical Medicine, Emeritus, HMS

1992 - 1996 Distinguished Physician, Veterans Affairs Medical Center, Brockton. West Roxbury.

#### **Honors and Awards:**

1966 - Elected to American Academy of Arts and Sciences

1972 - Elected to National Academy of Sciences, USA. Etc.

## **ALEXANDER LEAF, MD**

### **Abstract**

The antiarrhythmic effect of fish oil fatty acids was first demonstrated in late 1980's by Charnock and McLennan in Australia in studies on rats. We confirmed their findings in prepared dogs, reporting a significant prevention,  $P < 0.005$  and showed that the active principle in the fish oil are two long chain polyunsaturated n-3 fatty acids, Eicosapentaenoic Acid, (EPA, C20:4n-3) and Docosahexaenoic Acid (DHA, C22:6n-3). Using cultured neonatal rat cardiomyocytes we found that these two fatty acids will prevent fibrillation of the myocytes produced by cardiac toxins which cause fatal ventricular arrhythmias in humans. The mechanism of this protective effect is that the fish oil fatty acids modulate the ion channel of heart cells. It is their effect on the fast voltage- dependent sodium current, which initiates action potentials in the heart, and the L-type calcium channels, which cause the release of the calcium stored in the sarcoplasmic reticulum into the cytoplasm of cardiomyocytes and initiate thereby contraction of the heart, which seem largely responsible for their antiarrhythmic actions.

The paper will end with a brief review of the clinical studies which now strongly support the hypothesis that these fish oil fatty acids can prevent fatal ventricular arrhythmias in humans at risk for sudden cardiac death. Since there are some 300,000 to 400,000 deaths from cardiac arrhythmias annually in the USA alone and millions more world wide, this information provides important potential health benefits. Despite expenditure of hundreds of millions of dollars, the pharmaceutical industry has not succeeded in producing any safe and effective antiarrhythmic drug, whereas the fish oil fatty acids have been part of the human diet for hundreds of thousands of years and they are safe. Furthermore, they are more potent than any of the antiarrhythmic drugs so far produced by the pharmaceutical industries.

# New Hope for Severe Heart Failure: Update on Cardiac Resynchronization Therapy

**ANTHONY TANG, MD, FRCPC**

## Biography

Dr. Anthony Tang is a Professor of Medicine in the Faculty of Medicine at the University of Ottawa. He obtained his MD from the University of Toronto and his Internal Medicine and Cardiology Clinical training at the University of Ottawa. He then obtained a Heart and Stroke Research Fellowship to receive Electrophysiology research training at Duke University Medical Centre. Dr. Tang is presently Director of Electrophysiology, University of Ottawa Heart Institute as well as Director of Cardiology Research at the University of Ottawa Heart Institute.

Dr. Tang is a well published investigator recognized nationally and internationally for the research in device therapy for cardiac arrhythmia and heart failure.

Dr. Tang's main focus of research at present is funded by the Canadian Institute of Health research through the Clinical Trials University/Industry program. This research involves determining the efficacy of pacing therapy in patients with advanced heart failure and conduction abnormality.

Cardiovascular mortality is decreasing in most industrial countries, however mortality for congestive heart failure is increasing. The most important predictors of mortality in advanced heart failure patients are depressed left ventricular function, severity of symptoms (NYHA class), and ventricular conduction abnormality manifested as wide QRS. Recent advances in pharmacological therapy including ACE inhibitors, beta-blocker and spironolactone have resulted in improvement of symptoms and reduction in mortality. Population epidemiological studies demonstrated that mortality and hospitalization rate for advanced congestive heart failure remains very high despite recent pharmacological therapeutic progress. Recent short-term clinical trials demonstrated that cardiac resynchronization therapy (CRT) is effective in improving symptoms of heart failure, functional capacity and quality of life in patients with heart failure and conduction abnormality optimally treated with drug therapy. However, the data for morbidity is conflicting and there is not data on mortality.

Dr. Tang's objective of this study is to determine if the addition of CRT to Implantable Cardioverter Defibrillator (ICD) and medical therapy will reduce total mortality and hospitalization for Congestive Heart Failure (CHF) in advanced heart failure patients. There will be 23 Canadian Centres participation.

Dr. Tang has previously been successful in the area of electrophysiology research. The success of his research efforts are varied. He has been awarded funding from the Heart and Stroke Foundation for a number of research projects including effects of medication on defibrillation. He was the recipient of a Medical Research Council of Canada operating grant to investigate quality of life issues in relation to pacemakers. This year he has successfully been awarded a grant from Heart and Stroke to evaluate the effects of cellular telephones on defibrillators.

Dr. Tang an internationally renowned researcher and has been an invited speaker at national and international meetings and is a peer reviewer for five scientific journals as well as grant reviewer for Heart and Stroke and Canadian Institute of Health research.

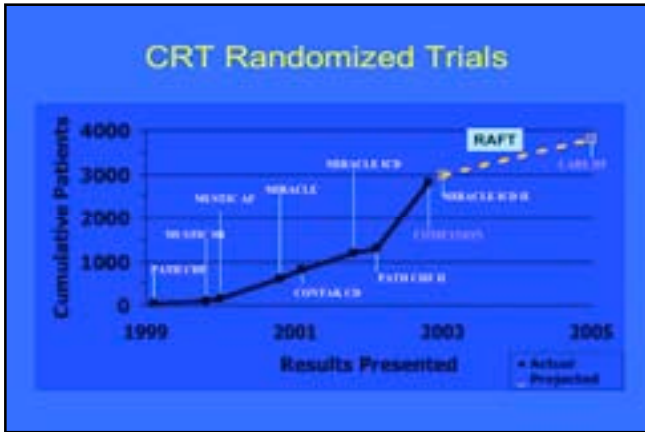
Presently his publication record includes 70 peer reviewed papers, 163 abstracts and 4 book chapters.

## **ANTHONY TANG, MD, FRCPC**

### **Abstract**

Congestive heart failure is a significant public health issue. The incidence of congestive heart failure is increasing and it is the leading cause of hospitalization in patients over the age of 65 in North America. At least 30% of patients with congestive heart failure due to systolic dysfunction have mechanical dyssynchrony. In spite of very good medical pharmacological therapy, these patients continue to have a high mortality and morbidity. Cardiac resynchronization is a therapy that potentially can improve mechanical dyssynchrony. Cardiac resynchronization therapy is an electrical therapy which attempts to resynchronize the ventricle to improve left ventricular function and therefore improve heart failure symptoms. Recent clinical trials demonstrated that cardiac resynchronization therapy is safe and effective in reducing symptoms and improving exercise capacity. This data is very encouraging and promising. Future studies will likely improve our understanding and choice of patients for this therapy.

Slide 1



Slide 4



Slide 2



Slide 5



Slide 3



Slide 6

- ### Limitations of recent CRT trials
- Most of these studies randomized patients only after initial successful device implantation.
  - Very short term data – many randomized trials are 6 months in duration.
  - There is a substantial placebo effect with device therapy. This effect was observed in many device studies: pacing for hypertrophic cardiomyopathy, pacing for vasovagal syncope and this is also observed in many CRT trials.
  - There is a large non-response (no improvement in functional capacity and well-being) rate and the magnitude of benefits is modest and diverse among studies.
  - There is no cost effective data.
  - The mortality benefit of ICD/CRT in the COMPANION trial may all be due to ICD alone.

# Catheter Ablation of Atrial Fibrillation: Hype or Hope?

**GEORGE J. KLEIN, MD**

## Biography

Dr. George J. Klein is currently the Chair of the Division of Cardiology and Professor of Medicine at the University of Western Ontario, London, ON, Canada. He received his medical degree in 1972 at the University of Toronto and his cardiology training at the U of Western Ontario and at Duke University. His major research interest has been management of cardiac arrhythmias and he has published five books, 80 book chapters and 345 papers and currently holds eight US patents. He received the Canadian Cardiovascular Society Research Achievement Award in 1988 and the Heart and Stroke Foundation of Ontario honored him with a Distinguished Research Professorship award from 1989-1994. He is an Associate Editor of Pacing and Clinical Electrophysiology, is on the Editorial Board of seven scientific journals and is currently chairman of the arrhythmia section for the American Board of Medical Examiners. His fellowship trainees can be found all over the world.

# GEORGE KLEIN, MD

## Abstract

Although many important and useful options are available for AF management, drug therapy continues to be the cornerstone of therapy. Non-pharmacological strategies are generally only contemplated when there is drug failure. It must be noted that these therapies generally don't obviate the need for anticoagulation if risk factors for stroke remain unless the intervention is clearly demonstrated to be curative.

Dual chamber pacemakers are generally only helpful in the presence of sinus node dysfunction, which in itself can initiate AF or complicates the initiation of appropriate antiarrhythmic therapy, which can aggravate bradycardia. Specific atrial pacing algorithms in the patient without bradycardia have not been shown to be clinically useful although they can reduce the "burden" of atrial fibrillation as assessed by the device.

AV node ablation with pacing continues to be very useful, especially in permanent atrial fibrillation with rate control not achievable with drugs.

"Curative" catheter ablation of AF is becoming more advanced and can be recommended especially in patients with drug refractory paroxysmal AF in the absence of significant cardiac or other co morbidity. Finally, operative cure of atrial fibrillation is useful in patients undergoing surgery for other cardiac morbidities such as mitral valve replacement and may become more attractive as a primary therapy with the further refinement of thoracoscopic techniques.

### Selected References: (1-5) (6)

1. Cooper JM, Katcher MS, Orlov MV. Implantable devices for the treatment of atrial fibrillation. *N Engl J Med* 2002;346:2062-8.
2. Falk RH. Atrial fibrillation. *N Engl J Med* 2001;344:1067-78.
3. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. *Circulation* 2001 Oct 23;104:2118-50.
4. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;344:1043-51.
5. Pappone C, Oreto G, Lamberti F, et al. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system [In Process Citation]. 1999 Sep 14;100:1203-8.
6. Todd DM, Skanes AC, Guiraudon G, et al. Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. *Circulation* 2003;108:3108-14.

Slide 1

Non Pharmacological Rx of AF



- Conventional cardiac pacing , multisite pacing
- AV node ablation... "ablate & pace"
- "Curative" surgery for AF
- "Curative" ablation for AF
- Atrial fibrillation algorithms , implantable atrial defibrillator

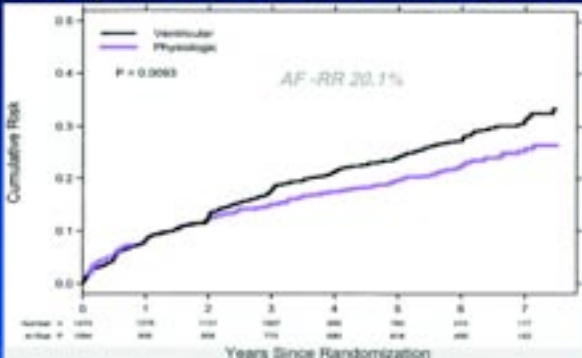
Slide 4

AV node ablation... "ablate & pace"

- Best candidate is older patient with permanent AF and inadequate rate-control with meds
- Excellent clinical results with resolution of tachycardia myopathy
- Still the cornerstone of non-pharmacological therapy for rate-control patient especially

Slide 2

Canadian Trial of Physiological Pacing .. Long-Term Follow-Up Kerr et al. *Circulation*. 2004;109:357-362



Slide 5

PV Isolation Procedure



- PV isolation - incisional with cryo completion
- Attachment of PV isolation to mitral annulus using cryo
- LAA removal
- IVC-TA isthmus (flutter) line using cryo

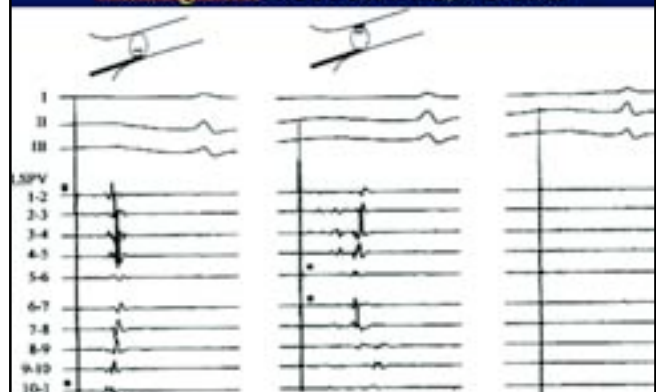
Slide 3

PA3 - Time to First AF Intention to Treat



Slide 6

Haissaguerre... *Circ* 2000;102:2463-2465







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