Recent Advances

Cardiology—II: Treatment of heart failure and atrial fibrillation and arrhythmias

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In the first part of our review of the advances in cardiology over the past year we considered treatment of myocardial infarction and angina.[1] In this part we summarise the most important advances in the treatment of heart failure, atrial fibrillation, and arrhythmias. A glossary of study abbreviations is given in the appendix.

Heart failure and digoxin

In the past year, more has been learnt about what does not help patients with chronic heart failure than what is of benefit. Important American guidelines on treatment have also been issued.[2]

Two trials have investigated whether digoxin is of benefit in patients with chronic heart failure who are in sinus rhythm.[3,4] In both trials the condition was stabilised by digoxin treatment before patients were randomly allocated in a double blind fashion to withdrawal (placebo substitution) or continuation of digoxin. In one study (PROVED) patients were not treated with an angiotensin converting enzyme inhibitor whereas in the other (RADIANCE) they were. During follow up of three months the patients in both groups who had had digoxin withdrawn showed clinical deterioration (table I).

The results of these trials are important advances in our understanding of the role of digoxin in chronic heart failure. For patients who remain symptomatic while taking a diuretic but cannot tolerate an angiotensin converting enzyme inhibitor, digoxin is an option. Similarly, patients who remain symptomatic despite taking an angiotensin converting enzyme inhibitor should also be treated with digoxin.

The one caveat to these conclusions is whether deterioration after digoxin withdrawal (as seen in the studies) is the same as clinical improvement when the drug is added to existing drug treatment. Other studies suggest that the addition of digoxin to diuretics is of benefit in at least some patients. Whether this is also the case in patients treated with an angiotensin converting enzyme inhibitor is unknown.

The effect of digoxin on mortality is not known, though it is under investigation by the Digitalis Investigators Group.

Heart failure and β blockers

The suggestion that β blockers might be of benefit in patients with chronic heart failure has been around for nearly 20 years, though it has only recently been tested in large clinical trials.[5]

In the MDC trial 383 patients with stable idiopathic dilated cardiomyopathy who tolerated a test dose of metoprolol were randomly allocated placebo or metoprolol in addition to full conventional treatment—that is, most received frusemide, digoxin, and an angiotensin converting enzyme inhibitor. A total of 211 patients were followed up for 12 months. Metoprolol treatment was started at a dose of 5 mg twice daily and was titrated over seven weeks to a target daily dose of 150 mg.

Metoprolol did not reduce mortality significantly, but it did have significant haemodynamic and clinical benefits (table II). The need for transplantation was also reduced in the metoprolol group (table II). Broadly similar findings have been reported in CIBIS, which is as yet unpublished. In CIBIS patients with chronic heart failure due to coronary artery disease were studied as well as those with idiopathic dilated cardiomyopathy. Interestingly, the beneficial effects of bisoprolol seemed to be confined to the patients with idiopathic dilated cardiomyopathy. If β blocker treatment is to make a major clinical impact on the problem of chronic heart failure, it will have to work in patients with chronic heart failure due to coronary disease (perhaps 75% of all patients with heart failure). More studies of β blockers in these patients are needed and are long overdue.

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TABLE I—*Outcomes after three months in trials of digoxin withdrawal in patients with chronic heart failure*[3,4]

Outcome	Proved			Radiance		
	Placebo (n=46)	Digoxin (n=42)	P value	Placebo (n=93)	Digoxin (n=85)	P value
Treatment failure (%)*	39	19	0·039	25	2	<0·001
Change in exercise time from baseline (s)	−96	+4·5	0·003	−26	+17	0·033
Change in body weight (kg)	+0·5	−0·9	0·044	+1	−1	<0·001
Change in LVEF (%)	−3	+2	0·016	−4	−1	0·001
Hospital admission for worsening heart failure (%)†	13	7		10	2	

LVEF=left ventricular ejection fraction. *Heart failure worsened during trial. †Withdrawn from study.

TABLE II—*Results of MDC trial*[5]

End point	Placebo (n=189)	Metoprolol (n=194)	P value
A Mortality (%)	10·05	11·85	0·69
B Need for transplantation (%)	10·05	1·03	0·0001
Both A and B	20·10	12·88	0·058
Increase in exercise capacity from baseline at 12 months (s)	15	76	0·046
Average no of hospital admissions per patient	0·47	0·28	<0·04
Increase in LVEF from baseline to 12 months (%)	6	12	<0·0001

LVEF=left ventricular ejection fraction.

Heart failure and amiodarone

The GESICA study investigated whether low dose amiodarone could reduce mortality in severe heart failure. Five hundred and sixteen patients receiving full conventional treatment (including an angiotensin converting enzyme inhibitor) were randomly allocated to a control group or to amiodarone (600 mg/day for 14 days, 300 mg/day thereafter).[6] Thirty per cent of patients had idiopathic dilated cardiomyopathy or Chagas disease as the cause of their heart failure and only around 40 per cent had documented previous myocardial infarction. Patients with previous ventricular fibrillation or symptomatic ventricular tachycardia were excluded, as were patients with 10 or more beats of non-sustained ventricular tachycardia.

A two year planned follow up was stopped early after 13 months. Mortality in the control group was 41·4% compared with 33·5% in the amiodarone group (risk reduction 28%, P=0·024). This equates to a reduction in 73 premature deaths per 1000 patient years of treatment. Both sudden death and death from progressive pump failure were reduced. A similar proportional reduction in mortality was seen in patients with and without non-sustained ventricular tachycardia at baseline. The New York Heart Association functional class of heart failure also improved significantly in patients treated with amiodarone. A low frequency of side effects was reported, though there was no placebo control and follow up was short.

Another, smaller, South American study (EPAMSA) using 400 mg amiodarone daily reported a similar benefit in patients with heart failure and asymptomatic arrhythmias.[7] A further small study of 200 mg amiodarone daily, however, showed no reduction in mortality in similar patients.[8] A large North American amiodarone mortality trial (CHF-STAT) in unselected patients has just reported (B N Singh, 16th congress of the European Society of Cardiology, Berlin, September 1994). Six hundred and seventy four patients with heart failure who were receiving full conventional treatment and had >10 premature ventricular contractions on 24 hour ambulatory electrocardiographic monitoring were randomly allocated to placebo or amiodarone (800 mg daily for 14 days, 400 mg daily for 50 weeks, 300 mg daily to end of study). Patients were recruited over 2·5 years and follow up was for an additional two years. Left ventricular ejection fraction increased with amiodarone treatment, but overall survival was not changed. There was, however, a strong trend for an improvement in survival in patients without coronary artery disease.

Further evaluation of the place of amiodarone in the management of patients with heart failure must await full publication of CHF-STAT. At present, however, it should not be used routinely in patients without symptomatic arrhythmias. Amiodarone may, however, be the best drug in patients with heart failure and symptomatic arrhythmias. Unlike other antiarrhythmic drugs amiodarone does not seem to further depress left ventricular function or increase mortality. It also has a low incidence of proarrhythmia.

TABLE III—*Stroke rates per 100 patient years in placebo controlled trials of warfarin in patients with non-rheumatic atrial fibrillation*

	Control/placebo	Warfarin
Primary prevention trials		
AFASAK (n=671)[9]	4·29	1·99
BAATAF (n=420)[10]	2·99	0·62
SPAF I study (n=421)[11]	6·97	2·69
CAFA study (n=378)[12]	3·72	2·95
SPINAF study (n=525)[13]	4·32	1·10
Secondary prevention trials		
SPINAF study (n=46)[13]	9·28	6·12
EAFT (n=439)[14]	12·34	3·94

TABLE IV—*Stroke rates per 100 patient years in placebo controlled trials of aspirin in patients with non-rheumatic atrial fibrillation*

	Control/placebo	Aspirin*
Primary prevention trials		
AFASAK (n=672)[9]	4·29	6·66
SPAF I study (n=1120)[10]	5·74	3·33
BAATAF[15]†	1·84	3·89
Secondary prevention trials		
EAFT (n=782)[14]	12·59	10·50

*Daily dose: 75 mg in AFASAK, 325 mg in SPAF I study and BAATAF, and 300 mg in EAFT.
†Retrospective analysis.

TABLE V—*Stroke rates per 100 patient years in controlled trials of aspirin versus warfarin in patients with non-rheumatic atrial fibrillation**

	Aspirin	Warfarin
AFASAK (n=671)[9]	6·66	1·99
SPAF II[16]:		
Aged ≤75 years (n=715)	1·94	1·73
Aged >75 years (n=385)	5·57	5·08
BAATAF[15]†	3·89	0·45

*No such data given in EAFT.[14] †Non-randomised.

Atrial fibrillation

PREVENTION OF STROKE

Non-rheumatic atrial fibrillation affects more than 5% of the population over the age of 69 years and as many as 10% over the age of 75. One of the most important therapeutic advances in cardiology is the use of warfarin and aspirin to prevent stroke in these patients.

WARFARIN V PLACEBO: PRIMARY AND SECONDARY PREVENTION

Five large controlled trials have shown that warfarin will prevent 20-30 strokes per 1000 patient years of treatment at a cost of 6-8 serious bleeding episodes per 1000 patient years (table III).[9-13] These trials can be considered as primary prevention trials as less than 5% of the patients studied had had a stroke.

The use of warfarin for secondary prevention in patients with atrial fibrillation and a previous stroke has been studied in EAFT (table III).[14] This recent study shows that 80 strokes can be prevented per 1000 patient years of treatment with warfarin. The SPINAF study also randomised a small group of patients with a history of stroke (table III).[13]

ASPIRIN V PLACEBO

The value of aspirin in the primary and secondary prevention of stroke in patients with atrial fibrillation has also been studied (table IV). Two of the three trials showed no significant benefit from aspirin, a conclusion also drawn from a retrospective analysis of BAATAF.[15] One study (SPAF I) did, however, show a significant benefit. Aspirin might prevent up to 20 strokes per 1000 patient years of treatment, though this may depend on the dose used and type of patient treated (see below).

WARFARIN V ASPIRIN

The relative benefits of warfarin and aspirin have been studied prospectively in three trials (table V).[9,14,16] In all three trials the rate of stroke was lower in the warfarin group, a conclusion also reached in a retrospective analysis of BAATAF.[15] In EAFT warfarin was significantly superior to aspirin with a hazard ratio of 0·38 (95% confidence interval 0·23 to 0·64, P<0·0001).

Warfarin seems to be more effective in older patients (though they also run a greater risk of intracranial haemorrhage) and in patients with risk factors for

stroke (see below). A dose of aspirin of 300 mg may be more effective than a dose of 75 mg. Patients younger than 75 years without risk factors for stroke who take 300 mg of aspirin daily have a low risk of stroke and other vascular events.

WHO IS AT RISK OF STROKE?

Further analysis of these trials has been undertaken to identify which patients are at highest risk of stroke and who have the greatest ratio of benefit to risk for warfarin treatment.[17,18]

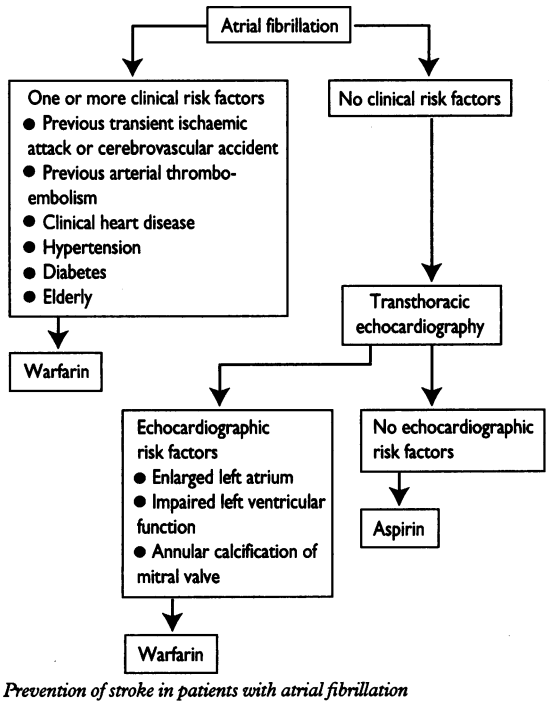
In the SPAF study hypertension, recent (within three months) heart failure, and previous arterial thromboembolism were risk factors for stroke. With no risk factors, the incidence of stroke was 2·5% per year, with one risk factor it was 7·2% per year, and with two or three risk factors it was 17·6% per year. No strokes occurred in patients under 60 who did not have any risk factors.

Left atrial enlargement and left ventricular impairment also increased the risk of stroke. In BAATAF older age and the presence of clinical heart disease and mitral annular calcification on echocardiography increased the risk of stroke.[15]

On the basis of these data it is possible to devise a treatment strategy that restricts the use of warfarin to those patients who are most likely to benefit from it (figure). Further refinement of risk for patients with atrial fibrillation and no conventional echocardiographic risk factors may be possible by using transoesophageal echocardiography to identify patients with so called spontaneous left atrial contrast, which is a predictor of stroke. This hypothesis remains to be tested in a clinical trial.

Ventricular arrhythmias and electrophysiological testing

Sudden death from heart disease remains a major cause of mortality, but resuscitation outside hospital has resulted in survival of an increasing number of patients, whose optimal management remains controversial. Electrophysiological studies to assess whether ventricular tachyarrhythmias can be induced by electrical stimulation may provide therapeutic and prognostic information, but the skills are not universally available. Two recent studies have resulted in the examination of the need for such invasive assessment, which often may require the transfer of patients to specialist centres.



Prevention of stroke in patients with atrial fibrillation

ESVEM STUDY

The ESVEM study compared invasive and non-invasive assessment of the efficacy of antiarrhythmic drugs in patients with life threatening ventricular arrhythmias.[19] Drug efficacy was predicted in 296 of the 486 patients randomly allocated to electrophysiological studies (108) or electrocardiographic (Holter) monitoring (188). Over six years of follow up there was no difference in recurrence of arrhythmia in the two groups. It cannot be concluded, however, that the two methods were equally good, but rather that they were equally bad. With both techniques the probability at four years of death from arrhythmia was about 20% and recurrence of any arrhythmia was over 60%. The patient population was highly selected, each patient having to be suitable for both methods of testing. In other words, patients had to have moderately frequent ventricular premature beats (an average of 10 or more an hour) and to have ventricular tachycardia or fibrillation induced by ventricular electrical stimulation at electrophysiological study. Less than half of the eligible patients satisfied these entry criteria (486 of the 1005 patients who were eligible from a total of 2103 enrolled). Another limitation of the ESVEM study in its application to routine practice is that amiodarone was not tested. The single most important result for clinical practice was that sotalol was more effective than the six other drugs tested and was recommended as the best treatment.[20]

CASCADE

The value of drug treatment being guided by the results of physical testing has been further challenged by the results of CASCADE. In 228 survivors of cardiac arrest amiodarone was more effective than conventional treatment—namely, treatment with class I antiarrhythmic drugs guided by electrophysiological testing or Holter monitoring if no arrhythmia was inducible.[21] Further benefit might have been achieved with guided amiodarone treatment or with sotalol, which was not tested. About half of the patients also received an automatic implanted cardioverter-defibrillator, and survival end points included a syncopal device discharge. Recurrence of cardiac arrest at four years was 34% with amiodarone and 48% with conventional treatment. Again, it is important to note the high recurrence rates in both groups. Thus, although amiodarone was superior to guided treatment with class I antiarrhythmic drugs, neither treatment was optimal.

The important message from these studies is less about the role of electrophysiological testing but more about the limited value of drug treatment in patients with life threatening arrhythmias.[22] Non-pharmacological treatments are available and attempts must be made to identify the patients most likely to benefit from them. Evaluation of risk and selection of appropriate therapies can best be obtained from the responses to ventricular electrical stimulation, so invasive electrophysiological studies in these high risk patients are recommended.[23]

Arrhythmias and implantable cardioverter-defibrillators

Advances in the technology of implantable cardioverter-defibrillators have increased the applicability of this potentially lifesaving device. Lead systems can now be implanted without thoracotomy in most patients. This removes almost totally the perioperative mortality experienced with previous systems that required thoracotomy to implant epicardial

patches.[24] Successful experience with transvenous systems that can be implanted by doctors,[25] the development of smaller generators that can be implanted pectorally rather than abdominally, and the development of single lead unipolar devices (the generator being the active cathode)[26] mean that implanting a cardioverter-defibrillator is approaching the simplicity and safety of implanting a pacemaker.[27]

These recent advances—knowledge of the limited value of current drug treatment and technological improvements in devices—have, however, raised questions about the cost and efficacy of implantable devices.[28-30] Implantation of a cardioverter-defibrillator almost totally abolishes the risk of dying suddenly because of arrhythmia, but the impact on overall outcome has not been tested in a prospective controlled study. Recent retrospective studies have shown significant improvements in mortality in patients with devices compared with those managed medically,[31 32] particularly in patients with left ventricular dysfunction, although total mortality from cardiac causes remains substantial (30% at 5 years).[32] Left ventricular dysfunction is a major determinant of total mortality, even in patients with implantable defibrillators.[32 33] Others have reported that the outcomes of patients with implantable devices were not dramatically different from those of patients treated with other methods, mainly guided by responses to electrophysiological testing, and therefore argued that prospective studies would be ethically justified.[34] A placebo controlled study in patients who have survived a cardiac arrest cannot be justified, but several large studies are now under way to compare implantable devices with drug treatment, particularly amiodarone, sotalol, and β blockade.[28-30 35] In addition, implantable defibrillators are being compared with no antiarrhythmic treatment in patients who are at high risk of sudden death because they have left ventricular dysfunction and non-sustained ventricular arrhythmias. The results of these studies over the next few years may clarify the place of drugs or devices, but for the present we must ensure that our patients are adequately assessed, including electrophysiological testing, and offered the treatments most likely to be of long term benefit, including the expensive option of implantable devices.

Arrhythmias and amiodarone after myocardial infarction

Most patients who die suddenly have coronary artery disease, and prophylaxis against myocardial infarction has improved.[36] The potential hazards of antiarrhythmic drugs, particularly in asymptomatic patients, were clearly demonstrated in CAST, in which treatment with class I drugs was associated with increased mortality.[37] The results with empirical amiodarone treatment look more optimistic.[38-40] Such treatment may be of greater value than β blockade after acute myocardial infarction.[40] Given the well known side effects of amiodarone, it is reasonable to reserve judgment until the results of ongoing studies are reported. For instance, EMIAT will assess the value of amiodarone after acute myocardial infarction in patients with left ventricular dysfunction whether or not they have documented ventricular arrhythmias; follow up will be complete in 1995.[41]

Arrhythmias and radiofrequency catheter ablation

The treatment of patients with recurrent paroxysmal supraventricular tachycardias has been revolutionised by the potentially curative technique of radiofrequency catheter ablation of either accessory pathways[42] or of atrioventricular nodal pathways.[43] (Ablation of the slow AVN pathway is preferred because of the low risk of inadvertent heart block.) High success rates can be achieved, but even experienced electrophysiologists need to be experienced in performing ablation to achieve these.[44] The past year has seen reports of the successful application of the technique in children[45 46] and elderly patients.[47] It has also been applied to other cardiac arrhythmias—notably, atrial flutter,[48 49] atrial tachycardia,[50] and ventricular tachycardia in patients without structural heart disease.[51-54] In patients with ventricular tachycardia secondary to ischaemic heart disease the technique has a more restrictive role as it is considered to be palliative rather than a definitive treatment.[55 56]

Recent advances in cardiology

Chronic heart failure

- Clearer understanding of the role of digoxin, especially when diuretics are insufficient and angiotensin converting enzyme inhibitors cannot be tolerated
- β Blockers for idiopathic dilated cardiomyopathy
- Amiodarone for patients with congestive heart failure and symptomatic arrhythmias

Atrial fibrillation

- Clearer understanding of primary and secondary prevention of stroke with warfarin in atrial fibrillation

Arrhythmias

- Increased understanding of the limitations of drug treatment
- Implantable cardioverter-defibrillators
- Radiofrequency catheter ablation

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Appendix

Study abbreviations

AFASAK, Danish atrial fibrillation, aspirin, anticoagulation trial
BAATAF, Boston area anticoagulation trial in atrial fibrillation
CAFA, Canadian atrial fibrillation anticoagulation trial
CASCADE, cardiac arrest in Seattle, conventional versus amiodarone drug evaluation study
CAST, cardiac arrhythmia suppression trial
CHF-STAT, congestive heart failure with amiodarone trial
CIBIS, cardiac insufficiency bisoprolol study
EAFT, European atrial fibrillation trial
EMIAT, European myocardial infarct amiodarone trial
EPAMSA, estudio piloto de muerte subita y amiodarona
ESVEM, electrophysiologic study versus electrocardiographic monitoring
GESICA, Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
MDC, metoprolol in dilated myopathy
PROVED, prospective randomised study of ventricular failure and efficacy of digoxin
RADIANCE, randomised assessment of the effect of digoxin on inhibitors of the angiotensin converting enzyme
SPAF, stroke prevention in atrial fibrillation
SPINAF, stroke prevention in non-rheumatic atrial fibrillation

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