# CARDIOLOGY 1999; REVIEW OF THE WITHERING BICENTENARY SYMPOSIUM HELD IN THE COLLEGE ON 5 FEBRUARY 1999

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William Withering, an eighteenth-century physician who graduated from Edinburgh University was the first to characterise the clinical pharmacology and utility of digoxin, especially in patients with heart failure. The Withering Bicentenary Symposium was organised by Professor David Webb on behalf of the College and the University of Edinburgh in recognition of the two hundredth anniversary of William Withering's death. The meeting brought together internationally renowned speakers to discuss many aspects of current practice in cardiology. The lessons relating to the use of digoxin, and the treatment of heart failure and atrial fibrillation are detailed here. The Sir Stanley Davidson Lecture was given by Professor William Haynes from the University of Iowa and is detailed elsewhere in *Proceedings*.

## DIGOXIN

### *Historical background*

The scene was set by Professor Brian Pentecost, Clinical Director of the British Heart Foundation who gave an eloquent biopic of William Withering, a graduate of Edinburgh medical school in 1766. William Withering (1741-1799), the son of an apothecary, was born in Wellington, Shropshire. Following graduation, he helped to found and then work in the infirmary in Stafford for the 'poor and destitute'. Whilst there, he met and later married one of his patients, Helena Cooks, a talented plant illustrator who may well have initiated his interest in botany. The impecuniosity of his position in Stafford made the offer of a prominent and well-paid position in Birmingham very attractive. Erasmus Darwin, a powerful and influential physician, with whom his relationship would later descend into public acrimony, succeeded in attracting Withering to work at the Birmingham General Hospital in 1775. Whilst overseeing the treatment of over 2,000 patients per annum free of charge, Withering became a member of several scientific societies - including the famous Lunar Society - where he fostered both his medical and botanical interests.

Digitalis was, at the time, used for wound dressings as well as in the treatment of such disparate illnesses as epilepsy and tuberculosis - rather ironically, the latter disease plagued, and eventually claimed, his life. However, Withering was the first to use and promote the use of digitalis in patients with 'dropsy' and published his first detailed account of this in his 1785 book - a facsimile of this book has recently been republished.[1] He discussed the timing of harvesting of the foxglove leaves and the profile of the associated toxicology, and made many critical, clinical and pharmacological observations based on his meticulous approach to the analysis, preparation and dosage of digitalis. He clearly recognised the small difference in dose between efficacy and toxicity (the 'narrow therapeutic window') and provided valuable advice on how to achieve the former without the latter. He was widely consulted over the use of digitalis in the treatment of patients with heart failure, and wrote many monographs on the subject before his untimely death from tuberculosis in Edgbaston Sanatorium on 1 October 1799.

William Withering (1741-1799):

- graduated from Edinburgh University in 1766,
- worked in Birmingham General Hospital from 1775,
- was a member of the prestigious Lunar Society,
- had keen botanical interests shared by his wife,
- described the clinical pharmacology and utility of digitalis in the treatment of heart failure.

## DIGOXIN IN HEART FAILURE: A MODERN PERSPECTIVE

Professor John Cleland, Professor of Cardiology in the University of Hull, gave a provocative and challenging talk on the place of digoxin in the contemporary treatment of heart failure. Five trials over the last ten years have addressed the efficacy of digoxin in those patients with heart failure who remain in sinus rhythm. Three trials, RADIANCE,[2] PROVED,[3] and DIG,[4] have been the most informative and were conducted in the presence of associated maintenance diuretic and angiotensin converting enzyme (ACE) inhibitor therapy. The PROVED and RADIANCE studies were small-scale trials of digoxin withdrawal versus continued maintenance therapy and, in keeping with many other major heart failure trials, the patients were unrepresentatively young. These two trials used high-maintenance doses of digoxin (0.375-0.4 mg daily) and demonstrated that digoxin withdrawal was associated with a significant deterioration in symptoms, exercise tolerance and left ventricular function.

The DIG study was a large-scale randomised placebo-controlled trial of digoxin involving 6,800 patients with approximately half the study population already receiving digoxin and the other half being digoxin naive. No effect of digoxin was identified on the primary end-point of all-cause mortality, but there was an associated reduction in hospitalisations (6% reduction), especially for worsening heart failure (23% reduction). Moreover, the combined secondary end-point of death or hospitalisation due to worsening heart failure was reduced by 19%. These findings were most marked in those patients with lower systolic ejection fractions and were consistent whether the patients had been previously maintained on digoxin or were digoxin naive. However, over 85% of the study population were prescribed

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digoxin at a dose less than, or equal to, 0.25 mg daily, and therefore at doses not shown to improve symptoms in the previous trials.

Digoxin has been shown to be safe at doses not shown to improve symptoms and to improve symptoms at doses not shown to be safe. Overall, digoxin has a small effect on hospitalisation and no effect on mortality. Whether these rather modest benefits remain in patients further maintained on a beta blocker and spironolactone, drugs recently shown to provide added mortality benefit in heart failure, awaits to be established and begs the question: 'Does digoxin still have a role in the management of patients with heart failure who remain in sinus rhythm?'

In patients with heart failure, digoxin:

- has no effect on all-cause mortality,
- reduces hospitalisation due to heart failure,
- improves symptoms of heart failure when used at relatively high doses.

## HEART FAILURE

### *Renin-angiotensin-aldosterone system inhibition in heart failure*

The benefits of ACE inhibition in the treatment of heart failure are well established but the completeness of the inhibition of renin-angiotensin-aldosterone system was questioned by Professor Allan Struthers from the University of Dundee. In patients with chronic heart failure maintained on ACE inhibitors, plasma aldosterone and angiotensin concentrations are significantly elevated in 40% and 15% of patients respectively. This finding is not only in part attributable to a lack of compliance with therapy; it is due to loss of vascular ACE inhibition as the disease progresses, and possibly also to the generation of angiotensin II by non-ACE mechanisms. The importance of this 'escape' from ACE inhibition is highlighted by the finding that persistently elevated plasma angiotensin II concentrations, despite ACE inhibition, are associated with a much higher mortality from heart failure.

Angiotensin II type 1 receptor ($AT_1$) antagonism is a novel method of potentially causing more complete blockade of the renin-angiotensin-aldosterone system either as an alternative to, or in combination with, ACE inhibition. As with ACE inhibition, $AT_1$ antagonism is associated with a symptomatic improvement in patients with heart failure.[5]

The ELITE study was the first major trial comparing ACE inhibition and $AT_1$ antagonism and assessed the effects of captopril and losartan on renal dysfunction in heart failure and found no significant differences in outcome.[6] However, although not designed as a mortality study, a significantly greater reduction in mortality attributable to losartan was observed. Confirmation of this tentative finding is awaited from the outcome of the ELITE II study, which is a properly designed, large-scale, comparative mortality trial of losartan versus captopril. However, these observed benefits of losartan over captopril are in keeping with the findings of the effects on QT dispersion (worsened by captopril), and survival studies of losartan and captopril in experimental animal models of heart failure. The underlying mechanisms producing these differential effects may relate to the pharmacological action of these compounds, such as the hyperstimulation of angiotensin II type 2 receptors during $AT_1$ antagonism, or the blockade of kinin metabolism by ACE inhibition.

Spironolactone provides a further approach to the blockade of the renin-angiotensin-aldosterone system through aldosterone receptor antagonism. The Randomized Aldactone Evaluation Study (RALES) trial has yet to be fully published,[7] but initial results were recently presented at the 71st Scientific Session of the American Heart Association. This was a randomised controlled trial of spironolactone, 25 mg daily, in 1,663 patients with severe (New York Heart Association class III or IV) heart failure maintained on ACE inhibitor and diuretic therapy. The trial was discontinued early when the data and safety monitoring board found overwhelming evidence of benefit with the study drug after an average follow-up of 24 months. Overall mortality was reduced by 27% with similar reductions in death due to progressive heart failure and sudden cardiac death. All admissions to hospital were reduced by 17% and hospitalisations for heart failure by 36%. The mechanisms through which spironolactone may produce these benefits include actions on the autonomic nervous system, salt and water balance, myocardial fibrosis, endothelial function and arrhythmogenesis.

Renin-angiotensin-aldosterone system blockade using ACE inhibitors remains the mainstay of treatment in patients with heart failure. In the presence of ACE inhibitor intolerance, $AT_1$ antagonism is a reasonable alternative but at present there is insufficient evidence to recommend $AT_1$ antagonism as first-line or combination therapy. In patients with severe heart failure, it would appear that spironolactone therapy has major additional benefits when given in combination with ACE inhibitors.

In patients with heart failure:

- inhibition of the angiotensin converting enzyme (ACE) has major mortality and morbidity benefits,
- ACE inhibitor therapy may provide incomplete blockade of the renin-angiotensin-aldosterone system,
- angiotensin II type 1 ($AT_1$) receptor antagonism improves symptoms but confirmation of potential mortality benefits are awaited,
- spironolactone may improve symptoms and reduce mortality when given in combination with ACE inhibitors.

## β-BLOCKER THERAPY IN HEART FAILURE

Established medical practice has been to avoid the use of β-blockers in patients with heart failure. Professor John McMurray from the University of Glasgow reviewed the compelling evidence from several recent large-scale randomised controlled trials of the major benefits associated with β-blocker therapy in patients with heart failure.

The reduction in cardiac output and reserve associated with heart failure causes neuroendocrine activation that involves both the sympathetic nervous system and the renin-

angiotensin-aldosterone system. Despite the beneficial effects of ACE inhibition, the mortality from heart failure remains high and additional inhibition of the sympathetic nervous system may provide further benefits. Indeed, as with angiotensin II, plasma adrenaline concentrations correlate with mortality in patients with heart failure. However, the theoretical benefits of β-blocker therapy need to be judged against the potential risks of symptomatic and clinical deterioration.[8,9]

The first recent evidence from large-scale randomised controlled trials came from a programme of four trials investigating the effects of carvedilol in patients with chronic heart failure. A single safety monitoring committee overseeing all four trials stopped the program early because the pooled data demonstrated a marked benefit of carvedilol over placebo. Carvedilol was associated with a reduction in all cause six-month mortality from 7.8% to 3.2%, all-cause hospitalisation from 27% to 19% and hospitalisation for cardiovascular disease from 20% to 14%. Because of the premature termination of the studies, none of the four trials reached their individual primary end-points except one that showed a reduction in the progression of the disease in patients with mild heart failure. Because of the unusual nature of the design and conduct of these trials some have expressed doubt about the validity of these findings. However, the CIBIS II trial,[10] published earlier this year, was designed to confirm and extend the findings of the carvedilol trials. In this single, large-scale, randomised controlled trial of 2,647 patients with moderate to severe heart failure maintained on diuretic and ACE inhibitor therapy, an up-titrated dose of bisoprolol was compared to placebo. Again, the study was terminated early as the second interim analysis showed a marked mortality benefit: 11.8% versus 17.3% - relative risk reduction of 32%. Similar reductions were also seen in sudden cardiac death and hospitalisation. Six further large-scale randomised controlled trials investigating the effects of β-blocker therapy in patients with left ventricular dysfunction are ongoing. The MERIT-HF trial has been provisionally reported[11] and, in keeping with the CIBIS II trial findings, demonstrated a 35% reduction in mortality with metoprolol.

It is widely recognised that β-blocker therapy can cause adverse effects in patients with heart failure. Although this may have been influenced by investigator bias, 6.8% of patients in the carvedilol trials had to be withdrawn from the open label up-titration phase because of worsening symptoms, compared to 4.6% with placebo. In contrast, during the double-blind maintenance phase, 11.6% were withdrawn from carvedilol compared to 22.3% from placebo. The permanent treatment withdrawals in the CIBIS II trial (15%) were similar for both placebo and bisoprolol treated groups. It should be remembered, however, that in these trials, β-blocker therapy was cautiously introduced in patients with stable chronic heart failure, using a protracted up-titration protocol and under close clinical supervision.

In summary, β-blocker therapy appears to produce a similar and additive morbidity and mortality benefit to that seen with ACE inhibition in patients with heart failure. The introduction of β-blocker therapy requires close clinical observation and cautious up-titration. However, under these circumstances, β-blockers can be used safely and effectively in patients with stable heart failure to improve both symptoms and prognosis.

In patients with heart failure who are maintained on angiotensin converting enzyme (ACE) inhibitor therapy:

- β-blocker therapy produces similar and additive mortality and morbidity benefits to those seen in ACE inhibition,
- should only be commenced in stable patients with chronic heart failure,
- β-blocker therapy requires close clinical observation and cautious up-titration.

## ATRIAL FIBRILLATION

### *Anticoagulation in atrial fibrillation*

Atrial fibrillation is one of the strongest risk factors associated with the development of stroke and Dr Gregory Lip, Senior Lecturer in Cardiology at the University of Birmingham, detailed the evidence and provided guidance for the appropriate anticoagulation of patients with atrial fibrillation.

Studies have shown that the use of warfarin in the primary[12] and secondary[13] prevention of stroke in patients with atrial fibrillation is associated with a two-thirds reduction in the annual stroke rate (from 4.5% to 1.4% and from 12% to 4% respectively). However, these studies had a wide anticoagulation range (INR 1.4-4.5), enrolled less than 10% of screened patients, and necessitated regular review and monitoring. In contrast, aspirin is much easier to use but the risk reduction is rather modest, at 21%,[14] and of borderline statistical significance. Indeed, head-to-head comparison between warfarin and aspirin demonstrates a relative risk reduction in stroke of 48% in favour of warfarin, although the risk of a major bleeding episode was 3% and 1% respectively. Moreover, studies looking at fixed low-dose warfarin, either alone or in combination with aspirin therapy, have failed to show clinical efficacy in stroke prevention to the same degree as dose-adjusted warfarin. It should also be remembered that the majority of patients who had a thrombotic stroke whilst on warfarin had an INR <2.0.

The use of warfarin is limited by the suitability of initiating therapy, particularly where frailty, co-morbidity, polypharmacy and bleeding risks exist. Competing influences are often present; for example, those elderly patients who are at the greatest risk, are also more likely to have significant co-morbidity or frailty. The risk/benefit assessment is, therefore, paramount, and in patients over 75 years it may be pertinent to reduce the target INR to 1.6-2.5 because of the associated increased risk of haemorrhagic stroke at this age, especially when the INR rises above 3.5.

Thromboprophylaxis is, therefore, indicated in patients with atrial fibrillation based on a risk stratification approach (Table 1). Patients intolerant of, or possessing contraindications to, warfarin therapy should receive aspirin. The evidence suggests that moderate risk patients have a stroke rate reduction from 4% to 1% whether given aspirin or warfarin, although further risk stratification with echocardiography may be necessary.

TABLE 1
Suggested guide to thromboprophylaxis in patients with atrial fibrillation.

| Level of Risk | Clinical Risk Factors | Annual Stroke Risk | Thromboprophylaxis |
|---|---|---|---|
| High | • Previous cerebrovascular accident or transient ischaemic attack<br>• Age > 75 years with diabetes mellitus or hypertension<br>• Structural heart disease including heart failure and enlarged left atrium<br>• Thyroid disease | >8% | Warfarin: INR 2.0-3.0<br>If intolerant of warfarin, then use aspirin 75-300 mg |
| Moderate | • Aged < 65 years and diabetes mellitus, hypertension or vascular disease<br>• Aged > 65 years | 4% | Aspirin 75-300 mg<br>Consider warfarin* |
| Low | • Aged < 65 years and no risk factors | 1% | Aspirin 75-300 mg |

*Further investigations may help to appropriately risk-stratify patients.

In atrial fibrillation:

- anticoagulation is associated with a major reduction in the risk of stroke, both in primary and secondary prevention,
- aspirin is associated wth a modest reduction in stroke rate,
- there is a risk of haemorrhage with both warfarin and aspirin,
- choice and appropriateness of anti-coagulation depends on an assessment of the risks and benefits of therapy.

*Restoration and maintenance of sinus rhythm following atrial fibrillation*

Dr Campbell Cowan, Senior Lecturer at the University of Leeds, discussed the importance of re-establishing sinus rhythm in atrial fibrillation not only to reduce the risk of thromboembolism but also to improve atrial function and systemic haemodynamic parameters including cardiac output. In the month following successful restoration of sinus rhythm the left ventricular ejection fraction can increase dramatically from 35% to 55%. Moreover, in patients with bundle of His ablations, irregular ventricular pacing is associated with a lower cardiac output than during regular pacing at an identical mean heart rate.

Both mechanical and electrical adaptive changes occur during atrial fibrillation, and the likelihood of remaining in atrial fibrillation increases with the passage of time: 'atrial fibrillation begets atrial fibrillation'. However, all patients with atrial fibrillation should have at least one attempt at restoring sinus rhythm with cardioversion. The factors which predict the likelihood of re-establishing and maintaining sinus rhythm are the duration of atrial fibrillation, the left atrial size, patient age, left ventricular function and a history of rheumatic heart disease. The initial success rate of cardioversion is approximately 80% irrespective of how long the patient has been in atrial fibrillation, but the subsequent return of atrial fibrillation is much more likely if it was present for more than a year beforehand.

Acute atrial fibrillation has a high spontaneous rate of reversion to sinus rhythm. Digoxin, the commonest drug to be prescribed for acute atrial fibrillation, is associated with a 50% reversion rate at 24 hours with a mean time to sinus rhythm of 5.1 hours. However, placebo has a very similar 24-hour reversion rate of 44% and a quicker time to sinus rhythm of 3.3 hours. This pattern is also seen with amiodarone: a more rapid return of sinus rhythm but no difference at 24 hours.

The drug treatment of patients with sustained or paroxysmal atrial fibrillation relies on class I and III agents, including flecainide, propafenone, sotalol and amiodarone, which are able to restore and sustain sinus rhythm in 30-90% of cases. Class IV agents, such as verapamil, have little if any role, with a success rate of only 5-10%. Non-pharmacological treatments are available, such as dual chamber and atrial pacing, implantable atrial defibrillators, ablation and surgical 'maze' procedures, and are suitable only in highly selected cases. The treatment and management of patients with paroxysmal atrial fibrillation remains a major challenge.

- Restoration of sinus rhythm is important to reduce the risk of thromboembolism and to improve cardiac performance.
- Electrical and pharmacological approaches should be used to re-establish and maintain sinus rhythm.
- The likelihood of re-establishing and maintaining sinus rhythm is dependent on the length of time in atrial fibrillation and clinical characteristics of the patient.
- Class I, II and III, but not IV, antiarrhythmic agents are useful in the treatment of patients with paroxysmal atrial fibrillation.

## CONCLUDING REMARKS

Over the 200 years since William Withering's death, many new strategies have been developed for the treatment of both heart failure and atrial fibrillation although it was as recently as 1988 that diuretic therapy was advocated as the sole therapy for heart failure.[14] The evolution of drug therapy has brought many new additions that have improved, and promise to improve further, the quality and the length of life of patients suffering from these conditions. Many unanswered questions still remain but we have come a long way from the therapeutic infusions of the digitalis leaf - William Withering would surely approve.

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THE SPEAKERS WERE:

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|---|---|
| Prof. B. Pentecost | Withering's legacy; the discovery of digoxin. |
| Prof. J.G.F. Cleland | Digoxin in heart failure; where are we now? |
| Prof. R.J.C. Hall | Optimal investigation in heart failure. |
| Dr G. Jackson | Secondary prevention - the evidence for men and women. |
| Prof. W.G. Haynes | Homocysteine and atheriosclerosis: potential mechanisms and major clinical implications. |
| Prof. A. Struthers | Inhibitors of the renin-angiotensin system, present and future |
| Prof. J. McMurray | β-blockers; a practical therapy in heart failure? |
| Dr G.Y.H. Lip | Who should be anticoagulated for atrial fibrillation? |
| Dr J.C. Cowan | Rate control versus restoration of sinus rhythm. |