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British Society for Heart Failure

NEWSLETTER

BSH Annual Autumn Meeting 2003

- In this issue we report on the 6th Annual Meeting of the BSH titled '*Heart failure beyond maximum medical management*' which took place in Oxford on 28 November 2003. This successful meeting was attended by nearly 300 participants including 14 exhibitors/sponsors.

AGM highlights

- Professor Henry Dargie, chairman of the BSH and Dr Theresa McDonagh, treasurer, presented encouraging news at the Society's AGM held before the Autumn meeting in 2003.
- The society now comprises nearly 500 members, with a particularly strong representation from cardiologists and nurses. Further efforts to expand membership, particularly among GPs, geriatricians, pharmacists and basic scientists, are ongoing.
- Successful meetings have been held throughout 2003, including satellite symposia at the British Cardiac Society meeting in Glasgow.
- The BSH is working with other groups and societies, such as the British Heart Foundation, the CHD collaborative, the Royal College of Physicians and the Royal Society of Medicine, on a number of projects.
- Further projects planned for 2004, in addition to the meetings and events listed below, include a heart failure database, further development of the BSH website and cardiac surgery workshops.
- The Society is now showing a healthy balance sheet with the much appreciated support of a number of old and new 'Friends of the BSH'. Full accounts can be accessed from www.bcs.com/affiliates/bsh.html.

Meeting and events in 2004

- The BSH will have three sessions at the British Cardiac Society Annual Scientific Conference in Manchester in May 2004. These will consist of a "teach-in" titled *Heart failure - delivering evidence-based care in the UK* on 24 May at 15.00–16.30 and two plenary symposia on 25 May titled *Electrical device therapy in heart failure: unmet need and unmet cost* (a joint BSH/BPEG symposium) at 09.00–10.30 and *Anti-thrombotic therapy for heart failure: which agent, if any?* at 11.30–13.00.
- A special meeting entitled *Development of mechanical circulatory support programmes for the UK: a consensus conference* will take place on 2 July in Oxford.
- The 7th Annual Autumn Meeting will be held in London on 25–26 November 2004 at the Novotel West Hotel.
- Following the autumn meeting, in the evening of 26 November, we will hold the 1st BSH Charity Ball at the Brewery (part of the Barbican).

Heart failure beyond maximum medical management – the Annual Autumn meeting of the BSH

This meeting took place on 28 November 2003 and focused on the management of advanced heart failure (HF), a chronic disease suffered by at least 25,000 people in the UK, when medical treatment alone is no longer sufficient. These patients suffer severe loss in quality of life despite use of the most effective treatments. In his introduction to the topic, Professor Philip Poole-Wilson (Imperial College, London) asked the question “What is maximum medical treatment?”. The treatment of HF has become an increasingly complex area with the large number of drugs available and Professor Poole-Wilson warned of the dangers of simply adding to multiple therapies.

Although the critical sources of evidence for treatment choice are large randomised controlled trials, Professor Poole-Wilson expressed concern over the selection of endpoints which may imply improved drug performance rather than necessarily benefiting patients. He reminded delegates that evidence-based medicine was originally conceived as the combination of clinical trials and the knowledge of experienced clinicians and expressed the view that maximum medical treatment is the treatment that a competent and experienced doctor considers appropriate for a particular patient having applied the latest knowledge from large HF trials. This should include a combination of diuretics (including loop, thiazide and spironolactone) together with an inhibitor of the renin-angiotensin system (angiotensin II receptor antagonist [AIIRA] and/or ACE-inhibitor) and a beta-blocker.

Figure 1. Symptoms experienced by patients with end-stage heart failure in the final year and final week of life.[1]

Symptoms	Final year (%)	Final week (%)
Pain	78	63
Dyspnoea	61	51
Cough	29	
Mental disturbance	59	
Insomnia	30	
Anxiety	43	

The role of palliative care

Dr Chris Ward (Ninewells Hospital, Dundee) summarised evidence that patients with advanced heart failure have a wide variety of poorly controlled symptoms (Figure 1)[1] and poor communication with their health care professionals.[2] Palliative care can effectively address these shortcomings whereas conventional cardiological treatment does not.

The National Service Framework for Coronary Heart Disease and the Coronary Heart Disease and Stroke "Strategy for Scotland" support for these suggestions has been hindered by perceived barriers to their implementation and a lack of understanding of what is involved. Many palliative care strategies, unlike most standard treatments, have the primary objective of improving quality of life (QOL).These include simple measures to improve the level of social support, of patient education and of self help, and the use of palliative care symptom control protocols. Dr Ward presented data showing that as heart failure becomes more limiting these measures to improve QOL become increasingly important to patients.[3,4] A high standard of care at the end of life is an imperative which can be addressed by using a management protocol such as the Liverpool care pathway for the terminally ill.

The management of heart failure patients no longer responsive to conventional treatment will require input from palliative care teams and from others with skills that cardiologists do not have. Dr Ward commented that it is logical that the BSH should take the lead in developing an appropriate realistic strategy.

Dr Miriam Johnson (St Catherine's Hospice, Scarborough) presented many practical aspects of palliative care from her own experience as a consultant palliative care physician, and described the efforts to move palliative care from being solely related to cancer care to becoming a feature of HF management. Physical symptoms of advanced HF and psycho-social issues are often neglected, with communication seen to be a particular problem.[5] A comparison with the experiences of lung cancer patients suggest that advanced HF patients are less well-informed, with less access to specialist services in the community, have increased comorbidity and there is increased pressure on carers.[6]

Specialist palliative care services are under-resourced and until now have concentrated on care of cancer patients. Specialist HF clinical nurse specialists will be particularly valuable, but at present they are not available in all areas. Improving palliative care services to HF patients will demand a shared care approach and increased resources, but will provide significant benefits to patients with end-stage HF and their carers.

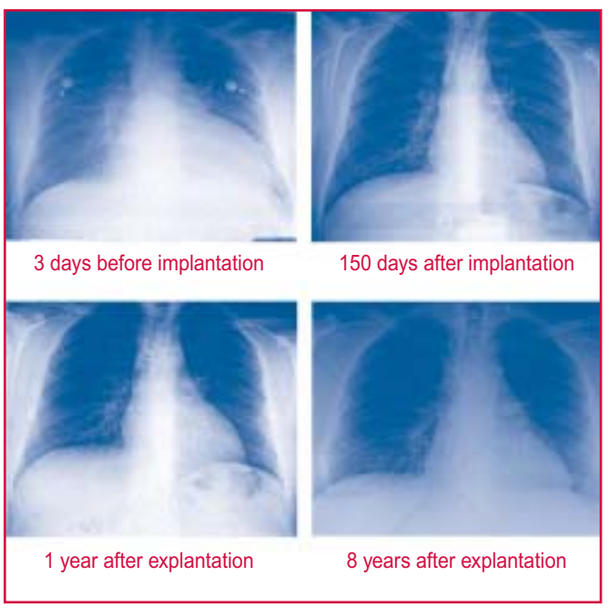
A patient's perspective

Mr Peter Houghton (Birmingham), provided a fascinating insight into the life of a patient with advanced HF. Mr Houghton, a psychotherapist who worked with terminal patients, was the first long-term patient in the UK to be fitted with a Jarvik left ventricular assist device (LVAD). He gave a powerful case for more patients to receive these devices and left the audience with a very personal testimony of life with advanced HF, and the challenges faced by these patients and their families.

New horizons in heart failure management

Mr Stephen Westaby (John Radcliffe Hospital, Oxford) introduced this session which focused on exciting potential developments in HF management. Dr Johannes Müller (German Heart Institute, Berlin) presented data on the mechanisms of myocardial recovery during cardiac support with an LVAD. Sustainable improvements in cardiac function have been seen in patients with LVADs due to unloading of the left ventricle. At present, 3 of the 4 patients weaned from LVADs at the German Heart Institute in 1995 remain asymptomatic and continue to show good cardiac function (Figure 2). Weaning has positive effects including removal of the risk factors associated with chronic use of LVADs, removal or postponement

Figure 2. Chest imaging of patient successfully weaned from an LVAD and stable at 8 years.



of the need for heart transplantation, and no need for immunosuppression.

Dr Müller's group is investigating whether there are predictive factors for successful weaning from these devices. He said that parameters which are highly predictive for long-term restored cardiac function at the time of removal of the device include LVEF >45%, LViDD<55 mm and duration of HF<5 years. Patients are also more likely to be successfully weaned if they have increased levels of neutral soluble collagen and acid soluble collagen at the time of implantation and a lower percentage of tryptase-positive degranulating mast cells in heart tissue.

Dr Müller concluded that, "Weaning from cardiac assist devices is feasible for selected patients with non-ischaemic, idiopathic dilated cardiomyopathy and is preferred to cardiac transplantation"[7] although those patients who were successfully weaned tended to be younger, with a shorter history of HF and with an ability for rapid improvement of heart function after device placement. The condition of the extracellular matrix is the predominant factor affecting improvement in cardiac function and work to optimise loading conditions or to enhance repair mechanisms by novel technologies such as stem cell or myoblast implantation is now being considered.

Professor Eric Alton (Royal Brompton Hospital, London) examined the potential for gene therapy in improving cardiac function. He showed that the master switch gene HIF1α, delivered epicardially and using adenovirus as a vector, produces significantly increased perfusion and fractional shortening in a pig model. Endocardial delivery also produced improvements in perfusion and would be the delivery route of choice in any clinical trial.

Stem cells offer another route for delivery of genes. Studies with skeletal myoblasts have resulted in a number of patients developing ventricular arrhythmias, but the use of autologous bone marrow appears to be safe to date. Early studies suggest that retrograde venous delivery may be at least as efficient as endocardial delivery but is a challenging procedure, even for the most experienced cardiologist. A double-blind placebo controlled clinical trial will start in 2004 to assess the impact of autologous bone marrow cells delivered by this venous route in patients with end-stage ischaemic heart disease. Professor Alton commented that both gene therapy and stem cells may well be promising treatments in chronic end-stage HF.

Dr Jagat Narula (University of California, Irvine, USA) discussed the role and regulation of apoptosis in HF. Apoptosis is an active process of cell death and although it was traditionally believed that apoptosis did not occur in terminally differentiated adult heart muscle cells, studies in explanted hearts from patients with end-stage HF undergoing transplantation have demonstrated apoptosis in a significant number of myocytes and other cells.[8]

Apoptosis is now known to contribute to the continuous decline of ventricular function in HF and the upstream cascade of apoptosis is affected by activation and upregulation of the terminal caspases such as caspase 3. Cytochrome C has been identified as the key step in the process in apoptosis and further studies showed that in dilated cardiomyopathy, cytochrome C and caspase 3 is released from mitochondria into the cytoplasm.[9] In spite of ongoing cytoplasmic proteolysis, there is no evidence of nuclear fragmentation in patients with end-stage HF. Although these cells will clearly contribute to systolic dysfunction, there remains the potential for revitalisation as their nuclei appear to resist apoptosis. Dr Narula presented a number of preclinical studies which demonstrated the potential for the reversibility of congestive HF at a biochemical level by inhibition of apoptosis.[10,11] This approach may provide the basis for novel therapies.

Non-transplant interventions

Professor Nicholas Peters (St Mary's Hospital, London) described the close relationship between electrophysiological function and HF. Studies have shown that the prevalence of left bundle branch block increases with the prevalence of impaired left ventricular (LV) function.[12,13] In addition, all-cause mortality increases when QRS width is broad.[14]

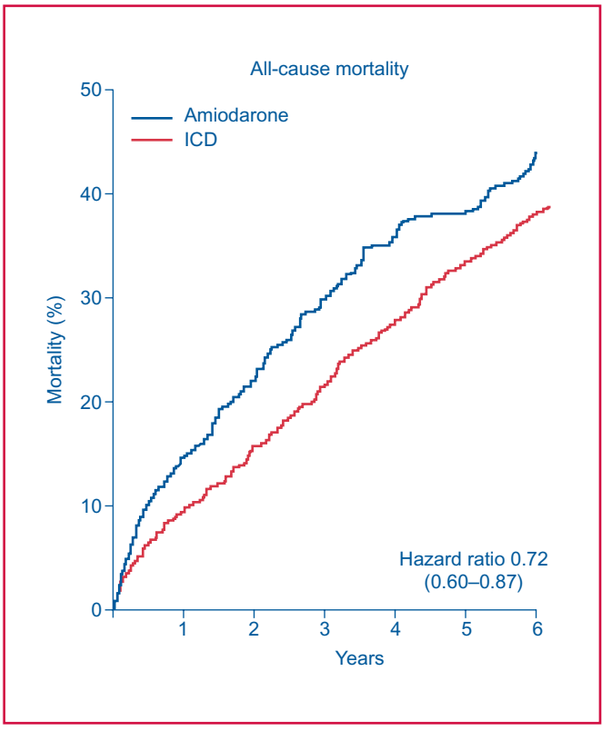
The benefits of cardiac resynchronisation therapy (CRT) have been shown in randomised controlled trials involving nearly 4000 patients. Two recent studies (COMPANION[15] and MIRACLE[16]) and a meta-analysis[17] show a statistically significant reduction in mortality from the use of CRT in addition to implantable cardiac defibrillators. There is also clear evidence from the MUSTIC and InSYNC trials that CRT improves quality of life, NYHA functional class and exercise capacity and that this is sustained over 1 year.

Perhaps the biggest challenge of RCT is appropriate patient selection. Professor Peters suggested that QRS duration is, "a fairly blunt tool for patient selection". The principal cause of QRS prolongation is increased LV activation time and this is not addressed with current resynchronisation therapy. He suggested that Tissue Doppler imaging may offer a superior tool for defining mechanical dyssynchrony, predicting patient response to CRT, and preventing unnecessary device implantation.

Professor Stuart Cobbe (Glasgow Royal Infirmary, Glasgow) reminded delegates of the significant problem of sudden cardiac death in HF and the important role of the implantable cardioverter defibrillators (ICDs). A meta-analysis of three secondary prevention trials of ICDs in patients with a history of life-threatening tachyarrhythmias showed evidence of reduction in all-cause mortality (Figure 3).[18] ICD therapy was shown to be of particular benefit to those patients at the greatest risk, and in particular those with LVEF <0.35.

Primary prevention trials of ICDs have been performed in patients with HF but who had never suffered a major

Figure 3. Reduction in all-cause mortality with use of implantable cardioverter defibrillator vs amiodarone.[18] Adapted with permission from the European Society of Cardiology.



arrhythmic episode (MUSTT, MADIT-I and MADIT-II). MADIT-I showed significant survival benefit in those patients with poor LVEF (<0.26) but no benefit for patients with LVEF 0.26-0.35.[19] Results from MADIT-II showing a 31% relative risk reduction in mortality for ICDs over conventional therapy has resulted in FDA approval in the US for an ICD indication for patients with previous myocardial infarction and LVEF <0.3.[20] These results have been confirmed by the early termination of the COMPANION trial where patients treated with CRT and ICDs showed a 43.4% relative risk reduction at 12 months compared with the optimum pharmacological therapy.[21]

Although there is now clear evidence that ICD therapy reduces mortality there remain questions over the amount of benefit gained. Professor Cobbe pointed out that several trials had been stopped prematurely because of early benefit and had not provided much evidence on the long-term effects of ICD's on morbidity and mortality. There is some evidence to suggest that event curves begin to converge with further follow-up in trials such as CIDS and CASH. The non-industry funded SCD-HEFT trial which will be presented next year, and which is continuing to its predetermined duration, should provide a more robust estimate of the relative benefit to be expected from ICD therapy in addition to optimum medical treatment.[22]

Professor John Pepper (Royal Brompton Hospital, London) reminded delegates that coronary artery disease (CAD) is the cause of 95% of HF, particularly in patients aged between 25-75, and that more than 50% of patients with HF and CAD have evidence of stress-induced ischaemia or hibernation. Coronary bypass surgery is an important form of treatment for patients with ischaemic cardiomyopathy.

The pathophysiology of this process involves myocyte loss with scar formation, chronic dysfunction in viable myocardium with some relationship between stunning and hibernation, and changes in remote myocardium, in particular dilatation and adverse remodelling. Hibernating myocardium appears to be different to other forms of ischaemic myocardium.

It has been suggested that hibernation could be, in part, due to changes in the myocardial β-adrenoreceptor axis. Studies by Professor Pepper's group showed that although there was similar pre-synaptic noradrenaline re-uptake, β-adrenoreceptor density and expression between hibernating and remote myocardium, there was reduced intracellular signalling in the pathway of β-adrenoreceptor stimulation which might explain the decreased contractility. These findings suggest that molecular adaptation in hibernation is different to that seen in other forms of HF.

Mr Stephen Westaby (John Radcliffe Hospital, Oxford) described the advances in LV restoration surgery. He recommended that patients with coronary disease and poor LV function with anterolateral akinesis or dyskinesis should be followed closely and considered for ventricular reconstruction when symptomatic on medical management or when there is evidence of increasing ventricular dimension, decreasing ejection fraction or progressive mitral insufficiency.

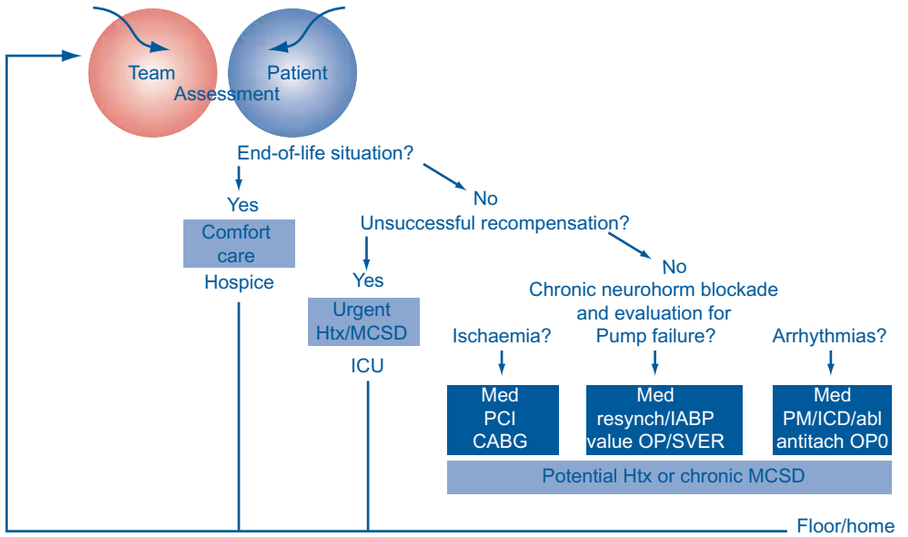
Patients should be selected for operation at a much earlier stage post-myocardial infarction to prevent extensive remodelling. The aims of LV restoration surgery are to:

- Decrease LV volume, wall tension and stress
- Restore ventricular geometry and shape towards normal and to correct Grade III or IV mitral regurgitation
- Include revascularization to improve ventricular function, prevent arrhythmias and relieve symptoms of HF

LV restoration therapy (the Dor procedure) is performed most successfully in patients with dyskinesia or akinesia (NYHA II-IV), and with LV end-systolic volume index 60–100 ml/m^2. Coronary bypass, mitral repair, and cryoablation for dysrrhythmia should also be performed in these patients. The operation is usually performed with the heart beating on cardiopulmonary bypass to allow easier identification of areas of dyskinesia and scarring.

Although the most seriously ill patients appear to receive most benefit from cardiac surgery, Mr Westaby expressed concern that many of these patients are being rejected for surgery to protect surgeon's mortality figures. This high-risk surgery needs expensive post-operative support techniques to

Figure 4. Algorithm for the management of advanced HF.[23]



allow the heart to recover from ischaemic injury, which up till now have not been available in the UK. However, with increasing investment these mechanical circulatory support devices will be hopefully be made available to more cardiac units.

Left ventricular assist or replacement?

Careful patient selection is required for heart transplantation or for LVADs. Professor Mario Deng (New York Presbytarian Hospital, USA) reminded delegates of an algorithm of treatment of advanced HF which takes into account the patients age, and urgency of treatment (Figure 4).[23]

Early study results provided overwhelming evidence of the benefit of heart transplantation,[24] but these assumptions have been challenged over the past two decades. There are now many more non-transplant treatment options available, and the improvement seen in heart transplant patients is under intense debate. A national study in Germany showed that only patients with a high mortality risk had survival benefit after transplantation over the first year.[25] These data have led to further worldwide debate over the relative merits of transplantation or other treatments. Professor Deng suggested that we are in a phase of redefining the role of transplantation in the light of new data and new therapies.

The REMATCH trial has shown that patients ineligible for transplantation, due to age or comorbidities, have a survival benefit and improved quality of life from implantation of a mechanical circulatory support device.[26] Professor Deng suggested that, in the future, far larger numbers of patients with advanced HF will benefit from use of these devices.

Dr Bud Frazier (Texas Heart Institute, Houston, USA) gave a stimulating presentation on his lengthy experience in heart transplantation and the development and implantation of various mechanical circulatory support devices. He summarized his talk by suggesting that improvements in device technology will allow the devices to be implanted in the earlier stages of heart disease. This, in turn, will allow improved benefits to a greater number of advanced HF patients.

Mr Stephen Westaby gave further insights into the use of implantable devices. Till recently in Europe implants have been restricted to non-transplant eligible patients, but now the use of implants as a bridge to transplant is being explored. He commented that the propensity for the unloaded heart to recover is exciting and is leading to new forms of treatment.

The REMATCH study showed that patients on LVADs died from device-related complications, primarily infections associated with power lines, suggesting that improved devices will lead to more patients being eligible for their use.[26]

Experience with the Jarvik pump has been encouraging. Infections associated with drive lines have been reduced dramatically by using the skull as a solid pedestal rather than exiting through abdominal fat.

Mr Westaby summarised the current situation by saying, “Artificial hearts are no longer just science fiction and they are not difficult to implant. Patients with Jarvik pumps have lived more than 3.5 years in the community. Although these devices are expensive many more patients should be considered for this type of treatment in the UK. We need a body of opinion to say that more people deserve this form of treatment.”

Clinical trials and new pharmacological developments

COMET

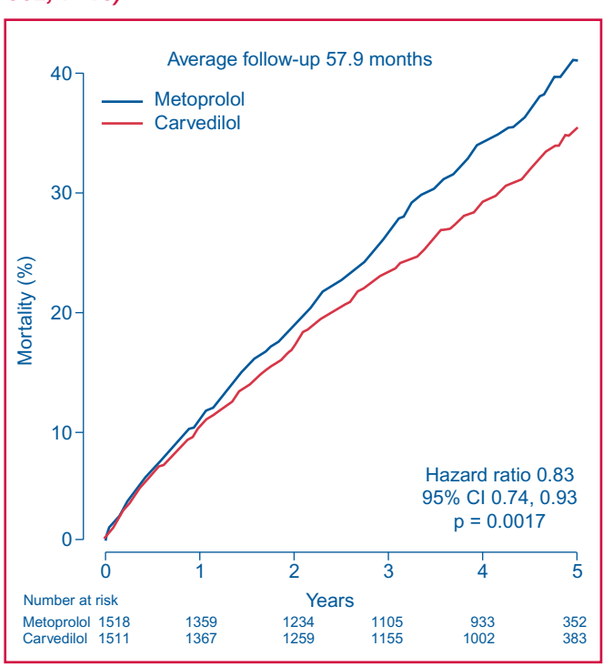
The COMET trial reported earlier in 2003, and was the first head-to-head study of two beta-blockers (metoprolol, 50 mg bd) and carvedilol (25 mg bd).[27] The study included 3029 patients with HF with an average follow-up of 57.9 months. Carvedilol showed an absolute risk reduction in mortality of 6% over metoprolol which resulted in a prolonged median survival by 1.4 years (Figure 5). Professor Poole-Wilson described this as, "A clear and definitive result, most probably due to β_2-blockade. Therefore carvedilol is the beta-blocker of choice in the treatment of HF".

The CHARM studies

Professor John McMurray (Western Infirmary, Glasgow) presented the CHARM programme of studies looking at the role of the AIIRA candesartan in patients with HF.[28] These looked at a broad spectrum of patients (n=7601) including those with or without preserved LVEF, and those being treated with an ACE-inhibitor or not.

Use of candesartan resulted in a 9% reduction in all-cause mortality (borderline significance, p=0.055) and a significant 16% reduction in CV mortality or CV hospitalisation (p<0.0001). These benefits were seen in patients already treated with effective therapies including beta-blockers and ACE-inhibitors. The consistent effects of candesartan across the three trials lead the investigators to suggest that addition of candesartan can be considered in all patients with HF, irrespective of ejection fraction, age and sex.

Figure 5. Mortality in the COMET study.[27] Reprinted with permission from Elsevier (*the Lancet*, 2003, 362, 7–13)



EPHESUS

Professor Allan Struthers (Ninewells Hospital, Dundee) presented data from the RALES trial showed that spironolactone (an aldosterone antagonist) reduced mortality in severe HF by 30%, but the drug had a poor side-effect profile.[29] The EPHESUS trial studied patients with acute myocardial infarction with HF randomised to eplerenone (a selective aldosterone antagonist), or placebo in addition to standard therapy (86% of patients were on an ACE-inhibitor or AIIRA).[30]

Eplerenone produced a 15% reduction in total mortality (p=0.008) and there was a 21% reduction in sudden cardiac death (p=0.03). Adverse events were generally low, and although serious hyperkalaemia was increased by 1.6%, hypokalaemia was decreased by 4.7%. In summary, these two trials show the benefits of blocking aldosterone in terms of reduced total mortality and that eplerenone side-effects are similar to placebo. It is hoped that eplerenone will be available in the UK in the near future.

Nesiritide

Dr Andrew Clark (Castle Hill Hospital, Kingston-upon-Hull) presented data on nesiritide, a recombinant human B-type natriuretic peptide (BNP) which has already shown some promise as a diagnostic tool and as a therapeutic target. It is now being considered in the EU as a treatment for acute HF.

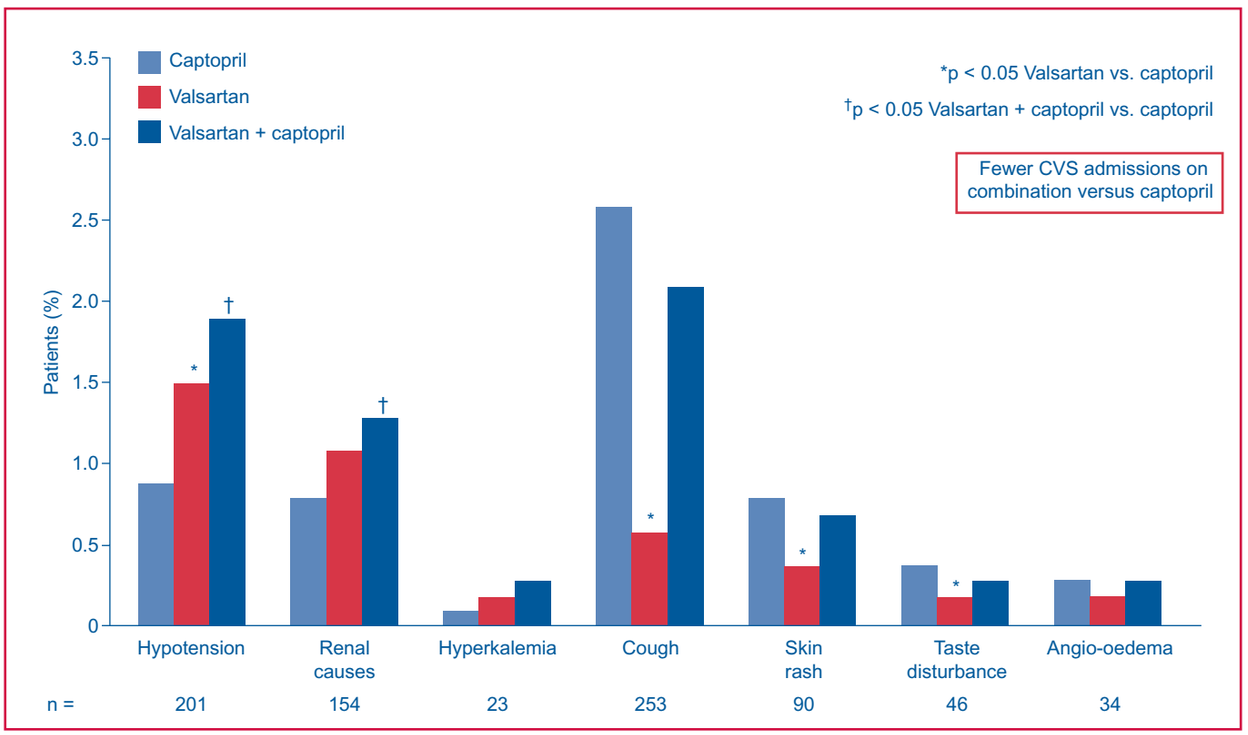
Nesiritide induces vasodilation and increases urinary flow, both of which are beneficial in HF management and Dr Clark described some of the major trials of the drug. The VMAC study is the largest study to date and compared nesiritide, intravenous nitroglycerin and placebo in the treatment of nearly 500 patients with acute exacerbation of HF.[31] Nesiritide improved haemodynamic function (including pulmonary capillary wedge pressure) and symptom scores, and was less prone to cause side-effects, such as headache, than the comparators.

The PRECEDENT trial compared nesiritide with dobutamine in 255 patients with acute exacerbations of HF and found both drugs effective at controlling signs and symptoms.[32] Whereas dobutamine increased ventricular tachycardia, nesiritide reduced ventricular ectopy or had a neutral effect. Nesiritide is currently approved for use in the USA with experience in over 150,000 patients and an application has been made for its use in the EU.

UK Peptide study

Diagnosis of HF is often inaccurate and all major guidelines recommend the use of objective measurement to prove cardiac dysfunction. Small, single centre studies have suggested that B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NTproBNP) can be used as a "rule out" test for HF. Dr Theresa McDonagh (Royal Infirmary, Glasgow)

Figure 6. Adverse events leading to study discontinuation in the VALIANT study.[34]



described the UK Peptide Study which aimed to test the diagnostic value of these peptides in the primary care setting when patients presented to their GP with symptoms suggestive of HF.[33] The study involved 5 centres across the UK and enrolled 306 patients. BNP can be measured immediately in the clinic, and NTproBNP is measured with a rapid ELISA assay.

About 34% of these patients had a diagnosis of HF confirmed when referred to a HF clinic. Concentrations of both BNP and NTproBNP were higher in patients with HF and the study confirmed the value of using these peptides as a "rule out" test. However further work is required to establish the best cut-off points for use in clinical practice.

VALIANT

Professor John Cleland (University of Hull, Kingston-upon-Hull) described the results of the VALIANT trial which compared valsartan, 160 mg bd, captopril, 50 mg tid and combination therapy in 14,703 patients with a recent myocardial infarction and evidence of HF.[34]

All three regimens produced similar results in terms of all-cause mortality. Valsartan was associated with fewer adverse effects but overall very few patients withdrew from the study due to side-effects (Figure 6). Interestingly, there were significantly fewer CV admissions on combination therapy than on captopril, but further data on symptoms and hospitalisation are required before this can be confirmed as a benefit for combination therapy. Professor Cleland concluded that valsartan is an effective alternative to captopril and is associated with fewer side-effects. Although combination therapy does not reduce mortality, it does reduce some types of hospitalisation, but has slightly more side-effects. Further analyses are required before combination therapy can be generally recommended.

Proposal for UK trial of LVADs

Mr Stephen Westaby proposed a multicentre, randomised trial of LVADs versus ongoing medical therapy in end stage HF. It remains to be seen whether the trial will include transplant-eligible patients. This trial would be similar to the REMATCH trial using the new generation of LVADs, such as the Jarvik, INCOR and Ventracor centrifugal pump in patients.

EUROPA

Professor Martin Cowie (Imperial College, London) presented the results of this study which investigated whether long-term administration of perindopril added to standard therapy leads to reduction in CV events in stable patients with low risk CAD.[35] A total of 12,218 patients were randomised to perindopril or placebo. There was a 20% relative risk reduction in mortality (p=0.0003) with use of perindopril (target 8 mg od), and a 24% RR in fatal and non-fatal myocardial infarction (p<0.001). In addition the risk of developing HF in these patients was reduced by 39% (p=0.02). These benefits were noted in addition to a high level of background therapy. The investigators concluded that perindopril should be considered for chronic therapy in all patients with coronary disease, although Professor Cowie pointed out that this should be set in context with the fact that perindopril, 8 mg od only prevents one CV death, non fatal myocardial infarction or cardiac arrest in every 50 patients treated for CAD every 4 years.

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