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Heart failure*

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Provision of care

Nice, audit and heart failure care. The national heart failure audit[1] in England and Wales continues to grow, and provides vital data for planning heart failure services. The first formal report relates to over 6000 patients who were the first 10 patients admitted with a primary diagnosis of heart failure each month to one of 86 hospitals contributing data. Most had left ventricular systolic dysfunction, but an echocardiogram result was available in only 75%. In patient mortality was 12%, and in survivors, 80% were receiving an ACE inhibitor (or ARB), 50% a β-blocker, and 30% an aldosterone antagonist at discharge.

The audit for 21 000 patients hospitalised with heart failure in 2009/10 is also available.[2] In-hospital mortality had fallen slightly to 10.5%, but there was no dramatic change in drug prescription rates. Some subsets of patients were particularly likely to be actively treated (so for men aged 55 to 64, β blocker prescription rate was over 70%) whereas others were much less likely to be treated (women over 85, β-blocker prescription rate 40%). Aldosterone antagonists were still prescribed for fewer than half the population.

Two striking features stand out from the data from both audits. Firstly, prescription rates vary greatly, with older patients and women being less likely to be treated, and with admission ward: patients admitted to cardiology wards are much more likely to receive active treatment. Secondly, not only was pharmacological treatment better for patients admitted under cardiologists, so was survival. Although a minority of patients admitted with heart failure are managed by cardiologists, the survival benefit persists after correction for age and sex (and other confounders).

The under-treatment of elderly patients with heart failure is a particular cause for concern at a time when patients aged >80 represent an increasing proportion of heart failure admissions.[3] Treatment of older patients is hampered not only by their associated co-morbidities and polypharmacy but also by their systematic exclusion from clinical trials, depriving physicians of the evidence base they need to guide management decisions.[4] Exclusion of the elderly by trialists shows no signs of going away: among 251 trials recruiting patients in Dec 2008, more than 25% had an upper age limit for enrolment and more than 80% excluded patients with co-morbid conditions.[4]

The National Institute for Clinical Excellence (NICE) has produced updated guidelines for heart failure care.[5,6] Whilst there has been a lot of comment on the importance of measuring natriuretic peptides as an entry point to heart failure care, NICE has also firmly recommended that care lead by a specialist in heart failure should be

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the norm. This is true at assessment and diagnosis (a patient suspected of having heart failure in the context of a previous myocardial infarct or with a very high natriuretic peptide level should receive "…specialist assessment within 2 weeks") and during an admission to hospital ("[w]hen a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure").

Such recommendations will impose new burdens. What is a "specialist"? NICE thinks it is "…a physician with sub-specialty interest in heart failure (often a consultant cardiologist) who leads a specialist multidisciplinary heart failure team of professionals …", but there are few of these individuals available to take up the responsibility. However a specialist is defined, there is no doubt that patients with heart failure fare better when cared for by professionals with a particular interest in their condition. This is reflected in recent US data that have shown lower mortality and readmissions for heart failure patients managed in high volume compared with low volume centres.[7]

One of the issues for a specialist heart failure service is access to advanced therapies such as heart transplantation. Transplantation in the UK is falling, partly due to a fall in the availability of donor organs,[8] but just as important is access to expert heart failure care.[9] We have managed to re-configure health services to provide primary angioplasty for patients with acute myocardial infarction (including for patients with non-ST elevation MI on rather flimsy evidence).[10] We should do so for patients with heart failure, for whom reconfigured services will have a more far-reaching benefit.

Telemonitoring. An exciting possible advance in patient care the use of remote monitoring to guide changes in therapy. Typically, automated devices in the home can measure weight, pulse rate and heart rhythm, and blood pressure and transmit the data to a centre. Abnormal results then trigger patient contact with possible change in therapy. Initial trials suggested that there may be a benefit from such systems, particularly when coupled with telephone contact.[11]

A particular problem with telemonitoring is what to do with the data. With a large number of patients potentially transmitting quantities of data daily, the resource required to deal with the data might become impossibly large. Attempts to use automated systems have proved disappointing: in a study of 1653 patients who had recently been hospitalised for heart failure, telemonitoring using an interactive voice-response system which collected daily information about symptoms and weight, Chaudhry found no impact on re-admissions and mortality at 6 months.[12] In another recent study,[13] remote monitoring did not improve outcomes amongst 710 patients randomised to remote monitoring using a system that transmitted ECG, blood pressure and weight and included a home emergency call system.

It is important to remember that telemonitoring itself doesn't save lives or admissions, but those actions taken in response to monitoring might. The reason recent trials have been neutral may be that "usual care" in these studies has progressed to the point where home monitoring can have little additional beneficial effect, and it may be that remote monitoring is only likely to be helpful in people at particularly high risk. It may be, too, that the variables measured are simply too crude to be helpful guides to changing therapy.

Another approach to remote monitoring is to use implantable devices to measure haemodynamic changes invasively. The Chronicle® device allows pulmonary artery pressure to be measured continuously, and an early trial (COMPASS) suggested that it might be helpful.[14] A more promising technique, perhaps, is the use of smaller devices implanted directly into the pulmonary artery and communicating using acoustic wireless communication.[15] In the CHAMPION trial,[16] 550 patients were randomised to have a CardioMEMS® device or usual care. The device was used to measure pulmonary artery pressure once a day: it has no internal power source, but uses externally applied radiofrequency energy. Its use was associated with a 30% reduction in the primary efficacy endpoint of heart failure hospitalisation at 6 months. It is not, of course, the devices that improve outcome, but the changes in treatment that follow from device readings. In COMPASS[14] and CHAMPION,[16] for example, patients with the device were on higher doses of medication to treat heart failure.

The final stage in the evolution of remote monitoring is likely to be to further empowerment of the patient. The devices can be used to transmit data to the person most concerned with the disease –the patient– who can then use the information to make daily changes to his or her therapy. In HOMEOSTASIS, 40 patients with severe heart failure were implanted with a device measuring left atrial pressure, and made changes to treatment based on the readings using a pre-programmed handheld patient advisor module.[17] It is impossible to draw firm conclusions from such a small observational study, but whilst diuretic therapy fell as a result of the intervention, β-blocker and ACE inhibitor/ARB treatment increased. At the same time, mean left atrial pressure fell, and there did seem to be a reduction in clinical events.

The fact that invasive monitoring leads to an increase in prescription of medical therapy for heart failure highlights another nagging question: although we have clinical trial results to guide us towards "target" doses of, for example, β blockers and ACE inhibitors, how are we to know how much is enough? One possible guide is the use of natriuretic peptides: perhaps treatment should continue to be increased until natriuretic peptide level is normal. Some small studies point in that direction, others do not: but there is evidence of publication bias in a meta-analysis.[18] A recent single centre trial in 364 patients with heart failure showed that treatment guided by NT-proBNP was associated with 1 year mortality identical to treatment guided by a clinical score.[19] The finding lends some weight to the argument against biomarker-guided treatment but the question will only be resolved by a definitive large trial.

Epidemiology

Heart failure with a normal ejection fraction. Heart failure with a normal ejection fraction (HeFNEF) remains enigmatic. Epidemiology suggests that it is common,[20,21] perhaps accounting for half of cases of heart failure. However, researchers recruiting patients to trials have

often found it extremely difficult to identify suitable patients. No clinical trial has as yet identified any successful treatment for HeFNEF, and some are sceptical of its existence as a single, well-defined entity.[22,23] Problems arise because at least in part, breathlessness is very common in older people, and because some of the diastolic echocardiographic changes thought to indicate that the heart is failing are simply consistent with aging.

One possibility that has been under-researched is that HeFNEF is more obviously a condition appreciated during exercise, and echocardiographic measurements during exercise may highlight diastolic abnormalities.[24] An important observation from a study of echocardiography and exercise of over 400 patients with possible HeFNEF[25] was that very few –possibly as few as 3%- actually had heart failure. Holland and colleagues[25] emphasised the importance of measuring the ratio between E and E' as an index of left ventricular filling pressure, but others have concentrated on much more subtle abnormalities of both systole and diastole in patients with HeFNEF that worsen with exertion.[26] Impaired left atrial function during exercise might also contribute.[27]

Whilst it remains a very active area of research, the cardinal problem with HeFNEF, and the main reason it has no (proven) treatment is the absence of a satisfactory case-definition. The incorporation of natriuretic peptides into the diagnostic pathway for HeFNEF should help as a raised level makes it more certain that the heart is the cause of any symptoms. However, natriuretic peptides may reveal that there has been considerable over-diagnosis of HeFNEF in the past. Potentially relevant in this respect is the recent analysis of mode of death data from I-Preserve: in patients with HeFNEF, death from heart failure was surprisingly rare, the majority succumbing to other cardiovascular events.[28]

Treatment

Neurohormonal manipulation. ACE inhibitors, ARBs and β-blockers, are of course, the mainstays of medical therapy for patients with chronic heart failure. ACE inhibitors or ARBs should be given to all patients with left ventricular systolic dysfunction, regardless of symptoms class, and there is general appreciation that the highest tolerated dose should be used, side effects permitting. Evidence for this approach comes from trials such as ATLAS, in which patients randomised to higher dose lisinopril fared better than those on a lower dose.

There has been less evidence with ARBs that high dose is better until the HEAAL study,[29] in which 3846 patients with heart failure and LVEF less than 40%, and who were intolerant of ACE inhibitor, were randomised to receive high (150 mg) or low (50 mg) dose daily losartan. After a median 4.7 year follow-up there was a lower rate of died or heart failure hospitalisation in the high dose group (hazard ratio [HR] 0.90, 95% CI 0.82 - 0.99; $p = 0.027$). and it does thus seem that up-titrating ARB doses confers clinical benefit.

With RALES[30] (spironolactone) and EPHESUS[31] (eplerenone), aldosterone blockade has also become important, with the proviso that aldosterone blockade has not been shown to be beneficial in patients with mild heart failure, at least until recently. In EMPHASIS-HF,[32] 2737 patients with heart failure due to systolic dysfunction and NYHA class II symptoms were randomised to eplerenone (up to 50 mg daily) or placebo, in addition to standard treatment. There was a 37% reduction in the risk of the primary endpoint (cardiovascular death or heart failure hospitalisation) in the eplerenone group, at a cost of a small increase in the risk of hyperkalaemia. It seems likely that guideline groups will now recommend the use of eplerenone in all those with heart failure due to left ventricular systolic dysfunction.

A problem with the more wide-spread use of aldosterone antagonists is that the risk of life-threatening hypokalaemia may increase. Certainly after the RALES report, there was a rapid uptake of spironolactone usage resulting in a marked increase in morbidity and mortality from hyperkalaemia.[33] A possible approach to preventing hyperkalaemia is to use potassium-binding resins. In PEARL-HF,[34] 105 patients with heart failure and a history of hyperkalaemia which had interfered with medical therapy, or who had chronic kidney disease, were recruited. The potassium binder, RLY5016, was given in addition to spironolactone and led to a marked reduction in the risk of hyperkalaemia compared with placebo (7.3% *vs.* 24.5%, $p = 0.015$); and a higher proportion of patients reaching spironolactone 50 mg/day (91% *vs.* 74%, $p = 0.019$). These are encouraging data, but lead to the obvious unanswered question: to what extent is the benefit of aldosterone antagonism mediated by hyperkalaemia? If the answer is "most", or "all", then potassium binding may not have much to offer.

Ivabradine. The mechanism by which beta blockers mediate their beneficial effects is not clear, but has long been thought to be related to their ability to reduce heart rate.[35,36] Ivabradine reduces heart rate by reducing sinus node discharge rate whilst having no other haemodynamic effect, and might thus both test the heart rate hypothesis and provide an alternative for patients intolerant of β-blockers.

In SHIFT,[37] 6558 patients with heart failure and a low ejection fraction and who were in sinus rhythm with a heart rate of at least 70 beats per min were randomised to receive ivabradine or placebo in addition to usual therapy (including β blocker, where tolerated). Ivabradine was associated with an 18% reduction in the primary endpoint (cardiovascular death or hospital admission for worsening heart failure), driven mainly by a reduction in hospital admission.

The findings of SHIFT have been much discussed. It's important to point out that the benefits of ivabradine were much more striking in those with a higher resting heart rate,[37,38] and that although around 90% of patients were taking a β blocker at baseline, only 23% were taking a target dose, only 49% were on 50% or more of a target dose, and 16% were on a β blocker not shown to be beneficial.

The SHIFT findings do suggest that there is a role for ivabradine in patients with chronic heart failure, but it is not a substitute for β-blocker use. There is an enormous body of evidence supporting the use of β-blockers, which

improve mortality as well as hospitalisation. Ivabradine should be considered only in those patients who still have a resting heart rate above 70 despite maximally tolerated doses of β-blockers (or perhaps used in patients truly intolerant of β-blockers). Data from "real world" populations of heart failure patients suggest that the proportion of patients who might be eligible is low, perhaps around 5%.[39]

Iron. Is iron deficiency a target for treatment? Anaemia is very common in patients with heart failure,[40] but iron deficiency without anaemia is also common. The best way to manage iron deficiency is not clear: oral iron therapy is widely believed to be ineffective, yet intravenous iron treatment is also thought to be difficult or dangerous. However, a new generation of intravenous iron preparations is now available which allows both rapid and safe administration of iron to patients.

Some preliminary studies suggested that intravenous iron repletion might lead to an improvement in exercise capacity,[41] and the FAIR-HF study was designed to see if iron might be beneficial in a larger group of patients.[42] 459 patients were randomised 2:1 to receive iron or placebo infusions (with only the patient blind to treatment). After 6 months, there was an improvement in patient self-reported global assessment (50% "much or moderately improved", compared with 28% of patients in the placebo group) as well as in secondary endpoints including distance covered in a six minute walk test (about 40 m increase compared with no change in the placebo group). There were similar improvements regardless of starting haemoglobin.

The results have to be treated with some caution: FAIR-HF was not a large trial, blinding was difficult and the end-points were to a varying degree subjective. Nevertheless, iron therapy appeared safe, and is now an option for patients who remain symptomatic despite medical therapy. An absolutely essential question to answer, though, is the extent to which patients with heart failure should be further investigated for an underlying cause for any iron deficiency, a question not addressed by FAIR-HF.

Another possible approach for correcting anaemia in heart failure is the use of erythropoiesis stimulating proteins. A meta-analysis of 7 randomised controlled trials found that treatment was associated with a significantly lower risk of hospitalization compared with placebo.[43] Mortality was unaffected. These outcomes are in contrast with studies in cancer and kidney disease, and prompted the authors to a call for a large phase III morbidity and mortality trial of anaemia correction with erythropoiesis stimulating proteins in patients with chronic heart failure.

Metabolic manipulation. The energy-generating processes of the failing cardiac myocyte are abnormal. Some investigators have focussed on substrate utilisation: fatty acid metabolism produces a lower yield of ATP for each molecule of oxygen consumed than glucose metabolism (although fatty acid oxidation yields more ATP per mole), and so it makes sense to try and switch metabolism from fatty acids to glucose.[44]

Various approaches have been tried: perhexiline, for example, blocks mitochondrial free fatty acid uptake by inhibiting carnitine palmitoyltransferase. In a small study, perhexiline led to improvements in exercise capacity and left ventricular function and more rapid recovery of phosphocreatine after exercise.[45] Trimetazidine inhibits lipid β-oxidation, and its use has been associated with both an increase in left ventricular ejection fraction and reduction in resting energy expenditure (known to be high in heart failure).[46] A meta-analysis of the available data for trimetazidine[47] even suggests that its use might improve mortality, and it is surely time for a large scale trial of metabolic modulators.

CRT. Cardiac re-synchronisation therapy (CRT: or biventricular pacing) is one of the most exciting new therapies for patients with chronic heart failure introduced in recent years. Particularly important is its effect on reducing mortality,[48] but around two thirds of patients gets marked symptomatic benefit from their devices.[49] That one third does not have led to the concept of the "non-responder" to CRT. How to define "non-response" varies from paper to paper with some using symptomatic criteria, and others using measures of left ventricular function. What has proved difficult to answer is whether "non-response" is related to lack of mortality benefit.

A great deal of time and effort has been expended on trying to identify which patients might get benefit from CRT. The severity of symptoms does not seem to matter greatly: those with modest symptoms appear to have as much mortality benefit to gain as those with worse NYHA class of symptoms.[50] In MADIT-CRT,[51] 1820 patients with NYHA class I or II symptoms were randomised 2:1 to receive CRT (or not) in addition to a defibrillator. There was a 34% reduction in the risk of death or a heart failure event (defined as congestion treated either: with intravenous therapy (diuretics, nesiritide or inotrope) for more than 2 hours, regardless of the setting, or: with an increased heart failure regimen during formal hospital admission. The reduction in risk was driven by a reduction in heart failure events. In RAFT,[52] which included 1 438 patients with mild (NYHA class II) symptoms, CRT added to a defibrillator lead to a reduction in the in rate of death and hospitalization for heart failure.

Another possible selection criterion is the presence of dyssynchrony on some form of cardiac imaging. Underlying this approach is the assumption that CRT works by improving ventricular co-ordination, which in turn must in some way be measurable. However, of the large, randomised trials showing a mortality benefit for CRT, none used measures of dyssynchrony as an entry criterion other than a minority of patients in CARE-HF. Vigorous efforts to prove the robustness of any of the very many potential measures of dyssynchrony have failed thus far, with the PROSPECT study of nearly 500 patients being the largest available set of data.[53] There was poor reproducibility of the measures, none of which related strongly to the assessment of response.

The only selection criteria consistently shown to be related to outcome are electrocardiographic. It is a commonplace observation that the mean QRS duration in the mortality trials of CRT was around 150 ms, and where it has been analysed, the broader the QRS, the greater the benefit. Subgroup analysis of PROSPECT showed some symptomatic benefit for CRT in patients with mechanical dysynchrony and a narrow QRS complex[54] and similar findings have been reported in small single centre trials.[55]

There is no doubt; however, that the benefits of CRT are largely confined to patients with left bundle branch block,[52] and it may even be that benefit is restricted to those with a QRS greater than 150 ms.[56]

Similarly, while small non-randomised studies have reported variable benefit of CRT for patients in AF, there is almost no evidence to support the practice from randomised trials.[57] The few trials that included patients in AF showed no benefit with CRT.[52] Although the European Society of cardiology guidelines updates suggest that CRT might be considered in patients in AF,[58] the class of recommendation was only IIa, level B or C.

What should all this mean in practice? CRT should certainly be considered for all patients with left ventricular systolic dysfunction and symptomatic heart failure who are in sinus rhythm and have left bundle branch block. CRT might be tried for those patients with intractable symptoms and atrial fibrillation (and left bundle branch block), but only if the ventricular rate is well controlled to maximise pacing. Better still, restoration of sinus rhythm in such patients may improve both quality of life and LV function[59] while ensuring a more favourable response to CRT.

A more far-reaching question is whether patients with a standard bradycardia pacing indication would benefit from biventricular pacing. A small study using echocardiographic endpoints suggested that biventricular pacing was associated with less deterioration in left ventricular function,[60] but whether wide-spread use of biventricular pacing is indicated will have to await the outcome of larger outcome studies.

Exercise training. The case for exercise training as a standard part of the management of patients with chronic heart failure has been building over several years.[61] Training undoubtedly improves patients' symptoms and several of the predictors of an adverse prognosis.[62] Mounting a properly powered survival study has proved difficult, not least because of the problems of blinding and the difficulty of cross-overs.

The ACTION-HF study managed to recruit 2331 patients randomised to usual care or an intensive training regime (36 supervised 30 minute sessions three times per week, followed by home exercise five times per week at moderate intensity for 40 minutes).[63] Although the primary end point of all-cause mortality and hospitalization was no different between the two groups at a median follow up of 30 months, there was a signal that training might be beneficial as after adjustment for baseline differences in predictors of outcome, training was associated with an 11% reduction in the primary end point. More importantly, perhaps, training was associated with a marked improvement in quality of life which appeared early during the intervention and continued throughout the course of the study.[64]

It is still unclear whether the *type* of training stimulus is important: most evidence relates to aerobic training. A recent systematic review of trials of resistance training found that the quality of the studies has been poor and effects were inconclusive for quality of life outcomes.[65]

Incorporating exercise training into standard heart failure management is difficult.[66] Compliance will always be a challenge–even in ACTION-HF, after a year, patients' compliance with exercise was only about 80%. Although home exercise is safe,[63] initial supervision may be helpful for both patients and their carers, and the resource implications are substantial. Whether a training programme is possible for many patients, who may be elderly, frail and suffer from multiple co-morbidities, is debatable. Nevertheless, patients can be reassured that exercise is safe and will improve their symptoms.

Revascularisation. The commonest cause of heart failure is underlying ischaemic heart disease. However, there is no good evidence that treatments directed at ischaemia with, for example, statins,[67] are beneficial, despite the intuitive feeling that treating ischaemia should be effective. One of the more challenging questions has been whether revascularisation for patients with heart failure and no angina might be beneficial. Observational studies suggest that revascularisation might indeed improve prognosis, particularly in those with demonstrable viability on functional testing,[68] but we now have two randomised trials that address the problem directly.

In HEART,[69] patients with heart failure and viable but dysfunctional myocardium were randomised to two strategies of care: conservative management or angiography with a view to revascularization. There was no difference in survival between the two groups at 59 months. Although the trial recruited slowly, and only 138 of the planned 800 patients were enrolled, there was no signal suggesting benefit.

STICH[70] included 1212 patients with an ejection fraction ≤35% who were considered suitable for CABG. The patients were randomised to CABG or continued medical therapy. Over a median follow-up of 56 months, there was no difference in all-cause mortality, the primary endpoint, between the treatment groups. There was a reduction in the combined end point of all-cause mortality and cardiovascular hospitalization in the CABG group, but the analysis exclude the hospitalization for the original operation, which is scarcely a negligible event: the 60 hospitalizations prevented by CABG required 555 hospitalizations for the CABG procedure itself.[71] There were more deaths in the CABG group for more than 2 years after randomization, emphasising that this is not a benign intervention.

Together, HEART and STICH show that there is, at most, a marginal benefit for revascularisation in patients with heart failure and underlying ischaemic heart disease. How the results relate to clinical practice is not clear: in STICH, the average age of patients was around 60, resting heart rate was over 70 (suggesting, perhaps, inadequate β blockade) and fewer than 10% had "chronic renal insufficiency" (creatinine is not reported in the paper). Despite the enormous expenditure of effort to answer the question, it is still not clear whether revascularisation is helpful for patients with heart failure.

Acute heart failure

After many years of clinical trials in patients with chronic heart failure, there has been renewed interest in the problem of acute heart failure, in part driven by the availability of new medications as potential treatments.

One of the most widely used new treatments for acute heart failure has been nesiritide, licensed for use in

the United States largely as a result of trials showing some improvement in haemodynamics.[72] It has always seemed a little strange from a European perspective that nesiritide has been so widely used, and the EMEA did not allow its use in the EU. A 7000 patient trial comparing nesiritide with placebo in addition to standard treatment has now completed.[73] There was no statistically significant difference in symptoms scores between the two groups, or in rehospitalisation or death at 30 days.

Another agent for possible use in patents with acute heart failure is rolophylline, an adenosine antagonist. Rolphylline might help prevent decline in renal function with diuretic therapy by interrupting glomerulo-tubular feedback. However, in a 2000 patient study, rolophylline had no effect on the primary endpoint (a composite "treatment success" score), renal function or mortality.[74,75]

Taken together, the trials of rolophylline and nesiritide highlight the importance of using clinical trials appropriately to drive the evolution of treatment. Reliance on relatively small trials with inappropriate end-points led to the nesiritide debâcle, whereas investigation of rolophylline followed an appropriate sequence with early small scale studies informing the design of a properly powered end-point study.

The correct diuretic dosing regime for patients admitted with fluid retention has often been a controversial question, and the DOSE trial[76] was designed to help guide this aspect of acute heart failure management. 308 patients with fluid retention due to heart failure were randomised to receive furosemide either as a bolus every 12 hours or by continuous infusion: both were given as either low or high dose. There were two co-primary end points: patients' global symptom assessment over 72 hours, and change in creatinine level from baseline to 72 hours.

There was no significant difference between bolus and infusion regimes, but a small (and statistically non-significant) greater improvement in symptoms in the high dose versus low dose groups. The high dose groups had a substantially greater diuresis.

It can be difficult directly to compare practice in the US with Europe. Typically, patients with acute heart failure are in hospital for around 5 days in the US, but 11 days in Europe, and any acute weight loss during admission (presumably reflecting fluid loss) is very much smaller, implying that patients are admitted in the US with very much less fluid overload than in Europe. Whether there are differences between frusemide given by bolus or continuous infusion over a longer time scale cannot be addressed by DOSE, but the message that high doses of frusemide (defined here as 2.5 times the patient's usual oral dose) cause a greater diuresis is clear.

References

1. Cleland JG, McDonagh T, Rigby AS, et al. National Heart Failure Audit Team for England and Wales. The national heart failure audit for England and Wales 2008-2009. Heart 2011;97:876-86.
2. National Heart Failure Audit. Report for 2008/09. http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS_National_Heart_Failure_Audit_09_INTERACTIVE.pdf accessed July 2011.
3. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. Am J Med 2011;124:136-43.
4. Gurwitz JH, Goldberg RJ. Age-based exclusions from cardiovascular clinical trials: implications for elderly individuals (and for all of us): comment on "the persistent exclusion of older patients from ongoing clinical trials regarding heart failure". Arch Intern Med 2011;171:557-8.
5. National Institute for Clinical Excellence. Chronic heart failure. Clinical Guidleine 108. London, August; 2010.
6. Al-Mohammad A, Mant J. The diagnosis and management of chronic heart failure: review following the publication of the NICE guidelines. Heart 2011;97:411-6.
7. Joynt KE, Orav EJ, Jha AK. The association between hospital volume and processes, outcomes, and costs of care for congestive heart failure. Ann Intern Med 2011;154:94-102.
8. Macgowan GA, Parry G, Schueler S, Hasan A. The decline in heart transplantation in the UK. BMJ 2011;342:d2483.
9. Banner NR, Bonser RS, Clark AL, et al. UK Guidelines for referral and assessment of adults for heart transplantation. Heart 2011;97:1520-7.
10. Riezebos RK, Ronner E, Ter Bals E, et al. OPTIMA trial. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. Heart 2009;95:807-12.
11. Inglis SC, Clark RA, McAlister FA, et al. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD007228. DOI: 10.1002/14651858.CD007228.pub2
12. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. N Engl J Med 2010;363:2301-9.
13. Koehler F, Winkler S, Schieber M, et al. Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation 2011;123:1873-80.
14. Bourge RC, Abraham WT, Adamson PB, et al. O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW; COMPASS-HF Study Group. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073-9.
15. Hoppe UC, Vanderheyden M, Sievert H, et al. Chronic monitoring of pulmonary artery pressure in patients with severe heart failure: multicentre experience of the monitoring Pulmonary Artery Pressure by Implantable device Responding to Ultrasonic Signal (PAPIRUS) II study. Heart 2009;95:1091-7.
16. Abraham WT, Adamson PB, Bourge RC, et al. CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.
17. Ritzema J, Troughton R, Melton I, et al. Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation 2010;121:1086-95.
18. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J 2009;158:422-30.
19. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009;55:53-60.
20. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
21. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.

22. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation 2003;107:656-8.
23. Brutsaert DL, De Keulenaer GW. Diastolic heart failure: a myth. Curr Opin Cardiol 2006;21:240-8.
24. Borlaug BA, Jaber WA, Ommen SR, et al. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart 2011;97:964-9.
25. Holland DJ, Prasad SB, Marwick TH. Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HFpEF). Heart 2010;96:1024-8.
26. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36-46.
27. Tan YT, Wenzelburger F, Lee E, et al. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010;96:1017-1023.
28. Zile MR, Gaasch WH, Anand IS, et al. I-Preserve Investigators. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 2010;121:1393-405.
29. Konstam MA, Neaton JD, Dickstein K, et al. HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374:1840-8.
30. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
31. Pitt B, Remme W, Zannad F, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
32. Zannad F, McMurray JJ, Krum H, et al. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.
33. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.
34. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 2011;32:820-8.
35. Levine HJ. Rest heart rate and life expectancy. J Am Coll Cardiol 1997;30:1104-6.
36. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986;57:43F-49F.
37. Swedberg K, Komajda M, Böhm M, et al. SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.
38. Böhm M, Swedberg K, Komajda M, et al. SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886-94.
39. Cullington D, Goode KM, Cleland JGF, Clark AL. How many patients with chronic heart failure might be suitable for ivabradine? Heart 2011 (we hope).
40. Witte KK, Desilva R, Chattopadhyay S, et al. Are hematinic deficiencies the cause of anemia in chronic heart failure? Am Heart J 2004;147:924-30.
41. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103-12.
42. Anker SD, Comin Colet J, Filippatos G, et al. FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436-48.
43. van der Meer P, Groenveld HF, Januzzi JL Jr, van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. Heart 2009;95:1309-14.
44. Beadle RM, Frenneaux M. Modification of myocardial substrate utilisation: a new therapeutic paradigm in cardiovascular disease. Heart 2010;96:824-830.
45. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. Circulation 2005;112:3280-8.
46. Fragasso G, Salerno A, Lattuada G, et al. Effect of partial inhibition of fatty acid oxidation by trimetazidine on whole body energy metabolism in patients with chronic heart failure. Heart 2011;97:1495-500.
47. Gao D, Ning N, Niu X, et al. Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. Heart 2011;97:278-86.
48. Cleland JG, Daubert JC, Erdmann E, et al. Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
49. Cleland JG, Calvert MJ, Verboven Y, et al. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. Am Heart J 2009;157:457-66.
50. Cleland JG, Freemantle N, Daubert JC, et al. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. Heart 2008;94:278-83.
51. Moss AJ, Hall WJ, Cannom DS, et al. MADIT-CRT Trial Investigators.Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
52. Tang AS, Wells GA, Talajic M, et al. Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
53. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008;117:2608-16
54. van Bommel RJ, Gorcsan J 3rd, Chung ES, et al. Effects of cardiac resynchronisation therapy in patients with heart failure having a narrow QRS Complex enrolled in PROSPECT. Heart 2010;96:1107-13.
55. Foley PW, Patel K, Irwin N, et al. Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. Heart 2011;97:1041-7.
56. Sipahi I, Carrigan TP, Rowland DY, et al. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy. Meta-analysis of randomized controlled trials. Arch Intern Med 2011;171:1454-62.
57. Lavalle C, Ricci RP, Santini M. Atrial tachyarrhythmias and cardiac resynchronisation therapy: clinical and therapeutic implications. Heart 2010;96:1174-1178.
58. Dickstein K, Vardas PE, Auricchio A, et al. Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 2010;31:2677-87.
59. Shelton RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). Heart 2009;95:924-30.
60. Yu CM, Chan JY, Zhang Q, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. N Engl J Med 2009;361:2123-34.

61. Conraads VM, Beckers PJ. Exercise training in heart failure: practical guidance. Heart 2010;96:2025-2031.
62. Rees K, Taylor RS, Singh S, et al. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004:CD003331.
63. O'Connor CM, Whellan DJ, Lee KL, et al. HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.
64. Flynn KE, Piña IL, Whellan DJ, et al. HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1451-9.
65. Spruit MA, Eterman RM, Hellwig VA, et al. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. Heart 2009;95:1399-408.
66. Conraads VM, Beckers PJ. Exercise training in heart failure: practical guidance. Heart 2010;96:2025-31.
67. Kjekshus J, Apetrei E, Barrios V, et al. CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.
68. Rizzello V, Poldermans D, Biagini E, et al. Prognosis of patients with ischaemic cardiomyopathy after coronary revascularisation: relation to viability and improvement in left ventricular ejection fraction. Heart 2009;95:1273-7.
69. Cleland JG, Calvert M, Freemantle N, et al. The Heart Failure Revascularisation Trial (HEART). Eur J Heart Fail 2011;13:227-33.
70. Velazquez EJ, Lee KL, Deja MA, et al. For the STICH Investigators. Coronary artery bypass surgery in patients with left ventricular dysfunction. N Eng J Med 2011;364:1607-1616.
71. Cleland JG, Freemantle N. Revascularization for patients with heart failure. Inconsistencies between theory and practice. Eur J Heart Fail 2011;13:694-7.
72. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531-40.
73. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32-43.
74. Massie BM, O'Connor CM, Metra M, et al. PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419-28.
75. Voors AA, Dittrich HC, Massie BM, et al. Effects of the adenosine A1 receptor antagonist rolofylline on renal function in patients with acute heart failure and renal dysfunction: results from PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function). J Am Coll Cardiol 2011;57:1899-907.
76. Felker GM, Lee KL, Bull DA, et al. NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.