The Year in Cardiology

The Year in Cardiology 2012: heart failure

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In 2012 there were a number of important advances within the clinical arena of heart failure. Recent new evidence was dissected, analysed, synthesized, and incorporated into the new European Society of Cardiology Heart Failure Guideline 2012 which will facilitate the translation of clinical research in heart failure into improved patient care. In addition there were new therapeutic treatment trials presented at two of the major scientific meetings, the European Society of Cardiology (ESC) Congress in Munich and most recently, the American Heart Association (AHA) Scientific Sessions in Los Angeles. Interestingly, these focused on two areas of great unmet need in heart failure therapy, acute heart failure (AHF) and heart failure with preserved left ventricular function (HFPEF).

This article summarizes the main heart failure highlights of the new guideline and those two meetings.

A. ESC Heart Failure Guideline 2012

John McMurray and his Task Force produced the new Guideline in time for presentation and publication at the ‘Heart Failure 2012’ meeting in Belgrade, Serbia. This version incorporated the results of 19 new large randomized controlled trials since the previous guideline that was published in 2008 (Figure 1).

Regarding the style of the guideline one important change that improves its comprehension for general clinicians is the linking of the class and level of evidence given for treatments to the clinical indication for that therapy. e.g. angiotensin-converting enzyme inhibitors (ACE-i) are given to patients with systolic heart failure to reduce the risk of hospitalization and premature death. This allows comparison with other indications, e.g. reduction in pulmonary capillary wedge pressure for some other therapy recommendations, and will be very useful for clinicians assessing the importance of implementing the treatments recommended.

The main changes in the new guideline include:

(1) An increased role for mineralocorticoid (aldosterone) receptor antagonists (MRA). Spironolactone or eplerenone is now recommended for all heart failure patients with persisting symptoms (NYHA Class II–IV) with a LV ejection fraction ≤35% despite treatment with an ACE inhibitor and a beta-blocker to reduce the risk of heart failure hospitalization and the risk of premature death (I-A recommendation).

(2) A new indication for the sinus node inhibitor ivabradine. Following publication of the SHIFT-trial two ivabradine should now be considered to reduce the risk of heart failure hospitalization in patients in sinus rhythm with an LVEF ≤35%, who have a heart rate ≥70 b.p.m., and persisting symptoms (NYHA Class II–IV) despite treatment with an evidence-based dose of beta-blocker, ACE-inhibitor and a MRA (IIa-B recommendation).

(3) An expanded place for cardiac resynchronization therapy (CRT). Evidence form the RAFT and MADIT-CRT studies have led to a recommendation for the use of CRT (preferably CRT-D) for heart failure patients in NYHA class II if they are in sinus rhythm with an LVEF ≤35% and who are otherwise candidates for surgery. Consideration of the STICH trial resulted in a I-B recommendation for CRT in patients with persisting symptoms (NYHA Class II–IV) with a LV ejection fraction ≤35%, who have a heart rate ≥70 b.p.m., and persisting symptoms (NYHA Class II–IV) despite treatment with an evidence-based dose of beta-blocker, ACE-inhibitor and a MRA (IIa-B recommendation).

(4) The incorporation of new information on the role of coronary revascularization in heart failure. Consideration of the STICH trial resulted in a I-B recommendation for the use of coronary artery bypass graft in patients with angina and two- or three-vessel coronary disease including a left anterior descending stenosis with an LVEF ≤35% and who are otherwise candidates for surgery with a life expectancy of ≥1 year with good functional capacity.

(5) Acknowledgement of the increasing role of ventricular assist devices. Left ventricular or biventricular assist devices are recommended in very selected patients who have had end-stage heart failure, for at least 2 months, despite optimal pharmacological and...
Figure 1. Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV).
device treatment and who are otherwise suitable for heart transplantation to improve symptoms and reduce the risk of heart failure hospitalization and to reduce the risk of premature death while awaiting transplantation (I-B recommendation). The recommendation also states clearly that this therapy should be delivered in highly specialized centres, that would usually also conduct cardiac transplantation.

(6) Transcatheter valve interventions also feature. Transcatheter aortic valve replacement should be considered in patients with heart failure and severe aortic stenosis who are unfit for surgery (usually due to severe pulmonary disease). In patients with secondary mitral regurgitation who are not operable or who have an unacceptably high-surgical risk, percutaneous edge-to-edge repair (MitraClip) may be considered in order to improve symptoms.

A treatment not recommended as part of the review of the evidence for this guideline was the use of Warfarin in patients with heart failure who do not have atrial fibrillation. The WARCEF trial of 2305 patients found no significant difference in the composite endpoint of death/haemorrhage between patients who took warfarin and those given aspirin.

Guidelines often highlight areas of unmet need in heart failure and prompt further studies to fine tune evidence. Perhaps as a result of the heart rate-lowering properties of ivabradine we will see more studies with that other heart rate lowering, but much older drug, digoxin! Castagnol et al. published a comparison of the relative reduction in the combined endpoint of cardiovascular deaths or hospitalizations for heart failure (the primary endpoint of the SHIFT Study) in the DIG study demonstrating a 15% reduction, very similar to the 18% reduction observed in SHIFT.

The guideline also acknowledges the lack of robust evidence for a number of commonly advised lifestyle interventions, e.g. sodium restriction in heart failure. It cites one randomized controlled trial of sodium restriction vs. normal sodium diet as having worse outcomes for heart failure patients. This has subsequently been underscored by the publication of a meta-analysis of sodium restriction in heart failure. These findings remind us of the lack of evidence for many lifestyle interventions in heart failure and the need for more research in this area.

A. ESC Congress 2012, Munich, Germany

At this year’s ESC two trials in the, as yet unfruitful area of therapeutics for heart failure with preserved ejection fraction (HFPEF), HFPEF were reported.

PARADIGM-HF

This Phase 2 randomized comparison of the angiotensin-receptor/ neprilysin inhibitor (ARNI) LCZ696 to valsartan reported favourable results in 301 patients with HFPEF (in NYHA Classes II–III with an LVEF ≥45% and NT-pro-brain-type natriuretic peptide (BNP) concentrations ≥400 pg/mL). LCZ696 both suppresses the renin–angiotensin–aldosterone system (RAAS) and increases circulating levels of BNP and other endogenous natriuretic peptides. Concentrations of NT-pro-BNP were reduced by 23% (P = 0.005) over 12 weeks and by 15% (P = 0.20) over 36 weeks among those receiving LCZ696 compared with valsartan. In addition, NYHA class also improved significantly with LCZ696 (P < 0.05) at 36 weeks, as did left atrial width (P = 0.03), left atrial volume (P = 0.003), and left atrial volume index (P = 0.007). These combined results showing a reduction in NT-pro-BNP and favourable effects on markers of atrial remodelling are very encouraging in an area where the blockade of the RAAS with ACE-I or ARBs has not shown any benefit to date. Maybe these results will trigger a large outcome trial in HFPEF patients.

ALDO-HF

The results reported in ALDO-HF were less positive. The trial randomized 422 patients with HFPEF (NYHA Class II with an LVEF ≥50% and tissue Doppler indices of diastolic dysfunction and reduced effort capacity) to receive spironolactone 25 mg/day or placebo in addition to the patients other medical therapy. The co-primary endpoints were peak VO2 and diastolic function (E/e’) at 1 year. E/e’ improved significantly with spironolactone vs. placebo at 6 and 12 months (P < 0.001 for both), while there were no significant differences between treatment groups in peak VO2 at either time point.

The left ventricular mass index decreased similarly in the treatment groups at 6 months (P = 0.16) and continued to drop significantly out to 12 months in the spironolactone group but not in the control group (P = 0.009). Concentrations of N-terminal pro-BNP fell in both groups by 6 months, but more so in the spironolactone group (P = 0.09). At 1 year, concentrations rose in both groups, but rose more in those assigned to placebo (P = 0.03). There were no significant differences in death or hospitalization rates.

The disconnect between markers of favourable LV remodelling and symptoms is intriguing in this study. However, we will know whether aldosterone antagonism is beneficial in HFPEF patients when TOPCAT—a large adequately powered outcome trial with spironolactone vs. placebo reports at the end of next year.

B. AHA Scientific Sessions 2012, Los Angeles, USA

Two new trials were presented here in another area of great unmet need, i.e. acute heart failure.

RELAX-HF

This study reported on the effects of a recombinant form of the pregnancy hormone relaxin-seralaxin vs. placebo in 1160 patients with acute heart failure, who had systolic blood pressures >125 mmHg. Seralaxin was given as a 48 h infusion within 16 h of presentation. Use of seralaxin was associated with a 19% improvement in the area under the curve from baseline to Day 5 on a dyspnoea visual analogue scale (the primary endpoint). There was a non-statistically significant improvement in dyspnoea measured on the Likert Scale. The secondary endpoints of days alive and out of hospital at Day 60 and cardiovascular deaths or heart failure/renal hospitalizations up to Day 60 were not significantly improved with seralaxin. In addition, seralaxin improved...
symptoms and signs of heart failure, the percentage of patients with worsening heart failure, reduced the length of stay and improved concentrations of NT-pro-BNP, creatinine, and troponin significantly. Interestingly there was a significant 37% reduction in both all-cause and cardiovascular mortality at 6 months.

Clearly, this drug improves symptoms in acute heart failure. The mortality benefits, based on small numbers in a non-pre-specified analysis need to be treated with caution. Nevertheless, selarxin looks very promising as a new treatment for AHF.

CARRESS-HF

This was the third trial of ultrafiltration in heart failure to report to date, and announced more disappointing news than the other two. CARRESS-HF randomized 188 patients with acute decompensated HF who had worsening renal failure to stepped pharmacological care or ultrafiltration. The results showed a similar degree of weight loss in both groups. There was little change in the creatinine in the diuretic arm. However, there was a significant deterioration in renal function in those assigned to ultrafiltration. While there was no difference in harder endpoints of death or hospitalization for HF between the two arms, there were more serious adverse events in the ultrafiltration group. This is an important trial which shows that there is no role for ultrafiltration in those who are responsive to diuretics; however, there is still a role for more randomized trials of ultrafiltration to define its place in the care of patients with HF who are unresponsive to diuretics.

In summary of the year in Heart Failure Cardiology 2012, we had the benefit of an up to date Heart Failure Guideline to facilitate the translation of recent evidence into clinical practice. We also had a number of trials reporting on outcomes in patients with HF preserved systolic function and acute heart failure. These should hopefully lead to new disease modifying therapies for these HF phenotypes, which have yet no treatments which improve patient outcomes.

References