Welcome to issue 48 of Heart Failure Research Review.

Research confirming the existence of a correlation between LV filling pressures and lung water content in HFREF begins this issue. Two papers selected for this issue report on the use of the TMVR (transcatheter mitral valve repair) technique for mitral regurgitation, with one reporting postmarketing surveillance data from nearly 3000 US patients, and the other reporting on its use in 50 patients, including some from Australia, with symptomatic, severe disease. We have also included the findings of a trial recently published in N Engl J Med comparing revasculatization with PCI initially of the culprit lesion only versus immediate multivessel PCI in patients with acute MI with cardiogenic shock. We conclude with Spanish data on early, unplanned readmissions following hospitalisation for HF over an 11-year period, highlighting the need for population-based strategies to address this issue.

As always, please feel free to send us your comments or questions.

Kind Regards,

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Correlation between pulmonary artery pressure and thoracic impedance: insights from daily monitoring through an implanted device in chronic heart failure

Authors: Perego GB et al.

Summary: Ten patients with HFREF implanted with an ICD that could measure thoracic impedance had a sensor for directly measuring PAP (pulmonary artery pressure) implanted, and both measures were remotely monitored daily for 405 ±141 days; after a 3-month period where PAP values were blinded to the investigators, they were then used to guide therapy. A significant decrease in diastolic PAP occurred during haemodynamic-guided therapy (from 27.8 to 24.0mm Hg [p<0.001]), during which variations in thoracic impedance were nonsignificant. They then used to guide therapy. A significant decrease in diastolic PAP occurred during haemodynamic-guided therapy (from 27.8 to 24.0mm Hg [p<0.001]), during which variations in thoracic impedance were nonsignificant. There was a significant negative correlation between thoracic impedance variations and PAP versus baseline (p<0.001). Thoracic impedance decreases of 5.6 ±3.9 days were preceded by episodes of sustained PAP increases, but the latter predicted the former with sensitivity of only 0.37.

Comment: There is currently considerable interest in the potential role of implanted devices to guide HF therapy in order to prevent periods of acute decompensation and the need for hospitalisation. CardioMEMs™, which is implanted in the pulmonary artery and allows measurement of PAP, and pacemakers/defibrillators that are capable of measuring thoracic impedance as an indirect measure of lung water content are two examples. In this small, single-centre observational study of patients with stable chronic HFREF implanted with both devices, the authors confirmed the sequential relationship between an increase in PAP followed by increase in lung water content (as reflected by decreased thoracic impedance) usually by days; however, they also noted that most instances of increased PAP were not followed by a decrease in thoracic impedance or acute decompensated HF. The authors speculated that any benefit of CardioMEMs™ in reducing episodes of acute decompensated HF is more likely related to a sustained reduction in PAP in response to PAP-guided medical therapy, rather than acute treatment responses to acute increases in PAP. They may well be right; however, this raises the question of whether a similar outcome could be achieved by intensified medical therapy in the absence of these implanted devices.


Abstract

In this issue:

- Correlation between PAP and thoracic impedance
- Pulmonary haemodynamics in pulmonary hypertension with HFREF vs. HFPEF
- Sodium bicarbonate for preventing ACE inhibitors for preventing LV dysfunction/HF during anthracyclines ±trastuzumab
- Postmarketing TMVR outcomes
- Early experience with new TMVR
- Adjunctive vitamin D, repletion in HF
- PCI strategies in acute MI with cardiogenic shock
- Age and outcomes with primary prevention ICDs in nonischaemic systolic HF
- Trends, causes and timing of readmissions after HF hospitalisation

Abbreviations used in this issue:

ACE = angiotensin converting-enzyme; CIN = contrast induced-nephropathy; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HFPEF/HFREF = HF with preserved/reduced EF; ICD = implantable cardioverter defibrillator; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; QOL = quality of life; TMVR = transcatheter mitral valve repair.

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Pulmonary hemodynamics in heart failure patients with reduced or preserved ejection fraction and pulmonary hypertension: similarities and disparities

Authors: Adir Y et al.

Summary: This retrospective chart review of patients with pulmonary hypertension due to HFREF (n=168) or HFPEF (n=86) sought to compare pulmonary haemodynamics for these two phenotypes when PAPs are similar, and also to assess if pulmonary vascular compliance and diastolic pulmonary gradient impact on survival. Average follow-up was 50 months. Diastolic pulmonary gradient was significantly higher in the HFPEF group than in the HFREF group (0.1 vs. 1.8 mmHg [adjusted p=0.025]), whereas pulmonary vascular compliance was similar. Pulmonary vascular compliance at previously described preset cutoffs of 2.15 and 1.1 mL/mmHg in HFREF and HFPEF, respectively, and based on a continuous scale significantly predicted survival, whereas survival was not affected by diastolic pulmonary gradient in either group.

Comment: This retrospective study compared and contrasted the pathophysiology of pulmonary hypertension in HFREF and HFPEF. As a group, HFPEF patients had higher PAPs and a higher diastolic pulmonary gradient, but also higher resting cardiac output. The authors concluded that for an equivalent elevation in LV filling pressure, patients with HFPEF had a stiffer pulmonary circulation. While they attempted to account for differences in baseline characteristics using multivariate analysis, it is hard to ignore the fact that the HFPEF patients were on average 13 years older with significantly higher prevalences of systemic hypertension, obesity and hypertension, all of which may contribute to vascular remodelling – suggesting that the whole vascular tree is stiffer in HFPEF patients!

Reference: Am Heart J 2017;192:120–7

Abstract

Usefulness of sodium bicarbonate for the prevention of contrast-induced nephropathy in patients undergoing resynchronization therapy

Authors: Alonso P et al.

Summary: Patients undergoing implantation of a cardiac resynchronisation therapy device (evaluable n=33) were randomised to a group that received intravenous volume expansion with isotonic saline and sodium bicarbonate solution or a control group that received no hydration. Compared with controls, participants from the hydration group had a significantly lower incidence of CIN (contrast-induced nephropathy; primary endpoint; 0% vs. 11% [p=0.02]) and a trend for a lower incidence of a composite endpoint of death, heart transplantation or HF hospitalisation at 12 months (12.5% vs. 22% [p=0.14]). A significant relationship was seen between CIN incidence and 12-month mortality.

Comment: While the results of this 93-patient single-centre study suggest a dramatic renoprotective effect of sodium bicarbonate in HF patients at risk of CIN, they stand in stark contrast to the results of the large international multicentre 5000-patient PRESERVE study (presented this week at the AHA Meeting and published simultaneously in N Engl J Med) that revealed no benefit of sodium bicarbonate or N-acetyl cysteine in patients at high risk of CIN.

Reference: Am J Cardiol 2017;120(9):1584–8

Abstract

Effect of prophylactic betablocker or ACE inhibitor on cardiac dysfunction & heart failure during anthracycline chemotherapy ± trastuzumab

Authors: Gujral DM et al.

Summary: These authors analysed data from eight studies (n=1048) reporting the effects of β-blockers or ACE inhibitors on LVEF and HF in patients receiving anthracycline chemotherapy with or without trastuzumab. Compared with controls, ACE inhibitor use did not significantly affect LVEF change (MWD -4.74 [95% CI –12.6 to 3.1]) or risk of new HF diagnosis (odds ratio 0.24 [0.03–1.73]), whereas β-blocker use was associated with a significantly smaller LVEF reduction (MWD –3.28 [–6.1 to –0.51]) and a significant decrease in new HF hospitalisation risk (odds ratio 0.33 [0.14–0.80]), the effect of β-blocker use on LVEF reduction lost significance in the subgroup of patients who received anthracycline chemotherapy without trastuzumab (MWD –3.05 [–7.22 to 1.12]).

Comment: Cardiotoxicity is a well-recognised complication of anthracycline chemotherapy and trastuzumab administration. In this retrospective review, the authors identified eight studies in which patients undergoing chemotherapy with an anthracycline with or without trastuzumab were treated with either prophylactic ACE inhibitors or β-blockers. Interestingly, only prophylactic β-blockade was shown to mitigate the decline in LVEF and reduce the incidence of new-onset HF, with the major benefit seen in patients receiving combination chemotherapy. This is an important area where further research is required.

Reference: Breast 2018;37:64–71

Abstract

Outcomes with transcatheter mitral valve repair in the United States

Authors: Sorajja P et al.

Summary: This report of data from the US STS/ACC TVT registry explored commercial experience with TMVR for mitral regurgitation. Data from 2952 patients were included, with data for 1867 of these linked to patient-specific Medicare and Medicaid services administrative claims. The patients’ median age was 82 years and their median predicted risks of mortality were 6.1% and 9.2% for mitral repair and replacement, respectively. The overall in-hospital mortality rate was 2.7%, and the procedural success rate was 91.8%. Among the patients with linked administrative claims data, the respective 30-day and 1-year mortality rates were 5.2% and 25.8%, and their 1-year repeat HF hospitalisation rate was 20.2%. A multivariate analysis revealed that increasing age, lower baseline LVEF, worse postprocedural mitral regurgitation, moderate or severe lung disease, dialysis and severe tricuspid regurgitation were associated with mortality or HF rehospitalisation.

Comment: There is a rapidly accumulating experience with the use of percutaneous TMVR with Mitra-Clip to correct moderate-to-severe functional mitral regurgitation in association with symptomatic congestive HF, particularly in patients who are at high surgical risk. This report from a prospective US registry described the outcomes of almost 3000 patients undergoing TMVR. Patients were elderly and although a high procedural success rate was reported, 1-year mortality and rehospitalisation rates for HF were substantial. A large ongoing randomised trial of TMVR versus optimal medical therapy for treatment of moderate-to-severe functional mitral regurgitation in association with symptomatic HF (COAPT, NCT01626079) will help to define the role of percutaneous mitral valve repair in the management of functional mitral regurgitation in congestive HF patients.

Reference: J Am Coll Cardiol 2017;70(19):2315–27

Abstract

Early experience with new transcatheter mitral valve replacement

Authors: Bapat V et al., for the Intrepid Global Pilot Study Investigators

Summary: This research included 50 consecutive patients from Australia, the US and Europe with symptomatic, severe mitral regurgitation at high or extreme risk who underwent TMVR; 86% were NYHA class III–IV and their mean LVEF was 24%. All but two patients underwent successful device implantation, with a median deployment time of 14 minutes. The 30-day mortality rate was 14%; there were no disabling strokes and no repeat interventions were needed. After median follow-up of 173 days, all patients who underwent successful implantation had mild or no residual mitral regurgitation on echocardiography, 79% had improved to NYHA class I–II from baseline (p<0.0001) and Minnesota HF questionnaire scores had significantly increased (from 31.7 to 56.2 [p=0.011]).

Comment: TMVR is a rapidly evolving technique with a number of devices undergoing clinical investigation for the treatment of symptomatic mitral regurgitation. Like transcatheter aortic valve repair, the initial target population has been made up of patients considered at high risk for surgical valve replacement or repair. This study, which included Australian investigators, reported the initial clinical experience in 50 consecutive patients with secondary mitral regurgitation, most of whom had severe symptomatic HF with low EF. Valve implantation was performed in a hybrid theatre via a left anterior thoracotomy and transapical approach. While technical success was high, so was early mortality (14% at 30 days). Beyond the first month, most patients reported improvements in symptoms and QOL. Similar symptomatic improvements (with a lower hospital mortality) were reported earlier this year with another transapical TMVR trial (Muller D et al. J Am Coll Cardiol 2017;69:381–9). While these reports are encouraging, prospective randomised trials are needed.

Reference: J Am Coll Cardiol; Published online Nov 1, 2017

Abstract

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CHF patients aged ≥ 70 years deserve an age-proven β-blocker¹,²

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of CHF patients aged ≥ 70 years*¹,²

*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

PBS Information: Restricted benefit. Moderate to severe heart failure. Refer to PBS Schedule for full restricted benefit information.

Please review full Product Information before prescribing. The Product Information can be accessed at www.menarini.com.au/pi

Nebilet® (nebivolol hydrochloride) tablets 1.25 mg, 5 mg, 10 mg. INDICATIONS: Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. CONTRAINDICATIONS: Hypersensitivity to the active or any of the excipients; liver insufficiency or liver function impairment; acute heart failure; cardiogenic shock or episodes of heart failure decompensation requiring IV inotropic therapy; sick sinus syndrome, including sino-atrial block; second and third degree heart block (without a pacemaker); history of bronchospasm (e.g. including COPD) and/or asthma; untreated phaeochromocytoma; metabolic acidosis; bradycardia (HR < 60 bpm prior to starting therapy); hypotension (systolic BP < 100 mmHg); severe peripheral circulatory disturbances. PRECAUTIONS: Avoid abrupt cessation unless clearly indicated – reduce dosage gradually over 1-2 wks; refer to full PI. If it must be withdrawn abruptly, close observation is required. Anaesthesia: untreated congestive heart failure, unless stabilised; bradycardia; peripheral circulatory disorders (e.g. Raynaud’s disease, intermittent claudication); first degree heart block; Prinzmetal’s or variant angina; lipid and carbohydrate metabolism – does not affect glucose levels in diabetic patients, but may mask symptoms of hypoglycaemia. Hyperthyroidism; COPD/asthma; phaeochromocytoma; various skin rashes; conjunctival xerosis; oculomucocutaneous syndrome; psoriasis; increased sensitivity to allergens and severity of anaphylactic reactions; galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption; driving vehicles or operating machines. Pregnancy (Cat C). Lactation. Children and adolescents. Renal and hepatic insufficiency – see Dosage and Administration. INTERACTIONS: Combination not recommended: Class I antiarrhythmics; calcium channel antagonists (verapamil/diltiazem); centrally-acting antihypertensives; other beta-blockers (incl. eye drops). Combination to be used with caution: Class III antiarrhythmic drugs; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine; for other combinations requiring careful consideration, see full PI. ADVERSE EFFECTS: Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, dyspnœa, oedema, slowed AV conduction/AV-block, bronchospasm. Post-marketing reports of hypersensitivity, angioneurotic oedema, abnormal hepatic function, acute pulmonary oedema, acute renal failure, myocardial infarction, others see full PI. DOSAGE AND ADMINISTRATION: Once daily dosing, can be given with or without meals, consistent approach is recommended. Hypertension: 5 mg daily. Renal insufficiency: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 65 years: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 75 years: caution must be exercised and these patients monitored closely. Chronic Heart Failure: The initial up titration should be done gradually at 1-2 wks intervals based on patient tolerability starting at 1.25 mg once daily, increased to 2.5 mg, then to 5 mg and then to 10 mg once daily. Initiation of therapy and every dose increase should be done under close supervision for at least 2 h. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 µmol/L) is not recommended. Data prepared 17 December 2015. References: 1. Nebilet Approved Product Information, 14 December 2015. 2. Flather MD et al. Eur Heart J 2005; 26: 215–25.

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Vitamin D₃ repletion versus placebo as adjunctive treatment of heart failure patient quality of life and hormonal indices

Authors: Moretti HD et al.

Summary: Forty patients with stable HF (NYHA class II-III) who were vitamin D deficient or insufficient were randomised to receive supplemental vitamin D₃ 10,000 IU/day or placebo in this trial. All results were adjusted for baseline 25-hydroxyvitamin D level. Compared with placebo, vitamin D₃ recipients experienced a significantly greater increase in baseline brain natriuretic peptide level (30 vs. 400 ng/mL [p=0.003]), a significantly greater increase in 25-hydroxyvitamin D serum level (49 vs. 4 ng/mL [p=0.001]), and significant improvements in QOL scores, including composite overall and clinical summary scores (p=0.01 for both). There were also improvements in parathyroid hormone level and exercise chronicotropic response index in the vitamin D₃ group, although statistical significance was lost after adjustments. Male, but not female, vitamin D₃ recipients also had an improvement in high sensitivity C-reactive protein level compared with placebo (+2 vs. +2 mg/L [p=0.05]).

Comment: The authors of this single-centre, prospective, randomised, placebo-controlled trial of high-dose vitamin D supplementation in patients with congestive HF and low plasma vitamin D₃ levels report that vitamin D₃ may improve QOL and some surrogate endpoints of congestive HF severity, including brain natriuretic peptide level, over 6 months of treatment. Although at first glance these results appear promising, they come from a relatively small, short-term study and are in sharp contrast to those of the much larger multicentre EVITA trial (reviewed in issue 45 of Heart Failure Research Review) that failed to demonstrate any clinically meaningful benefit in congestive HF patients treated with vitamin D 4000 IU daily for 3 years. Indeed, there was even a hint of harm in the EVITA study, with vitamin D-treated patients having a significantly increased requirement for mechanical circulatory support.

Reference: BMC Cardiovasc Disord 2017;17:274

Abstract

PCI strategies in patients with acute myocardial infarction and cardiogenic shock

Authors: Thiele H et al. for the CULPRIT-SHOCK Investigators

Summary: Patients with acute MI with cardiogenic shock and multivessel disease were randomised to initial revascularisation with PCI of the culprit lesion only with the option of staged revascularisation of nonculprit lesions (n=344) or immediate multivessel PCI (n=341). Compared with immediate multivessel PCI, the culprit lesion PCI group had lower incidences of the composite primary endpoint (death or renal-replacement therapy; 45.9% vs. 55.4%; relative risk 0.83 [95% CI 0.71–0.96]) and its two components respective relative risks 0.84 [0.72–0.98] and 0.71 [0.49–1.03]. There was no significant between-group difference for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Reference: N Engl J Med; Published online Oct 30, 2017

Abstract

Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure

Authors: Elming MB et al.

Summary: These researchers explored the relationship between age and outcome in primary prevention ICD in prespecified subgroup analyses of 1116 participants, median age 63 years, with nonischaemic systolic HF from the DANISH study. A significant, linearly decreasing relationship was identified between ICD and mortality according to age. Age 70 years was the optimal cutoff, with patients aged ≤70 years having reduced all-cause mortality with ICD (hazard ratio 0.70 [95% CI 0.51–0.96]), a relationship that was not evident in those aged >70 years (1.05 [0.68–1.62]). Patients aged ≤70 years had respective sudden and non-sudden cardiac death rates of 1.8 and 2.7 events per 100 patient-years, whereas for those aged >70 years, these were 1.6 and 5.4 events per 100 patient-years; there was a significant difference between the two age groups for mode of death (p=0.01).

Comment: The primary outcome results of the DANISH study (published 12 months ago in N Engl J Med and reviewed in issue 41 of Heart Failure Research Review) reported that primary prevention ICDs did not improve survival despite a reduction in sudden death in symptomatic patients with nonischaemic dilated cardiomyopathy. In a prespecified analysis of the original study, the authors did report a significant reduction in total mortality in patients less than 68 years of age who received primary prevention ICD. In this post hoc analysis, they examined in detail the relationship between age and the protective effect of primary prevention ICD. They found a linear relationship between age and the impact of primary prevention ICD on mortality. In other words, the younger the patient, the greater the mortality benefit with primary prevention ICD. This benefit declines progressively up to age 70 years, beyond which there is no survival benefit. This is not surprising given that other factors such as frailty and comorbidities contribute to mortality in the older congestive HF patient.


Abstract

Trends, causes, and timing of 30-day readmissions after hospitalization for heart failure

Authors: Fernandez-Gasso L et al.

Summary: This population-based analysis with linked data explored unplanned 30-day readmissions, their causes and timing over 11 years for HF cases in Spain. Thirty-day readmission rates increased by 1.36% per year during the period 2003–2013, increasing from 17.6% to 22.1%; when only same-hospital readmissions were considered, the rate fell from 22.1% to 19.8%. Similar trends were seen for CV and non-CV causes. CV causes contributed to 60% of readmissions, with HF the most common and contributing to 34%. Readmission timing data showed an early peak on postdischarge day 4 due to causes other than HF, followed by a gradual decline. Readmission for HF decreased steadily from day 1 to day 7. In-hospital mortality rates for HF and non-CV-related readmission were higher compared with index hospitalisation (12.7 and 13.3%, respectively, vs. 9.2% [p<0.001]). The main predictors of any readmission were age and comorbidity burden; however, poor performance was seen for a predictive model.

Comment: Thirty-day readmission after hospitalisation for HF has become a key performance indicator for healthcare services, particularly in the US. This big-data study using national linked administrative data from Spain showed a slow but steady increase in 30-day readmission after hospitalisation for HF over the decade from about 18% in 2003 to 22% in 2013. The 2013 readmission rate is in line with rates reported in other Western countries including Australia. Not surprisingly, the main determinants of readmission were patient age and comorbidities. Interestingly, causes for readmission were roughly evenly divided between three diagnostic categories: HF, other CV causes and non-CV causes. Given the ageing population, 30-day readmission rates are likely to increase further unless, as the authors suggest, a population-based strategy incorporating early and multidisciplinary intervention is adopted.

Reference: Int J Cardiol 2017;248:246–51

Abstract

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