Concerns have been raised about the safety of DPP-4 (dipeptidyl peptidase-4) inhibitors or gliptins in cardiovascular health, particularly in the context of heart failure (HF). Zannad F et al., for the EXAMINE Investigators, examined the safety profile of alogliptin, a novel DDP-4 inhibitor, in patients with type 2 diabetes and acute coronary syndrome. The study was a post hoc analysis of a large prospective study examining the effect of alogliptin on CV outcomes in patients with type 2 diabetes and recent acute coronary syndrome.

**Summary:** These researchers investigated HF hospital admissions among EXAMINE trial participants with an acute coronary syndrome and type 2 diabetes who had been randomised to receive alogliptin (n=2701) or placebo (n=2679) added to standard antidiabetes and CV disease prevention therapy. During median follow-up of 533 days, no difference was seen between the alogliptin and placebo arms for the prespecified exploratory extended endpoint of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, urgent revascularisation due to unstable angina or hospital admission for HF (16.0% vs. 16.5%; HR 0.98 [95% CI 0.86–1.12]), HF hospitalisation admission as the first event (3.1% vs. 2.9%; 1.07 [0.79–1.46]) or the post hoc analysis composite endpoint of CV death or HF hospitalisation (HR 1.00 [0.82–1.21]). These results did not differ according to BNP level. Similar significant NT-pro-BNP level decreases were seen at 6 months in both groups.

**Comment:** Concerns have been raised about the safety of DPP-4 (dipeptidyl peptidase-4) inhibitors or gliptins in patients with or at risk of HF. Retrospective analyses of administrative data registries have linked two members of this class, saxagliptin and sitagliptin, to increased rates of HF. This post hoc analysis of a large prospective study examining a novel DDP-4 inhibitor, alogliptin, in patients with type 2 diabetes and acute coronary syndrome did not reveal any excess of HF in the alogliptin cohort compared with placebo. Almost 30% of patients entered into the trial had a past history of HF and they, like the remainder of the study patients, did not experience any excess in HF events. This is a reassuring result; however, caution should still be exercised in the use of this class of oral hypoglycaemics in patients with a history of chronic HF.

**Reference:** Lancet 2015;385(9982):2067–76

**Abstract**

Independent commentary by Professor Peter Macdonald.

Peter Macdonald is a Conjoint Professor of Medicine in the University of New South Wales, senior staff cardiologist in the Heart & Lung Transplant Unit at St Vincent’s Hospital, Sydney and co-head of the Transplantation Research Laboratory at the Victor Chang Cardiac Research Institute. He is a past President of the Transplantation Society of Australia & New Zealand (TSANZ). His major research interests over the last 20 years have been in the areas of heart failure, pulmonary hypertension, transplant allograft rejection, donor management and organ preservation. He has published six national guidelines, 15 book chapters and over 200 peer-reviewed scientific papers.

**PBS Information:**

**Authority Required (STREAMLINED).** For patients with chronic heart failure who meet the clinical criteria set out in the PBS schedule.

**STREAMLINED AUTHORITY CODE 4979**

Follow RESEARCH REVIEW Australia on Twitter now:

@ResearchRevAus

Visit https://twitter.com/ResearchRevAus

---

**Abbreviations used in this issue:**

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CV = cardiovascular; EF = ejection fraction; GFR = glomerular filtration rate; HF = heart failure; HFr/Ef = EF = HF (with preserved/reduced) EF; HR = hazard ratio; IABP = intra-aortic balloon pump; L/RVAD = L/RV assist device; LVEF = LV ejection fraction; (NT-pro-)BNP = (N-terminal prohormone of) brain natriuretic peptide.
Prolonged intra-aortic balloon pump support in biventricular heart failure induces right ventricular reverse remodeling

Authors: Ntalianis A et al.

Summary: The effects of prolonged IABP support (13–155 days) on RV, renal and hepatic functions were investigated in 15 patients with end-stage systolic HF, contraindications for any lifesaving procedure and RV dysfunction. Echocardiographic and hemodynamic investigations revealed significant decreases for right atrial pressure (from 12.7 to 3.8 mm Hg [p<0.001]), pulmonary artery pressure (from 35.7 to 25 mm Hg [p=0.001]) and RV end-diastolic diameter (from 34.0 to 27.8 mm [p<0.001]), and significant increases for cardiac index (from 1.5 to 2.2 L/min/m² [p=0.003]) and RV stroke work index (from 485 to 688 mm Hg × mL/m² [p=0.043]). In addition, tricuspid annular systolic tissue Doppler velocity increased (from 9.6 to 11.1 cm/sec [p<0.029]) and serum creatinine and bilirubin levels decreased (2.1 to 0.9 mg/dL and 2.0 to 0.9 mg/dL, respectively [p values 0.002 and p<0.001]).

Comment: Patients with advanced idiopathic dilated cardiomyopathy may present with severe biventricular failure complicated by hepatic and renal dysfunction. Such patients would generally be considered unsuitable for implantation of an isolated LVAD; however, as demonstrated in this extraordinary case series from Greece, prolonged support of the left ventricle with an IABP enables RV recovery with associated improvements in renal and liver function. The presumed mechanism is via sustained reduction in RV afterload during IABP support. The broader implication is that for similar patients who require long-term mechanical circulatory support (either as destination or bridge to transplant), LVAD with or without temporary RVAD support may be sufficient rather than a permanent biventricular assist device.

Reference: Int J Cardiol 2015;192:3–8

Abstract

Improvement in left ventricular ejection fraction and reverse remodeling in elderly heart failure patients on intense NT-proBNP-guided therapy

Authors: Kaufmann BA et al., for the TIME-CHF investigators

Summary: To define the evolution of LVEF under intensified therapy in relation to age and NT-pro-BNP guidance, these researchers analysed baseline, 12-month and 18-month echocardiographic data from TIME-CHF study participants aged 60–74 and ≥75 years with chronic HF who received NT-pro-BNP- versus symptom-guided therapy. Symptom- and NT-pro-BNP-guided therapy significantly increased LVEF from 31.3% to 39.1% and from 30.3% to 44.0% at 18 months (p<0.001 for both), but the increase was significantly greater with NT-pro-BNP-guided treatment (p=0.006 for interaction); this held true for both age groups (p=0.091 for interaction in both). Decreases in LV end-diastolic and end-systolic volume indices were not affected by study group allocation.

Comment: The role of BNP or NT-pro-BNP-guided treatment of chronic HF remains controversial, with some studies reporting improved clinical outcomes and others reporting no benefit over treatment based on evidence-based guidelines. The original TIME-CHF trial was published in JAMA in 2009 and reported no significant benefit of NT-pro-BNP-guided therapy over symptom-guided therapy in terms of freedom from all-cause hospitalisations or quality of life. A post hoc analysis revealed a benefit of NT-pro-BNP-guided therapy in patients <75 years of age with chronic HF. In this follow-up study, the investigators showed that both NT-pro-BNP-guided and symptom-guided therapy were associated with improved LVEF over time, but the extent of improvement was greater with NT-pro-BNP-guided therapy. In addition, the improvement in LVEF was seen at all ages.

Reference: Int J Cardiol 2015;191:286–93

Abstract

PBS Information: Authority Required

STREAMLINED

PBS Authority Required STREAMLINED1

STREAMLINED AUTHORITY CODE 4979

Before prescribing, please review Product Information by clicking here. Further information available on request from Servier.

Servier Laboratories (Australia) Pty. Ltd. Hawthorn, VIC 3122.
ABN 54 004 838 500. Material prepared: July 2015
TAC10394 7/15
Short-term effects of catheter-based renal denervation on cardiac sympathetic drive and cardiac baroreflex function in heart failure

Authors: Booth LC et al.

Summary: This animal research investigated the short-term effects of catheter-based renal denervation on BP, heart rate and cardiac sympathetic nerve activity and on baroreflex function in six conscious adult ewes paced into HF (EF <40%) that underwent bilateral catheter-based renal denervation and six that underwent a sham procedure. Compared with the sham procedure, renal denervation was associated with significant decreases in resting diastolic BP, mean arterial BP and the BP at which cardiac sympathetic nerve activity was at 50% of maximum, but no change was seen for resting heart rate or cardiac sympathetic nerve activity.

Comment: The future of catheter-based renal denervation to treat hypertension (and HF) has been cast into doubt following the negative results of the sham-controlled SIMPPLICITY HTN-3 trial published in the N Engl J Med in 2014. In this experimental study in a sheep model of HFREF, catheter-based renal denervation lowered BP, but did not alter resting heart rate or cardiac sympathetic activity in the short term – it is difficult to speculate on what this means in terms of long-term outcomes for patients with HFREF. Currently there are ten clinical studies of renal denervation in HFREF and HFREF registered on the NIH Clinical Trials website. While the results of these trials are awaited with interest, the enthusiasm for renal denervation as a new major interventional therapy for HF has rapidly waned.

Reference: Int J Cardiol 2015;190:220–6

Outcome of patients discharged from a heart failure disease management program following their clinical and echocardiographic recovery

Authors: Proctor P et al.

Summary: Outcomes were reported for patients with severe systolic HF discharged from a disease management programme in full clinical and echocardiographic recovery. Mean EF at enrolment was 19% and at discharge was 53%. During postdischarge follow-up of 46.2 months, 56% of patients had presented to an ED, 34% had been hospitalised and 20% had died. Among patients who required hospitalisation for HF, mean EF upon rehospitalisation had fallen to 23.4%.

Comment: Most patients with HFREF show symptomatic and echocardiographic improvements in LV function in response to evidence-based therapy. A minority of these patients regain normal LV function. This ‘cautionary tale’ highlights the ongoing risk faced by patients with HFREF, including those who regain normal cardiac function. Not uncommonly, these patients ask their clinicians whether it is safe for them to stop their HF medications. Clinicians faced with this question can now direct their patients to the sobering findings of this study before advising them to continue with their medications.

Reference: Cardiology 2015;131(3):197–202

Effect of combining ivabradine and β-blockers: focus on the use of carvedilol in the SHIFT population

Authors: Bocchi EA et al.

Summary: These authors reported outcomes of SHIFT study participants with systolic HF who received carvedilol (n=2596), bisoprolol (n=1483), metoprolol (n=1424) or nebivolol (n=197) with ivabradine or placebo for a mean duration of 19 months. β-blocker agent did not significantly modify the effect of ivabradine on the primary composite endpoint (CV death or HF hospitalisation; HR 0.80 [95% CI 0.68–0.94]), HF hospitalisation (0.73 [0.61–0.88]) and CV hospitalisation (0.80 [0.69–0.92]); carvedilol dosage did not affect the outcomes and no unexpected safety issues were reported.

Comment: The SHIFT study published in the Lancet in 2010 demonstrated that in patients with HFREF and a resting heart rate in sinus rhythm >70 beats/min after treatment with a maximally tolerated dose of a β-blocker, the addition of the selective heart rate slowing drug ivabradine significantly reduced the composite primary endpoint of CV death or hospitalisation for HF. This post hoc analysis revealed that the benefits of ivabradine were independent of the choice or dose of β-blocker used. Current PBS authority approval for ivabradine requires the patient to have a resting heart rate in sinus rhythm >77 beats/min (which was the median baseline heart rate of patients enrolled in the SHIFT study) while on a maximally tolerated dose of a β-blocker.

Reference: Cardiology 2015;131(4):218–24

Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction

Authors: Jackson CE et al., on behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)

Summary: This individual patient meta-analysis of data from 22 HF studies sought to establish the prognostic value of pulse pressure in HFREF (EF ≤50%; n=5008) and HFREF (n=22,038), in which there had been 828 and 4980 deaths at 3 years, respectively. Pulse pressure quintiles were analysed in a multivariable model adjusted for MAGGIC prognostic variables. Compared with higher quintiles, participants with HFREF in the lowest pulse pressure quintile had the greatest mortality risk (adjusted HR 1.68 [95% CI 1.53–1.84]). Conversely, increasing pulse pressure increased mortality risk in participants with HFREF, but the effect was lost after adjusting for other prognostic variables.

Comment: Low pulse pressure is a recognised risk factor for increased mortality in patients with HFREF, but the prognostic significance in HFREF has not previously been evaluated. Subjects with HFPEF are typically older, female with higher rates of systemic hypertension than those with HFREF. In this very large international observational meta-analysis led by investigators from Auckland, the authors observed that the relationship between pulse pressure and mortality in patients with HFREF was the opposite to that observed in HFREF – viz HFREF subjects with the highest pulse pressure had the highest mortality. This result was not entirely unexpected given that HFREF patients were older and had higher rates of systemic hypertension and (presumably stiffer arteries) than patients with HFREF. Pulse pressure is a simple, readily available physical examination finding that is probably underutilised by clinicians in their clinical evaluation of patients with all forms of HF.

Reference: Eur Heart J 2015;36(18):1106–14

Predictors of long-term outcomes in patients with hypertrophic cardiomyopathy undergoing cardiopulmonary stress testing and echocardiography

Authors: Mañà A et al.

Summary: Outcome predictors were identified for 1005 patients with hypertrophic cardiomyopathy who underwent cardiopulmonary stress testing with echocardiography (78% NYHA [New York Heart Association] class I–II), with a mean LVEF of 62%, a mean postexercise LV outflow tract gradient of 92mm Hg and a mean peak VO2 (peak oxygen consumption) of 21 mL/kg/min. Peak VO2 values that were >100%, 50–100% and <50% of predicted for age and gender were seen in 8%, 77% and 15% of patients, respectively. An LV outflow tract gradient of ≥30mm Hg was seen in 83% of the patients, and abnormal heart rate recovery in 23%. The composite endpoint event rate (death, appropriate defibrillator discharges, resuscitated sudden death, stroke or HF admission) at 5.5 years follow-up was 9%; 50% underwent surgery for LV outflow tract obstruction. A multivariable Cox proportional analysis revealed that significant (p<0.05) predictors of outcomes were age–gender predicted peak VO2 (HR 0.96 [95% CI 0.93–0.98]), normal versus abnormal heart rate recovery (0.48 [0.32–0.73]), higher LVEF (0.96 [0.93–0.98]), surgery (0.53 [0.33–0.83]) and atrial fibrillation (1.65 [1.04–2.60]).

Comment: This large observational study of consecutive patients with hypertrophic cardiomyopathy highlights the high prevalence of exercise-induced abnormalities in this group of patients and associated adverse clinical outcomes. It is noteworthy that the large majority of patients had either no or only mild symptomatic limitation (NYHA class I–II). The prevalence of exercise-induced LV outflow tract obstruction (gradient >30mm Hg) was striking, as was the favourable impact of surgical relief of LV outflow tract obstruction, which was performed in 50% of patients. The favourable impact of surgery on outcome is all the more impressive when one compares the surgical and nonsurgical groups; the surgical group had worse exercise performance, higher resting and exercise-induced LV outflow tract gradients and more severe mitral regurgitation at rest and on exercise. The authors concluded that cardiopulmonary exercise testing combined with echocardiography provides excellent risk stratification of patients with hypertrophic cardiomyopathy.

Effect of additive renin inhibition with aliskiren on renal blood flow in patients with chronic heart failure and renal dysfunction (Additive Renin Inhibition with Aliskiren on renal blood flow and Neurohormonal Activation in patients with Chronic Heart Failure and Renal Dysfunction)

Authors: Schroten NF et al.

Summary: These researchers had randomised 41 patients with HFREF (LVEF ≤45%) and estimated GFR 30–75 mL/min/1.73m², receiving optimal medical therapy, to receive aliskiren 300mg once daily or placebo in a 2:1 ratio when the trial was terminated due to futility on an interim safety analysis. At 26 weeks, renal blood flow had decreased nonsignificantly with aliskiren compared with placebo (−7.1 vs. +14 mL/min/1.73m² [p=0.16]), and there were significant decreases in GFR (−2.8 vs. +4.4 mL/min/1.73m² [p=0.01]), filtration fraction (−2.2% vs. +1.1% [p=0.01]) and plasma renin activity (p=0.007); no significant between-group difference was seen for plasma aldosterone level, NT-pro-BNP level, urinary tubular markers or adverse events.

Comment: Aliskiren is a first-in-class orally active direct renin inhibitor that is undergoing clinical trials in hypertension and HF. Aliskiren has been shown to increase renal blood flow in healthy subjects, and the hypothesis behind this mechanistic study was that it would also increase renal blood flow in patients with HFREF. Unfortunately this did not prove to be the case. Indeed the trend was towards lower renal blood flow, which was associated with significant worsening of renal function. This result comes on top of the ALTITUDE study, which compared aliskiren with placebo in over 8000 subjects with type 2 diabetes and renal impairment. This study was stopped prematurely because of an excess rate of hyperkalaemia and symptomatic hypotension in aliskiren-treated patients. ATMOSPHERE is a large ongoing phase 3 clinical trial of aliskiren in HFREF, which has almost completed follow-up. Initial results from this important trial are expected later this year and are awaited with interest.

Reference: Am Heart J 2015;169(5):693–701

Abstract

Outcome in acute heart failure: prognostic value of acute kidney injury and worsening renal function

Authors: Berra G et al.

Summary: This research in a retrospective cohort of 646 patients hospitalised with acute HF revealed that the risk of death or HF readmission was significantly increased by acute kidney injury (adjusted HR 1.29 [95% CI 1.13–1.47]) and worsening renal function (1.24 [1.06–1.45]), and significantly decreased by ACE inhibitor/ARB uptitration (0.79 [0.64–0.97]). No excess mortality was evident in patients with ACE inhibitor/ARB uptitration despite worsening renal function.

Comment: This is an interesting and provocative study. Acute kidney injury is a well-recognised risk factor for increased morbidity and mortality in patients admitted with acute decompensated HF. The natural tendency for clinicians when faced with acute decompensated HF patients with acute kidney injury on admission or who develop worsening renal function after admission is to withhold any potentially nephrotoxic agents, particularly ACE inhibitors/ARBs. In this ‘real world’ observational study from Switzerland, the authors reported that uptitration of ACE inhibitors/ARBs despite acute kidney injury or worsening renal function was actually associated with reduced morbidity and mortality. Limitations of the study include its retrospective design and a lack of a systematic strategy for adjusting ACE inhibitors/ARBs in the face of acute kidney injury or worsening renal function. ACE inhibitor/ARB uptitration was defined as discharge dose being higher than admission dose, and it is unclear at what stage during the admission uptitration occurred. In addition, only 60% of patients admitted with acute decompensated HF were taking an ACE inhibitor or ARB at the time of admission, and it is unclear why the remaining 40% were not.

Reference: J Card Fail 2015;21(5):382–90

Abstract

Before prescribing, please review Product Information by clicking here.
Further information available on request from Servier.

Servier Laboratories (Australia) Pty. Ltd. Hawthorn, VIC 3122.
ABN 54 004 838 500. Material prepared: July 2015
TAC10394 7/15

© 2015 RESEARCH REVIEW
www.researchreview.com.au