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High evening salivary cortisol is an independent predictor of increased mortality risk in patients with systolic heart failure

Authors: Hammer F et al.

Summary: These researchers measured morning (8am) and evening (9pm) salivary cortisol levels in 229 participants with HF from the Interdisciplinary Network for Heart Failure programme. Compared with evening salivary cortisol levels, the median morning level was significantly higher (0.59 vs. 0.25 ng/mL [p<0.001]) and had greater variance. The 18-month mortality rate of 11% was not predicted by morning salivary cortisol level; however, the likelihood was increased in participants in the highest evening salivary cortisol level quartile (adjusted HR 2.49 [95% CI 1.01–6.14]).

Comment: There is a need for better prognostic markers in HF; however, repeated sampling limits the use of plasma for long-term surveillance. Salivary testing offers theoretical advantages by avoiding the need for blood tests, which require trained health professionals, and may provide a more accurate reflection of unbound bioactive cortisol activity. This study suggests that evening salivary cortisol could be used to identify HF patients at high-risk of short-term mortality. These results require prospective validation in an independent cohort to determine the independent prognostic utility of salivary cortisol level.

Reference: Int J Cardiol 2016;203:69–73

Abstract
Efficacy and safety of LCZ696 (sacubitril-valsalartan) according to age

Authors: Jhund PS et al., on behalf of PARADIGM-HF Investigators and Committees

Summary: The efficacy and safety outcomes associated with LCZ696 in the PARADIGM-HF trial were investigated according to age in 8399 participants with New York Heart Association functional class II–IV HFREF (LVEF ≤40%); the participants had been randomised to receive LCZ696 or enalapril. The primary outcome rate (CV death or HF hospitalisation) increased from 13.4 per 100 patient-years for participants aged <55 years to 14.8 per 100 patient-years for those aged ≥75 years, with no significant interaction between age category and treatment and an overall HR of 0.80 (95% CI 0.73–0.87). Outcomes for HF hospitalisation were similar for CV and all-cause mortality, and no significant age category by treatment interaction were seen. For the prespecified safety outcomes of hypotension, renal impairment and hyperkalaemia, increases were seen in both arms with age, but the between-treatment differences were consistent across age categories.

Comment: LCZ696 was more beneficial than enalapril in the PARADIGM-HF study, with similar comparative safety and efficacy in older and younger patients. Similarly, other treatments such as mineralocorticoid receptor antagonists have been shown to be beneficial in patients aged 75 years and older in the EMPHASIS-HF study. Whilst side effects are generally more common in the elderly, clinicians should aim to use the same treatments to improve survival and reduce HF hospitalisation in HFREF patients regardless of age.

Reference: Eur Heart J 2015;36(38):2576–84

An absolute risk prediction model to determine unplanned cardiovascular readmissions for adults with chronic heart failure

Authors: Betihavas V et al.

Summary: These researchers set out to develop a model for predicting the absolute risk of unplanned CV readmissions posthospitalisation for chronic HF. They used an inception cohort of 280 participants from the prospective ‘WHICH?’ RCT comparing home- and clinic-based interventions, among who the respective 28-day and 18-month CV (including HF)-related readmission rates were 13% and 53%. A competing risk model (C-statistic 0.80) included the following factors associated with an increased risk of hospitalisation for chronic HF: i) each 10-year increase in age (HR 1.07 [95% CI 0.90–1.26]); ii) living alone (1.09 [0.74–1.59]); iii) sedentary lifestyle (1.44 [0.92–2.23]); and iv) ≥5 vs. (1) comorbidities (1.69 [0.38–7.58]).

Comment: There is a need for reliable models to determine the risk of rehospitalisation in HF, with the main aim being to allow clinicians to reliably identify a low-risk cohort who do not require resource-intensive interventions. The authors of this study utilised a number of readily available sociodemographic and clinical characteristics to develop a model from patients enrolled in the ‘WHICH?’ trial. This model requires independent validation in larger, unselected HF cohorts, and testing of additional variables such as frailty to determine whether we can reliably identify which patients have a high risk of either HF or all-cause hospitalisation.


Relation between process measures and diagnosis-specific readmission rates in patients with heart failure

Authors: Bottle A et al.

Summary: These authors used HF admissions data from 123,644 patients attending acute hospitals in England to explore relationships between cause-specific readmission and National Heart Failure Audit process-of-care measures. The mortality rate during the index admission was 14.7%. Among index live discharges (n=105,441), 6.5% and 19.1% were readmitted as emergencies within 7 days and 30 days, respectively. Positive but weak correlations were seen between index admission mortality rates and non-HF (but not HF) readmission rates. A modest positive correlation was seen between 7-day HF and non-HF readmission rates (r=0.24) but not 30- or 365-day rates. Modest, significant correlations were seen between the six process measures (proscription of ACE inhibitors and β-blockers, echocardiogram, cardiology inpatient and follow-up by cardiologist and HF liaison) and lower 7-day HF readmission rates while only three measures correlated at 30 days. Only cardiology follow-up was correlated with non-HF readmission at 7 and 30 days. All associations were reduced at 365 days.

Comment: There is growing interest in measuring quality of care in HF. Outcome measures such as postdischarge mortality and rehospitalisation require risk adjustment, and may not allow timely modification of clinical practice. This audit of HF hospitalisations in England identified that process measures including medication prescription rates, use of echocardiography and follow-up arrangements were associated with lower 7-day HF rehospitalisation rates; however, these correlations diminished over time, and there was no correlation with non-HF hospitalisation. This study emphasises that other quality metrics are required to evaluate subsequent non-HF hospitalisation risk, which comprises the dominant reason for rehospitalisation in HF patients.

Reference: Heart 2015;101(21):1704–10

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Authors: González-López E et al.

Summary: These researchers prospectively screened 120 consecutive patients aged ≥60 years admitted with HFPEF (LVEF ≤50%) with LV hypertrophy (>12mm) with 99mTc-DPD scintigraphy. Sixteen patients had moderate-to-severe uptake on 99mTc-DPD scintigraphy. No patients with a positive scan and who underwent TTR (transthyretin) gene testing had mutations. Four patients had wild-type TTR amyloidosis confirmed on an endomyocardial biopsy. There were no differences between patients with wild-type TTR amyloidosis and those with other HFPEF forms for age, gender, hypertension, diabetes, coronary artery disease or atrial fibrillation. Patients with wild-type TTR amyloidosis had a higher median NT-proBNP level [6467 vs. 3173 pg/L (p=0.019)], median troponin I level (0.135 vs. 0.025 µg/L (p<0.001)), mean LV maximal wall thickness (17 vs. 14mm (p=0.001)), pericardial effusion rate (44% vs. 19% [p=0.047]) and pacemaker use rate (44% vs. 12% [p=0.004]). However, there was high clinical overlap between wild-type TTR amyloidosis and other HFPEF forms.

Comment: In this single-centre, prospective study, 13% of an unselected cohort of patients with HFPEF had moderate-to-severe cardiac uptake on 99mTc-DPD scintigraphy and no mutations on TTR genetic testing. This suggests that wild-type TTR cardiac amyloidosis may be an under-recognised cause of HFPEF, and confirms similar findings in a previous HFPEF autopsy study. There were no clinical features that readily distinguished these patients, although a higher proportion had pericardial effusions and pacemakers, NT-proBNP and cardiac troponin levels were higher, the ECG voltages were lower (adjusted for LV mass), and LV mass and wall thickness were higher. These findings require independent, multicentre validation, and highlight the need to better clarify the HFPEF phenotype in clinical trials evaluating the safety and efficacy of new treatments.

TWO MANY PATIENTS ARE FALLING THROUGH THE CRACKS IN HEART FAILURE MANAGEMENT. 1–3

- Up to 50% of patients remain undiagnosed4
- Over 40% of patients do not receive guideline-recommended ACEI or ARB treatment4,5
- 50% of patients die within 3–4 years of diagnosis – many as a result of medication non-adherence6


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Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures

Authors: Allen LA et al., on behalf of the American Heart Association’s Get With The Guidelines Heart Failure (GWTG-HF) Investigators

Summary: HF registry data were analysed to characterise prescribing, indications and contraindications for ACE inhibitors/ARBs, β-blockers, aldosterone antagonists, hydralazine/isosorbide dinitrate and anticoagulants among 158,922 patients discharged from hospital with a primary diagnosis of HF. Initiation of ACE inhibitors/ARBs was indicated in 18.1% of patients; β-blockers in 20.3%, aldosterone antagonists in 24.1%, hydralazine/isosorbide dinitrate in 8.6% and anticoagulants in 18.0%; the proportions of eligible patients not receiving these respective therapies at admission were 55.5%, 50.5%, 67.4%, 93.1% and 58.0%. Cumulatively, 4.0%, 4.1%, 9.4%, 10.1% and 22.7% of patients were eligible for five, four, three, two and one new medication group, respectively. 15.0% were ineligible for new medications due to adequate prescribing at admission and 38.4% were ineligible for any recommended medications. The mean number of actual new prescriptions was lower than indicated medications (1.16 vs. 1.45).

Comment: A number of medications have been shown to improve survival in chronic HFREF. This study aimed to quantify the burden imposed by starting medications in HF patients during the acute hospital phase. Prior studies demonstrating that inpatient initiation results in a higher proportion of patients not receiving the prescribed therapy long term have focused on individual drugs, without the support of comprehensive disease management programmes. Future studies will need to address the comparative safety and tolerability of starting multiple medications in hospital versus delayed, sequential postdischarge medication initiation in HFREF.


Sodium nitrite improves exercise hemodynamics and ventricular performance in heart failure with preserved ejection fraction

Authors: Borlaug BA et al.

Summary: Twenty-eight patients with HFPEF underwent invasive cardiac catheterisation with simultaneous expired gas analysis at rest and during exercise before and after receiving sodium nitrite or placebo in this RCT. Before study treatment, pulmonary capillary wedge pressure increased from 16 to 30mm Hg (p<0.0001). Compared with placebo, sodium nitrite was associated with an improvement in the pulmonary vascular resistance index (42% decrease from baseline). In the sitting position during exercise, heart rate and cardiac output increased similarly in both groups and pulmonary arterial wedge pressure decreased by 40% (p<0.0001). This was associated with a greater reduction in filling pressures (p<0.0001), which was not observed in the recumbent position during exercise. The study concluded that sodium nitrite may improve exercise performance in HFPEF patients with possible implications for guideline recommendations.

Comment: This study undertook a cluster-based phenotype approach to subclassify patients with HFPEF. Whilst the authors identified a subgroup of patients with worse outcomes and better treatment response to inhaled nitric oxide, there was no treatment effect from candesartan in CHARM-Persist (albeit the latter study was under-powered for this subgroup). These findings require prospective evaluation with a larger number of clinical variables to determine whether we can identify a subpopulation of HFPEF patients who may benefit from neurohormonal modulation.

Reference: Eur J Heart Fail 2015;17(9):925–35

Challenging the two concepts in determining the appropriate pre-discharge N-terminal pro-brain natriuretic peptide treatment target in acute decompensated heart failure patients: absolute or relative discharge levels?

Authors: Stienen S et al.

Summary: These researchers used data from seven cohorts of patients with acute decompensated HF (n=1266) to determine if absolute (<1500, <3000 and <5000 ng/L) or relative (<30%, >50% and >70% reductions) NT-proBNP levels should be used as a predischARGE treatment target. A percentage reduction corresponding with each absolute NT-proBNP level that resulted in similar population-attributable risk fraction (NT-proBNP level proportion of all-cause 6-month mortality that would be reduced if all patients attained the NT-proBNP target) was found. NT-proBNP levels of <1500 ng/L or >70% reduction had the highest population-attributable risk fraction at ~60–70%, but attainability values were low at 27% and 22%, respectively. NT-proBNP level on admission was the strongest predictor of not achieving target. The population-attributable risk fractions were significantly different for the absolute but not relative targets across admission NT-proBNP level tertiles.

Comment: This study suggests that clinicians may either target relative reductions or absolute levels of NT-proBNP level prior to hospital discharge with a diagnosis of acute HF. Whilst both greater reductions in NT-proBNP and lower NT-proBNP targets are associated with lower 6-month mortality, RCTs are required to address whether changes in management based upon targeting lower NT-proBNP levels prior to hospital discharge leads to better outcomes compared with standard care.

Reference: Eur J Heart Fail 2015;17(9):936–44

Effect of semirecumbent sleep position on severity of obstructive sleep apnea in patients with heart failure

Authors: Basoglu OK et al.

Summary: Thirty consecutive patients with HF and OSA underwent polysomnography during one sleep session lying flat and another in a semirecumbent position; the two sessions were conducted within 7 days of each other. Compared with lying flat, the semirecumbent position was associated with a significantly lower mean apnoea-hypopnea index value (17.8 vs. 30.8 events per hour [p<0.0001]), a lower oxygen desaturation index value (12.7 vs. 22.3 events per hour [p<0.0001]), improvements in the percentage of sleep time with SpO2 (oxygen saturation) <90% (p=0.036) and lowest SpO2 (p=0.004) and a lower percentage of N2 sleep (39.6% vs. 47.0% [p=0.014]).

Comment: Whilst some HF patients may choose a semirecumbent sleeping position to avoid orthopnoea, this study suggests a beneficial effect on OSA. Whether this improves daytime sleepiness or quality of life requires further study. However, it would seem a reasonable strategy, especially in patients who can’t tolerate positive pressure ventilation to treat OSA.

Reference: J Card Fail 2015;21(10):842–7

Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response

Authors: Kao DP et al.

Summary: These researchers characterised 4113 participants with HFPEF from the I-PRESERVE trial, randomised to ibersartan or placebo, according to 11 clinical features. Six HFPEF subgroups with significant differences in event-free survival were identified using latent class analysis. The subgroup definitions were applied to a validation cohort of 3203 CHARM-Preserved participants, among whom similar clinical profiles and prognoses were seen. Subgroups C and F represented the subgroups with the worst event-free survival, and they were characterised by a high prevalence of obesity, hyperlipidaemia, diabetes mellitus, anaemia and renal insufficiency and by female predominance, advanced age, lower body mass index and high rates of atrial fibrillation, valvular disease, renal insufficiency and anaemia, respectively.

Comment: This study undertook a cluster-based phenotype approach to subclassify patients with HFPEF. Whilst the authors identified a subgroup of patients with worse outcomes and better treatment response to ibersartan in I-PRESERVE, there was no treatment effect from candesartan in CHARM-Preserved (albeit the latter study was under-powered for this subgroup). These findings require prospective evaluation with a larger number of clinical variables to determine whether we can identify a subpopulation of HFPEF patients who may benefit from neurohormonal modulation.

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