Abstract 77 Figure 1

attributed primarily to heart failure. The data collection tool is web-based with >250 fields. Mandatory data include age, sex, deprivation-index, admission symptoms, aetiology and comorbidity, electro- and echo-cardiographic data, standard laboratory tests and discharge medications. Patients are followed up for re-admissions and deaths through linkage to national records.

Purpose To describe the contemporary in-patient and post-discharge mortality of patients with a primary death or discharge diagnosis of heart failure reported by hospitals in England & Wales, stratified by age, sex and left ventricular phenotype.

Methods Descriptive. Patient characteristics are described as medians with inter-quartile ranges. Time to event analyses using Kaplan-Meier.

Results Altogether, 157,682 unique patients (>75% of all relevant admissions) were entered into the registry between April 2014-March 2018, of whom 45% were women (median age of 82 (75–88) years; 56% with LVEF <40%) and 55% were men (median age of 78 (69–85) years; 74% with LVEF <40%). Amongst 45,772 patients surviving to discharge in 2017–18 with an LVEF <40%, 92% were discharged on a loop diuretic, 22% on digoxin, 72% on an ACE inhibitor, 23% on an ARB, 83% on an ACE inhibitor and/or ARB, 89% on a beta-blocker and 56% on an MRA. Patients who received disease-modifying agents were younger and had a better prognosis.

Age, but neither sex nor LVEF, was a strong determinant of both in-patient and post-discharge mortality. In-patient mortality ranged from 3.2% in those aged <45 years to 16.5% in those aged >85 years. One-year mortality for patients who survived to discharge ranged from 10.4% in those aged <45 years to 45.6% in those aged >85 years (figure shows age-stratified, post-discharge, one-year mortality for people enrolled 2014–17).

Conclusion More than 60% of people hospitalised primarily for heart failure in England & Wales are aged >75 years and most have a reduced left ventricular ejection fraction. Treatment and outcome are strongly influenced by age. In-patient and post-discharge mortality remain high for older patients hospitalised with a primary diagnosis of heart failure.

Conflict of Interest None

78

EFFECTS OF SHORT-TERM OMISSION OR INCREASE IN LOOP DIURETIC THERAPY ON CARDIAC FUNCTION IN PATIENTS WITH CHRONIC, STABLE HEART FAILURE

¹Muhammad Khan*, ²Pierpaolo Pellicori, ²John GF Cleland. ¹University of Glasgow, ²Robertson Centre for Biostatistics

10.1136/heartjnl-2019-BCS.76

Background The effects of short-term variations in loop diuretic (LD) agents on haemodynamics in patients with chronic, stable heart failure has rarely been studied.

Purpose To investigate the effects of increasing or omitting LD for 48 hours on clinical, biochemical and echocardiographic variables in patients with chronic, stable heart failure and a reduced left ventricular ejection fraction (LVEF <50%).

Methods Patients were studied on two occasions and observed for 3 hours following oral administration of their usual daily dose of LD. Echocardiography, weight and blood pressure assessments were performed hourly.

Results Eight patients [mean age 67 (7) years, 75% NYHA I/II, 50% men, 25% in atrial fibrillation] were enrolled. Compared to omitting LD, increasing LD reduced plasma NT-proBNP (from 644ng/L to 369 ng/L; $p=0.017$), left ventricular end-diastolic volume (LVEDV, from 188 ml to 162 ml, $p=0.045$), left atrial volume (LAV, from 82 ml to 73 ml, $p=0.007$) and systolic (from 133mmHg to 116mmHg, $p=0.005$) and diastolic (from 74mmHg to 64mmHg, $p=0.043$) blood pressure, and increased haemoglobin (from 129 g/L to 136 g/L, $p=0.028$), haematocrit (0.40% to 0.42%, $p=0.04$), serum urea (6.3 mmol/L to 9.6 mmol/L, $p=0.008$) and the ratio of jugular vein diameter after Valsalva to that at rest by ultrasound (JVD ratio, from 5.6 to 6.6, $p=0.043$). There was no significant change in body weight, serum creatinine or LVEF.

Significant reductions on LVEDV and LAV and an increase in JVD ratio were evident within one hour from oral LD administration and persisted after 3 hours, without a change in body weight or blood pressure. These acute effects of LD administration on echocardiographic variables were more pronounced when patients had previously had their diuretic therapy omitted for 48h.

Conclusion LD have important and rapid effects on intra-cardiac and vascular volume. This has important implications for the conduct of clinical trials that use changes in cardiac volumes or NT-proBNP as measures of cardiac remodelling and/or therapeutic benefit.

Conflict of Interest None

79

EFFECTIVE CARDIOPROTECTION AGAINST ANTHRACYCLINE CARDIOTOXICITY IN ISOLATED CARDIOMYOCYTES AND RABBITS IS BASED ON DEXRAZOXANE INTERACTION WITH TOPOISOMERASE II BETA INSTEAD OF IRON CHELATION BY ITS METABOLITE ADR-925

¹Eduard Jirkovsky*, ¹Anna Jirkovska, ¹Hana Bavlovic-Piskackova, ¹Veronika Skalicka, ²Zuzana Pokorna, ¹Galina Karabanovich, ²Petra Brazdova, ²Olga Lencova-Popelova, ²Yvona Mazurova, ²Michaela Adamcova, ¹Jaroslav Roh, ¹Petra Sterbova-Kovarikova, ¹Tomas Simunek, ²Martin Sterba. ¹Charles University, Faculty of Pharmacy in Hradec Kralove; ²Charles University, Faculty of Medicine in Hradec Kralove

10.1136/heartjnl-2019-BCS.77

Introduction Anthracyclines (ANT; e.g. doxorubicin, epirubicin or daunorubicin) are still indispensable part of modern chemotherapy regimens, despite of their well-known risk to induce cardiotoxicity leading even to heart failure. Thus, there is a need for effective cardioprotective strategy. Dexrazoxane (DEX) is the only clinically approved drug clearly effective both in clinics and clinically relevant experimental models. However, mechanisms of ANT-cardiotoxicity induction as well as DEX protection are not elucidated yet. Traditionally, ANTs have been believed to induce iron-catalyzed oxidative damage to cardiomyocytes. DEX should prevent this via its metal-chelating metabolite ADR-925, but direct evidence is missing. This paradigm has been recently challenged by topoisomerase II β (TOP2B) hypothesis of ANT cardiotoxicity. Hence, the aims of this study were to examine if ADR-925 is really the protective agent in DEX-afforded cardioprotection against daunorubicin (DAU) cardiotoxicity, along with the involvement of TOP2B interaction in this process.

Methods Firstly, a pharmacokinetic studies were employed to set up ADR-925 doses ensuring same or even higher exposition of isolated rat neonatal ventricular cardiomyocytes (NVCs) and rabbits' heart than after endogenously formed ADR-925 after DEX administration. Cardioprotective effects of DEX and ADR-925 (both in 10–100 μ M) were compared using NVCs treated with DAU (1.2 μ M). In rabbits (n=50), cardiotoxicity was induced with DAU (3 mg/kg IV, once weekly/10 weeks). Prior to each DAU dose, ADR-925 was administered in two schedules (60 mg/kg 30-min-infusion alone or with additional the same s.c. bolus dose after 2 hrs). Cardiotoxicity markers, LV function and interaction with TOP2B were compared to effects of DEX pre-treatment (60 mg/kg IP).

Results ADR-925 administration did not provide any meaningful cardioprotection against ANT cardiotoxicity in NVCs. Regardless various administration schedule in rabbits, ADR-925 did not protect against DAU-induced mortality due to end-stage heart failure, decrease of LV

function (dP/dtmax and LVFS), increase of cTnT levels, ANP or BNP mRNA as well as histopathological changes. This sharply contrasted with remarkable cardioprotective effects of DEX. Further experiments documented that the parent compound can inhibit and deplete TOP2B and prevent DAU-induced genotoxic damage in cardiomyocytes in contrast to ADR-925.

Conclusion The present investigation strongly encourages the shift of mechanistic paradigm in clinically translatable cardioprotection against anthracycline cardiotoxicity - from metal chelation and protection from direct oxidative damage towards a TOP2B interaction. This study was supported by the Czech Science Foundation [Grant n. 18–08169S], the Charles University Research Program PROGRES [Grant n. Q40/5] and by the project EFSA-CDN (No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by ERDF.

Conflict of Interest None declared

80

THE DIRECT EFFECTS OF INORGANIC NITRITE ON LEFT VENTRICULAR FUNCTION IN HUMANS: AN INVASIVE PRESSURE-VOLUME LOOP STUDY

¹Kevin O'Gallagher*, ¹Ana Rita Cabaco, ¹Ali Roomi, ¹Matthew Ryan, ¹Luke Dancy, ²Amy Hoare, ²Narbeh Melikian, ¹Phil Chowienzyk, ¹Andrew Webb, ³Ajay Shah. ¹King's College London; ²King's College Hospital NHS Foundation Trust; ³NIHR King's College London BRC and King's College Hospital NHS Foundation Trust

10.1136/heartjnl-2019-BCS.78

Introduction Inorganic nitrite is a potential nitric oxide (NO)-augmenting therapy that is of considerable interest due to the lack of tolerance to its effects, in contrast to organic nitrates. Previous work has shown that NO has beneficial effects on myocardial relaxation and diastolic function while abnormalities of NO-cGMP signalling are implicated in Heart Failure with Preserved Ejection Fraction (HFpEF). Systemic preparations of inorganic nitrite have therefore been tested in small clinical trials for its effects in patients with HFpEF. In humans, nitrite is an arterial dilator, demonstrating selectivity for conduit arteries over resistance arterioles but its direct cardiac effects in vivo have not been established. We hypothesised that intracoronary inorganic nitrite has direct beneficial effects on cardiac diastolic function.

Methods 20 patients with angiographically normal coronary arteries and normal left ventricular function were given an intracoronary infusion of sodium nitrite (8.7 micromol/min for 5 min, followed by 26 micromol/min for 5 min). LV pressure-volume relations were obtained via a micromanometer-conductance catheter, with recordings taken at baseline and after each dose of nitrite.

The primary end-point was change in LV End-diastolic pressure (LVEDP). Secondary end-points included other indices of LV diastolic and systolic function. Statistical analyses were performed using ANOVA for repeated measures (or non-parametric equivalent) with multiple comparison testing, reported as mean [95% CI] unless otherwise specified.

Results Intracoronary nitrite was associated with a significant dose-dependent decrease in LVEDP (P=0.001). The 26 micromol/min dose of nitrite resulted in a decrease of 1.9mmHg