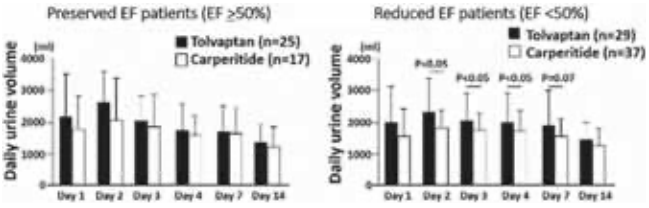
EF (>50%, n=42) was not difference, however, this was significantly higher in tolvaptan group than in carperitide group in patients with reduced EF (<50%, n=66). Daily urine volume was not difference between these two groups in patients with hypertension (BP>140 mmHg, n=39), however, this was significantly higher in tolvaptan group than in carperitide group in patients without hypertension (BP<140mmHg, n=70).



Conclusions: The present study reveals that tolvaptan is more effective especially in ADHF patients with reduced left ventricular systolic function and without hypertension compared to carperitide.

P836 | BEDSIDE

Heart rate reduction in heart failure: analysis of 1000 consecutive outpatient clinic visits to a heart failure clinic

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Background: Amongst patients with heart failure (HF) due to left ventricular systolic dysfunction (LVSD) in sinus rhythm, those with higher resting heart rate (HR) have a worse prognosis. Reducing sinus rate to 50-60 bpm might improve outcomes. If beta blockers (BB) are not tolerated or HR remains >70 bpm despite BB, ivabradine may reduce HR and improve outcome.
Aims: To characterize patients attending a HF clinic and identify the proportion eligible for optimization of BB or ivabradine treatment. The clinic accepts referrals from primary and secondary care and offers long term follow-up to patients regardless of LVEF.
Methods and results: Between January 2013 and July 2013, 1000 consecutive HF clinic follow-up appointments were reviewed and demographic, clinical and echocardiographic data were collected in patients who attended (n=959, 644 men). The median duration between initial assessment and follow-up was 941 (IQR 347-2153) days. Most patients had mild to moderate HF (25% NYHA I, 51% NYHA II and 24% NYHA III/IV). Median age was 76 (IQR 68-82) years, NTproBNP 1091 ng/L (IQR 396-2230) and ejection fraction (EF) 45 (IQR 36-54)%, with 370 patients (39%) having a reduced EF (<40%), of whom 257 were in sinus rhythm (mean HR 69±12 bpm) and 113 in atrial fibrillation (mean HR 75±15 bpm). Patients treated with BB (n=331, 92%) had a mean HR of 69±12 bpm compared to 82±19 bpm in those not taking BB.
In those with LVSD, sinus rhythm and a HR above 70 bpm (n=90), 18 patients were already treated with target doses of BB, 24 had BB dose increased, 19 were known to be intolerant of higher dose and 26 were eligible for uptitration of BB but did not receive appropriate advice ("missed indication"). Thirty seven patients who were receiving maximally tolerated BB doses or were BB intolerant were eligible for ivabradine. Seven patients were already taking ivabradine at the time of assessment and in 5 of these the dose was increased, 13 were started on treatment following the clinic visit, and in 17 patients, the indication was initially "missed".
Conclusion: Among patients with LVSD (about 37% of those with HF), most are treated with a BB at a dose that maintains HR <70bpm and only about 10% are eligible for ivabradine (~4% of overall HF clinic population). However, even in an expert clinic missed opportunities to intervene to reduce HR are common. Education and audit should increase awareness among physicians about the importance of managing heart rate in patients in sinus rhythm.

P837 | BENCH

A debate about the impact of DPP4 inhibitors on heart failure- Cardiac dysfunction and remodeling induced by pressure-overload is reversed by DPP4 inhibition by modulating myofilament Ca2+ sensitivity

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Purpose: According to the SAVORTIMI53 trial, DPP-4 inhibitor (DP4-I) saxagliptin was unexpectedly found to increase incidence of heart failure (HF). In contrast, EXAMINE trial with alogliptin (ALO) demonstrated that ALO had no worsening effect on HF. Several reports demonstrated the beneficial effect of vildaglipin on HF. Thus, the impact of DP4-I on HF remains controversial and we examined the impact of ALO on HF.
Methods: To clarify the simple impact of ALO on HF, we chose mouse HF model induced by thoracic aortic constriction (TAC) without any comorbidity. Male C57BL6 mice (14w/o) were allocated into;TAC-induced HF with and without ALO (10mg/kg/day for 4 weeks; TAC-ALO and TAC-CON) and sham counterparts.
Results: TAC-CON exhibited marked increase in casual blood glucose level compared to sham-CON (in mg/dl; 214.0±14.6 for TAC-CON versus 152.8±8.1) and concomitant decrease in circulating GLP-1 (in pM; 0.86±0.10 for TAC-CON versus 2.13±0.54) without affecting body weight. ALO normalized the hyperglycemia in TAC with simultaneous increase in GLP-1 (in pM; 3.78±0.56). Echocardiography revealed that TAC-promoted systolic and diastolic LV dysfunction was ameliorated by ALO. TAC-CON exhibited cardiac hypertrophy and fibrosis, which were ameliorated by ALO. Although the only one report demonstrated the lack of GLP-1 receptor (GLP1R) mRNA in ventricular myocardium (Nat Med 2013), we confirmed the expression of GLP-1R at mRNA and protein levels by careful dissection into each chamber of left and right atria, interventriacular and ventricular free walls. Furthermore, Myocardial cyclic AMP (cAMP) concentration, which is the 2nd messenger of the GLP-1/GLP1R axis was reduced in TAC-CON (in pmole/mg protein; 33.0±1.4 and 42.2±1.5 for sham-CON), which was reversed in TAC-ALO (in 65 pmole/mg protein). We next examined changes in signaling related to myocardial remodeling (Akt, AMPK, ERK, and mTOR/S6K) and contractility [SERCA, phospholamban (PL), troponin T/C and I (TnT/C, TnI), cardiac α- (MYH6) and β-myosin heavy chain (MYH7)]. There was no changes in the remodeling-related signaling. MYH7, the PKA-dependent Ca2+ sensitizing myofilament proteins, was increased and the PKA-dependent phosphorylation of PL was decreased in TAC-CON. Myocardial PKA activity was reduced in TAC-CON, all which were reversed by ALO.
Conclusions: HF induced by TAC exhibits decline in the inotropic peptide GLP-1. ALO reverses cardiac remodeling and dysfunction in TAC by modulating myofilament Ca2+ sensitivity-related proteins [PL & MYH7] via GLP1/GLP1R-mediated cAMP/PKA activation.

P838 | BEDSIDE

Time of enrollment impacts time to randomized treatment in clinical trials of acute heart failure: findings from the RELAX-AHF study

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Purpose: Enrollment rates in acute heart failure (AHF) clinical trials have been historically low. Reduced capability of hospitals during nighttime compared to daytime may influence enrollment performance in this setting. In this post-hoc analysis we evaluated time trends of enrollment rates of AHF patients (and their clinical characteristics) included in RELAX-AHF trial.
Methods: We compared patients with pulmonary congestion, dyspnea, mild-to-moderate renal impairment and systolic blood pressure (SBP) >125mmHg enrolled in the RELAX-AHF study (NCT00520806) according to the time of presentation (TP): daytime (D) and nighttime (N) (presented between 08:00 and 19:59h, and 20:00 and 07:59h, respectively). Patients were enrolled and randomized to treatment within 16 hours of TP. Baseline (BL) characteristics of patients and enrollment were assessed related to TP.
Results: Overall, 2/3 (67%) of enrolled patients presented during D. As for enrollment rates, D accounted for 69.4% of total enrolled patients of whom 86.2% were enrolled during business hours (08:00-17:00h). Eastern Europe accounted for 53.1% of N vs. D patients compared with Western Europe, South America, North America, and Israel (12.7%, 5.4%, 10.1%, and 18.7%, respectively, p=0.0260 versus Eastern Europe). At BL, D had higher proportion of males (65.7% vs. 56.0%, p=0.0013), increased mean weight (kg) (83.3 vs. 80.4, p=0.0125) and fewer cases of NYHA class I at 1 month before admission (2.4% vs. 3.4%, p=0.0234) compared with N. Nighttime patients had higher mean levels of troponin T (mcg/L) (0.041 vs. 0.032, p<0.0001) and lower prevalence of atrial fibrillation (32.7% vs. 45.6%, p<0.0001), mitral regurgitation (26.9% vs. 33.2%, p=0.0031), and beta-blocker use (62.2% vs. 71.5%, p=0.0013). No difference in mean ± SD SBP at the end of screening was found between D and N groups (142.0±17.0 vs. 142.7±15.7, p=0.4814). However, mean time (h) from presentation to randomization was significantly longer for N compared with D (10.0±4.0 vs. 6.8±4.6, p<0.0001).
Conclusion: Time of presentation impacts enrollment rates and time to randomized treatment in clinical trials of patients with AHF. Such findings are important not only for the design of future studies to facilitate recruitment, but also in terms of routine clinical practice.

P839 | BEDSIDE

Wireless left ventricular endocardial cardiac resynchronisation in heart failure patients: 12 months follow-up

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Purpose: HF pts remain untreated due to peri-operative and long-term compli-

cations or lack of response to CRT in >40% of cases. These issues have been addressed through alternative approaches including the Wireless Cardiac Stimulation System, WiCS-LV, a novel system which provides ultrasonic based wireless endocardial LV pacing synchronously with RV pacing via a co-implanted PM or ICD. The WiCS-LV comprises a subcutaneous battery-powered transmitter, implanted in an appropriate acoustic window identified during mandatory pre-implant TTE, and a leadless, passive electrode anchored to LV endocardium via retrograde aortic approach using a steerable delivery system. Sensing of RV pacing output from co-implanted device synchronously triggers, within 3ms, ultrasonic energy transmission to the 9mm x 3mm passive electrode, which converts this energy into electrical energy with consequent stimulation of the LV.
Methods: 13 (76.4%) of 17 pts enrolled in this first in man study, WiSE-CRT, were implanted. Pre-operative TTE screening identified adequate acoustic window in all patients between 4-7th intercostal spaces. The leadless, passive electrode was placed in the LV mid-lateral wall. Study duration was 6m but pts continue in a registry. We report 12 month results on 10 pts with mean ± SD follow-up time of 371±15 days. 3pts were not evaluable, x2 high threshold and x1 death.
Results: Baseline characteristics for this group, all NYHA III, were: mean ± SD age = 66.7±7.8yrs, LVEF =24.6±4. 7%, intrinsic QRS duration 188±32ms. Implantation was uneventful. At 12 month follow-up, mean ± SD LVEF had increased to 33.2±7.8%, with only 1 (10%) pts showing a reduction, and NYHA was 2.1±0.6, with 8 (80%) pts showing a reduction of at least one functional class 1 with the remaining 2 pts showing no change. The mean ± SD % QRS duration was reduced to 141±43ms with BiV pacing.
Conclusions: WiCS-LV has provided CRT successfully over 12 months in 10 pts, including 5 (50%) pts who could not have otherwise received CRT therapy due to failed implant attempt(s) or no response to conventional CRT therapy. Additional studies are in progress to further evaluate the potential of this novel pacing approach.

P840 | BEDSIDE
Trimetazidine, but not isosorbide dinitrate, improves endothelium-dependent reactivity of muscular type arteries in patients with stable angina and heart failure

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Background: Several small randomized controlled trials showed that trimetazidine (TMZ) improves cardiac function parameters, exercise tolerance, quality of life and even prognosis in patients (pts) with heart failure (HF). The improvement in endothelium-dependent vasodilation by TMZ may be considered as one of the explanations of the positive effects of this agent in this category of pts. The aim of our study was to compare the effects of TMZ modified release (MR) and isosorbide dinitrate (ISDN) on endothelium-dependent reactivity of the radial artery in pts with stable angina and HF.
Methods: 41 male pts (mean age 56.1±4.1 years) with stable angina (CCS 2.4±0.2) and HF (NYHA 2.2±0.2) were included into this open, parallel-group randomized clinical trial. Pulse wave velocity (PWV) was calculated by automatic computerized system. In order to assess endothelium-dependent reactivity of the radial artery we used a technique based on the change in PWV in the radial artery during reactive hyperemia. Measurements were made at baseline and after 4 months of the treatment with TMZ MR, 70 mg/day, or ISDN, 80 mg/day. All pts with stable angina and HF received a guideline-based therapy, which remained unchanged.
Results: A significant reduction in the number of angina attacks and the number of short-acting nitrates per week was noted during the treatment with both compared agents. However, TMZ MR therapy, but not ISDN, resulted in a significant decrease in the NYHA functional class (-22.7%, $p<0.05$ vs -9.5%, NS). After 4 months of therapy, carotid-femoral PWV did not change in pts with stable angina and HF. The decrease % in PWV in the radial artery during reactive hyperemia in pts with stable angina and HF grew from 15.4% to 19.5% ($p<0.05$). An opposite effect was observed in the group of pts receiving ISDN: initially the decrease % in PWV in the radial artery during reactive hyperemia was 14.8%, and after 4 months of treatment just 4.4% ($p<0.01$). Moreover, ISDN increased, whereas TMZ MR significantly decreased, the number of paradoxical responses for PWV in the radial artery during reactive hyperemia unchanged in pts with stable angina and HF.
Conclusion: Trimetazidine modified release, but not isosorbide dinitrate, improves endothelium - dependent reactivity of muscular type arteries in patients with stable angina and heart failure. This effect can be of great importance for the choice of agents in the treatment of this category of patients.

P841 | BENCH
Diastolic Ca2+ leak and the role of the Na+/Ca2+ exchanger (NCX) in a model of heart failure with preserved ejection fraction

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Background: Heart failure with preserved ejection fraction (HFPEF) is increasingly common but the established HF drugs are not effective. The underlying cellular mechanisms are incompletely understood. Therefore we investigated cardiomyocyte function and intracellular Ca2+ homeostasis in a model of HFPEF.
Methods: Young male Wistar rats were subjected to subtotal nephrectomy (NXT) or sham operation (SOP). Serial blood/urine samples, echocardiography and pressure-volume loops at 8 and 24 weeks were performed. After sacrifice, left ventricular (LV) hypertrophy and NCX function (Caffeine induced Ca2+ transient, TAU) and protein expression (Western blot) were determined. Cardiomyocyte function (Ca2+ transients, sarcoplasmic reticulum (SR) diastolic Ca2+ leak (Ca2+ sparks) and SR Ca2+ content) were quantified in cardiomyocytes with and withou NCX inhibitor SEA0400 (300nM).
Results: NXT rats showed stable compensated renal impairment and significantly hypertrophied LV at 8 weeks with a further increase after 24 weeks. LV systolic function was preserved. End diastolic pressure (EDP) volume relationship was markedly shifted left- and upwards and lung weight was significantly increased, indicating HFPEF with pulmonary congestion. LV cardiomyocytes from NXT showed no significant differences in amplitudes of Ca2+ transients. However, time for early (50%) decay of the Ca2+ transients at 8 weeks was significantly prolonged with a further increase after 24 weeks (RT50 17.2±2.9 and 30.8±2.7 vs. 27.6±1.8 and 41.8±2.6 ms; $n\geq20$; $p<0.05$); this was significantly correlated with diastolic dysfunction in vivo. TAU was significantly prolonged at 8 and 24 weeks indicating reduced NCX forward mode activity, while NCX protein expression was upregulated. At 8 weeks, Ca2+ spark frequency tended to be increased ($p=0.07$) while SR Ca2+ content was unchanged. SEA0400 accelerated Ca2+ transient decay but did not affect Ca2+ spark frequency. At 24 weeks, Ca2+ spark frequency was increased (4.3±0.7 vs. 11.5±1.8 sparks/s/μm^3; $n\geq20$; $p<0.05$) and SR Ca2+ content was decreased ($p<0.05$). SEA0400 significantly accelerated Ca2+ transient decay and reduced Ca2+ spark frequency in NXT.
Conclusion: In this model of HFPEF, cytosolic Ca2+ decay of the LV cardiomyocytes was slower. Diastolic Ca2+ leak increased significantly during diseases progression. Whereas NCX forward mode activity was already reduced early despite increased NCX protein expression. Acute treatment with NCX inhibitor SEA0400 normalized cytosolic Ca2+ transients in young NXT rats, suggesting a role of reverse mode NCX activity and decreased Ca2+ leak at later time points.

P842 | BEDSIDE
The effect of exercise on left ventricular twist in patients with type 2 diabetes and diastolic dysfunction

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Purpose: Type 2 diabetes mellitus (T2DM) is associated with diastolic dysfunction (DD). Left ventricular (LV) twist and untwist are important for normal LV function, and have been found to be altered in patients with diastolic dysfunction. We sought to find out how the effect of high intensity interval exercise (HIIE) alter LV twist parameters in patients with T2DM (duration <10 years) and DD, compared to moderate intensity exercise (MIE), in accordance to International Diabetes Federation recommendations.
Methods: A total of 36 patients (mean age 57 years, 22 male) with T2DM and DD (early diastolic tissue velocity (e') <8 cm/s) were randomized to either HIIE (4x4minutes) at 90-95% of maximal heart rate 3 times/week (n=19) or MIE for 210 minutes/week (n=17). LV twist and untwist were measured by two-dimensional speckle tracking echocardiography pre and post the 12-week period of exercise.
Results: Diastolic function improved significantly in both groups after 12 weeks of exercise (HIIE mean difference e' 1.8±1.1, $P<0.001$ versus MIE 0.5±0.7 cm/s, P=0.017). The amplitude of twist, twist rate and untwist rate decreased, but the time to peak untwist rate from aortic valve closure was shorter after exercise (Table).

Left ventricular twist parameters

Parameters	Moderate intensity exercise			High intensity interval exercise		
	Baseline	Post 12 weeks	P	Baseline	Post 12 weeks	P
Peak twist °	13.3 (4.6)	9.3 (5.9)	0.024	12.5 (3.6)	9.4 (3.9)	0.010
Peak twist rate, °/s	95.8 (29.8)	67.9 (26.8)	0.033	78,7 (27.3)	58.1 (21.3)	0.019
Peak untwist rate, °/s	–98.9 (37.0)	–69.7 (17.2)	0.008	–87.0 (28.7)	–67.3 (37.2)	0.046
Time to peak early apical untwist rate, % of diastole	18.2 (9.9)	12.4 (6.4)	0.044	21.3 (9.8)	12.4 (8.7)	0.001
Time to peak early basal untwist rate, % of diastole	21.9 (17.3)	13.6 (9.3)	0.046	18.6 (9.1)	9.1 (5.6)	0.02
Time to peak early untwist rate, % of diastole	24.3 (14.4)	13.1 (13.4)	0.081	22.0 (18.0)	9.9 (11.9)	0.003

Values are expressed as mean (standard deviation), % of diastole – the total length of the diastolic period was set to 100% and the time to peak early untwist rate was definded as the time from AVC to peak untwist rate divided by the diastolic period.

Conclusions: In T2D patients with diastolic dysfunction, exercise shortened the time to peak untwist rate as well as improved the diastolic dysfunction, especially in the high intensity exercise group.