contrast to PARADIGM-HF (all on stable ACEI/ARB dose at baseline) and TITRATION (6.6% were naïve). Pre-admission use of beta-blockers and MRAs in TRANSITION was lower (Table). Baseline LVEF was comparable across studies, but pts recruited to TRANSITION were older, more likely to be female, with worse eGFR, and a higher proportion of atrial fibrillation and diabetes.

Table 1. Baseline characteristics

	Titration (N=498)	Paradigm-HF (N=8442)	Transition (N=1002)
Age (mean), years	64	64	67
Male, %	79	78	75
Black patients, %	5	5	1
Baseline LVEF (mean), %	30	29	29
NYHA Class II / III / IV, %	71 / 29 / 0	70 / 24 / 1	64 / 34 / 1
SBP (mean), mm Hg	131	121	124
eGFR (mean), mL/min/1.73m^2	70	68	62
ACEI / ARB / BB / MRA, %	67 / 27 / 95 / 60	78 / 23 / 93 / 56	51 / 25 / 42 / 33
Hypertension / Diabetes / Atrial fibrillation, %	40 / 12 / 27	71 / 35 / 37	75 / 46 / 48

Conclusion: TRANSITION recruited a more severe HFrEF population with more comorbidities, closer to everyday clinical practice, including new-onset HFrEF and ACEI/ARB naïve pts. TRANSITION will provide complementary evidence to PARADIGM-HF and TITRATION about the safety and tolerability of S/V initiation after ADHF admission.

Funding Acknowledgements: The TRANSITION, PARADIGM-HF, and TITRATION studies are funded by Novartis

P6532
Oral donepezil markedly suppresses the progression of cardiovascular remodeling and improves the prognosis in spontaneously hypertensive rats with myocardial infarction

M. Li, C. Zheng, T. Kawada, M. Inagaki, K. Uemura, T. Shishido, M. Sugimachi.
National Cerebral and Cardiovascular Center, Department of Cardiavascular Dynamics, Osaka, Japan

Introduction: Acetylcholinesterase inhibition by donepezil has been shown to improve long-term survival in chronic heart failure (CHF) rats following myocardial infarction (MI). We examined whether donepezil is effective in the treatment of a CHF model complicated with hypertension.
Methods: CHF was induced by extensive MI (49±1%) in spontaneously hypertensive rats. After one week recovery, we implanted a blood pressure transmitter for monitoring daily hemodynamics. Survived animals were randomly assigned to untreated (UT, n=23) or oral donepezil treated (DT, n=22, 5 mg/kg/day) group. At the 8th week, the effects of donepezil were evaluated by hemodynamics, neurohumoral states, inflammatory markers, immunohistochemistry, morphology, and 50-day survival rate.
Results: Compared with UT, DT significantly decreased the heart rate (305±12 vs. 335±11 bpm, $P<0.05$). DT also improved 50-day survival (76% vs. 43%, P=0.006), through suppressing the progression of cardiac hypertrophy (3.83±0.05 vs. 4.09±0.07 g/kg, $P<0.05$), preventing cardiac dysfunction (cardiac index: 101±4 vs. 89±4 ml/min/kg, $P<0.05$; LVEDP: 12±3 vs. 22±2 mmHg, $P<0.05$; LV dp/dt max: 5145±308 vs. 4267±118, $P<0.05$) and coronary artery remodeling (wall thickness: 25.8±1.5 vs. 34.1±0.5 mm, $P<0.01$; media-to-lumen ratio: 3.71±0.72 vs. 8.59±0.84, $P<0.001$), and increasing capillary density (74±5 vs. 33±3 cells/field, $P<0.001$). Additionally, DT not only decreased plasma levels of norepinephrine (183±35 vs. 3414±1955 pg/ml, $P<0.05$), BNP (365±21 vs. 560±69 pg/ml, $P<0.01$), AVP (955±97 vs. 1509±249 pg/ml, $P<0.01$) and angiotensin II (20±1 vs. 33±1 pg/ml, $P<0.01$), but also improved the systemic inflammation (CRP: 339±19 vs. 393±19 μg/ml, $P<0.05$; TNF-a: 4.2±1.5 vs. 9.2±1.7 pg/ml, P=0.01).
Conclusions: Oral donepezil treatment suppressed the progression of cardiovascular remodeling, cardiac dysfunction and improved the prognosis of CHF in hypertensive rats, suggesting that donepezil may be used as a new pharmacotherapy for patients with CHF complicated with hypertension.

P6533
Donepezil treatment prevents the progression of cardiac remodeling and dysfunction in obesity-induced hypertensive rats with reperfused myocardial infarction

M. Li, C. Zheng, T. Kawada, M. Inagaki, K. Uemura, T. Shishido, M. Sugimachi.
National Cerebral and Cardiovascular Center, Department of Cardiavascular Dynamics, Osaka, Japan

Introduction: We have demonstrated that acetylcholinesterase inhibition by donepezil improves long-term survival of chronic heart failure rats with permanent myocardial infarction (MI). This study aimed to investigate whether donepezil is applicable to the treatment of obesity-induced hypertension with reperfused MI (RMI)
Methods: We implanted a blood pressure transmitter to the high fat-fed, obesity-induced hypertensive rats for monitoring daily hemodynamics. RMI was created by occluding the left coronary artery (30min) followed by reperfusion. Survived animals were randomly assigned to untreated (UT, n=16) or donepezil treated (DT, n=16, 3 mg/kg/day) group. At the 11th week, the effects of donepezil were evaluated by hemodynamics, blood biomarkers, immunohistochemistry and morphology.
Results: Compared with UT, DT decreased the heart rate (296±5 vs. 318±8 bpm, $P<0.05$), but did not change the mean blood pressure. DT significantly prevented the progression of cardiac remodeling and dysfunction (cardiac index: 91±4 vs. 73±9 ml/min/kg, $P<0.01$; LVEDP: 11±1 vs. 20±2 mmHg, $P<0.01$; LV dp/dt max: 5347±206 vs. 3637±433 mmHg/s, $P<0.01$), through reducing myocardial infarcted area (17±2 vs. 24±2%, $P<0.05$), suppressing cardiac hypertrophy (2.35±0.04 vs. 2.70±0.14 g/kg, $P<0.01$) and coronary artery remodeling (wall thickness: 30.1±1.4 vs. 36.7±1.8 mm, $P<0.01$; media-to-lumen ratio: 2.3±0.2 vs. 6.2±1.6, $P<0.001$). DT decreased plasma levels of insulin (2.2±0.2 vs. 3.5±1.0 ng/ml, $P<0.05$), norepinephrine (345±55 vs. 1293±412 pg/ml, $P<0.05$), BNP (378±13 vs. 456±28 pg/ml, $P<0.05$), angiotensin II (37±12 vs. 73±13 pg/ml, $P<0.05$) and CRP (207±8 vs. 345±11 μg/ml, $P<0.001$).
Conclusions: Donepezil treatment significantly prevented the progression of cardiac remodeling and dysfunction following RMI in obesity-induced hypertensive rats, suggesting that donepezil may be used as a potential candidate for post-RMI therapy in obesity-induced hypertensive patients.

P6534
Increased dose of diuretics correlates with severity of heart failure and renal dysfunction and does not lead to reduction of mortality and rehospitalizations, data from AHEAD registry

M. Pavlusova[1], R. Miklik[1], K. Benesova[2], R. Spacek[3], K. Zeman[3], S. Littnerova[2], M. Felsoci[1], L. Pohludkova[3], L. Dusek[2], J. Spinar[1], J. Parenica[1], J. Jarkovsky[2]. *[1]University Hospital Brno, Department of Cardiology and Internal Medicine, Brno, Czech Republic; [2]Institute of Biostatistics and Analyses of Masaryk University, Brno, Czech Republic; [3]Hospital in Frydek-Mistek, internal department, Frydek-Mistek, Czech Republic*

Background: Diuretics are being used to reduce symptoms of congestion and fluid retention in heart failure patients but their effect has not been studied in randomized clinical trials. The data about positive or negative effect of loop diuretics depending on their dose is conflicting and controversial. The aim of this analysis is to evaluate whether the relatively small increase in the dose of furosemide can reduce the incidence of readmissions for acute heart failure decompensation and / or total mortality.
Methods and results: We evaluated a total of 1,119 patients admitted for ADHF who were discharged from the hospital back home in a stable condition. All surviving patients were followed up for at least two years. The primary endpoint was a combination of hospital readmissions for acute heart failure and overall mortality. The primary analysis showed significantly different characteristics and prognosis of patients who did not require any loop diuretic and those requiring furosemide dose >125 mg. Therefore we compared a group of patients with low-dose furosemide (10–40mg) with a group of patients with high-dose furosemide (41–125mg) only. The higher dose of diuretics correlated well with disease severity (lower systolic blood pressure, more frequent chronic exertional dyspnea NYHA III, lower left ventricular ejection fraction, increased creatinine levels). Long-term mortality and the number of rehospitalizations were lower in the low-dose diuretic group (p=0.037 and p=0,036, respectively) but after adjustment using the propensity score matching the incidence of the primary endpoint was comparable in both groups. Conclusion
The dose of a loop diuretic recommended to patients with acute heart failure at hospital discharge correlates well with the severity of heart failure. When comparing the groups of patients with a higher dose of furosemide (41–125mg) and a lower dose of furosemide (10–40mg) we found that after adjustment using propensity score matching the higher dose of loop diuretic had a neutral effect on the incidence of the composite endpoint of overall mortality and/or readmission for ADHF.

P6535
Differing efficacy of beta blockers on long-term clinical outcomes between ischemic heart failure patients with reduced and mid-range ejection fraction following percutaneous coronary intervention

J. Shitara[1], T. Kasai[1], K. Miyauchi[1], H. Endo[1], H. Wada[1], S. Doi[1], R. Naito[1], H. Konishi[2], S. Tsuboi[2], M. Ogita[2], T. Dohi[1], S. Okazaki[1], K. Isoda[1], H. Daida[1]. *[1]Juntendo University, Circulation, Tokyo, Japan; [2]Juntendo University Shizuoka Hospital, Circulation Department, Izunokuni, Japan*

Background and objective: Beta blockers (BB) are frequently used in patients with coronary artery disease (CAD). In particular, BB therapy improved mortality in patients with left ventricular systolic dysfunction. However, whether effects of BB on long-term outcomes differs between ischemic heart failure patients with reduced ejection fraction (rEF; <40%) and those with mid-range EF (mrEF; 40–49%) remains unknown.
Methods: We prospectively enrolled 3507 consecutive CAD patients who underwent percutaneous coronary intervention (PCI) at our institution and identified 201 with rEF and 316 with mrEF. Associations between use of BB and incidence of clinical events including all-cause death and/or acute coronary syndrome were assessed separately in patients with rEF and those with mrEF.
Results: During a median follow-up period of 5.4 years, 188 patients (36%) had clinical events. In patients with rEF, multivariable Cox regression analysis includ-