posure to the vascular endothelial growth factor-receptor antagonist SU5416 and hypoxia (SuHx). To separate pulmonary from cardiac effects, isolated right heart failure was induced by pulmonary trunk banding (PTB) in another set of rats. In both models, the development of right ventricular (RV) dysfunction was verified by echocardiography before randomization to treatment with LCZ696 (60 mg/kg/day) or vehicle. After five weeks of treatment, effects were evaluated by echocardiography, cardiac magnetic resonance imaging and invasive pressure-volume measurements. The study followed the "Principles of laboratory animal care" (NIH Publication no. 85–23 revised 1985) and was conducted according to Danish national law.

Results: In the SuHx rats, treatment with LCZ696 decreased RV pressure (mean difference: -12±4 mmHg, p=0.004) and reduced RV hypertrophy (RV weight corrected for tibia length, mean difference: -2.3±0.7 mg/mm, p=0.003) compared to vehicle. Moreover, RV end-diastolic volume (EDV) and end-systolic volume (ESV) were reduced in the rats treated with LCZ696 compared to vehicle treated rats (mean difference EDV: -0.09±0.04 mL, p=0.03; mean difference ESV: -0.11±0.03 mL, p=0.005) but without an increase in stroke volume or RV ejection fraction. Treatment with LCZ696 reduced systemic mean arterial blood pressure in both the SuHx rats (mean difference: -12±5 mmHg, p=0.02) and the PTB rats (mean difference: -20±7 mmHg, p=0.02) compared to vehicle. In the PTB model, LCZ696 had no effects on RV pressure, hypertrophy or volumes.

Conclusions: Combined angiotensin II receptor antagonism and neprilysin inhibition reduced RV pressure, hypertrophy and dilatation in the SuHx model of pulmonary arterial hypertension. These effects may be attributed to pulmonary changes, as similar effects were not seen in rats with isolated right heart failure induced by banding of the pulmonary trunk.

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3022

Relative bioavailability and pharmacokinetic (PK) performance of a ralinepag extended-release (XR) tablet oral formulation and the effect of food and gender in healthy human subjects

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Background/Introduction: Ralinepag is an orally available, potent and selective prostacyclin (IP) receptor agonist in development for the treatment of pulmonary arterial hypertension (PAH). Ralinepag demonstrates a longer terminal half-life (~24 h) than selexipag (≤2.5 h) and its active metabolite MRE-269 (≤13.5 h), and based on in vitro studies is more potent and efficacious than selexipag at increasing cellular cyclic adenosine monophosphate (cAMP) levels. Initial clinical studies used an immediate-release (IR) capsule. When formulated as extended-release (XR) tablet, designed to allow convenient once-daily dosing, ralinepag may be an attractive oral alternative to currently available prostacyclin analogues and IP agonists for PAH treatment.

Purpose: To compare single-dose pharmacokinetics (PK) of ralinepag IR, selexipag IR, and ralinepag XR tablet formulations, and to evaluate multiple-dose PK properties/performance of the ralinepag XR tablet formulation under fed/fasted conditions and in both genders.

Methods: Two single-center, open-label, non-randomized PK studies were conducted in healthy subjects. Study 1: cohort 1 (n=12) subjects took single oral doses of ralinepag in the fasted state given in a sequential manner over 4 treatment periods: 0.03 mg IR capsule, and then 0.06, 0.12, and 0.18 mg doses of an XR tablet. Cohort 2 (n=12) subjects took single oral doses of selexipag IR in the fasted state given sequentially over 3 treatment periods: 0.2, 0.4 and 0.6 mg IR tablets. Study 2: fasted (cohort 1; n=19) or fed (cohort 2, n=18) subjects received ralinepag XR tablet formulation in a dose-escalation sequence over 25 days (once-daily dosing started at 0.06 mg and was slowly titrated, depending on individual subject tolerability, by additional 0.06 mg dose increments every 5 days up to 0.3 mg once daily).

Results: Study 1: Dose-adjusted peak plasma exposure (Cmax/D) measures were lower, as expected, for ralinepag XR versus the IR formulation [geometric mean ratios (GMRs) ranged up to 41.2%]. Dose-adjusted total plasma exposure (AUC/D) measures were similar for both XR and IR formulations (GMRs ranged up to 97.9%). Selexipag and MRE-269 plasma PK profiles were consistent with the need for selexipag twice-daily administration. Study 2: Dose-dependent ralinepag plasma exposure measures were observed for the XR tablet formulation given once daily, with low peak–trough fluctuation and little effect of food seen across dose levels. Somewhat higher mean plasma exposure measures were observed in females versus males.

Conclusion: The ralinepag XR tablet formulation offers improved PK performance over both ralinepag and selexipag IR formulations, by providing extended drug exposure and maintaining low peak–trough fluctuation with once-daily dosing. These highly favorable and desirable PK characteristics support ralinepag XR tablet use in Phase 3 clinical studies.

Funding Acknowledgements: Arena Pharmaceuticals

HYPERTENSION – EPIDEMIOLOGICAL AND DIAGNOSTIC ASPECTS

3023

Effects of low blood pressure on cardiovascular events in diabetic patients with coronary artery disease after revascularization - The CREDO-Kyoto cohort-1

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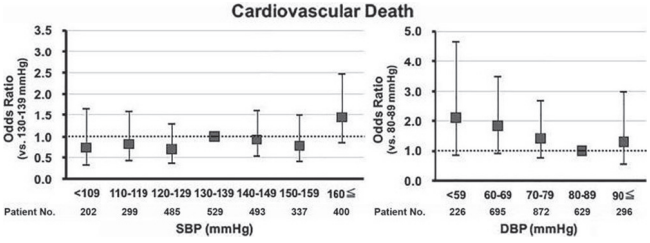
Background: The new 2017 ACC/AHA high blood pressure (BP) guidelines lowered the target BP for patients with diabetes mellitus (DM) to 130/80mmHg or less. However, there is a concern that extremely low BP may increase cardiovascular (CV) events in DM patients, especially in DM patients with coronary artery disease (CAD). Coronary revascularization has become prevalent in diabetic CAD patients.

Purpose: We investigated the effects of low SBP and DBP on CV events in diabetic CAD patients after coronary revascularization.

Methods: We examined 2,718 DM patients with stable, chronic CAD registered in the CREDO-Kyoto cohort-1, a prospective multi-center registry, enrolling 9,877 CAD patients who underwent the first CABG or PCI.

Results: CV death was not affected by low SBP, whereas DBP below 70 mmHg slightly but not significantly increase CV death (Figure). Low SBP and DBP did not change the risk of non-fatal myocardial infarction and non-fatal stroke. On multivariate Cox proportional hazard regression analysis, DBP below 70 mmHg was not a significant factor for increasing CV death, while creatinine clearance (hazard ratio [HR] 0.970 [95% confidence interval; 0.961–0.978], p=0.000), statin use (HR 0.428 [0.227–0.844], P=0.014), pulse pressure (HR 1.016 [1.003–1.030], P=0.015), hypertension (HR 2.420 [1.090–5.373], P=0.030), and prior myocardial infarction (HR 1.804 [1.037–3.139], P=0.037) were the independent factors for CV death.



Conclusions: In diabetic CAD patients after coronary revascularization, low BP is not a significant factor for increasing CV events. Along with the management of risk factors and comorbidities, strict BP control targeting less than 130/80 mmHg is important for improving the prognosis of diabetic CAD patients after revascularization.

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3024

Incident Cardiovascular events among hypertensive patients with optimally controlled blood pressure: the Campania Salute Network

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Background: Data from last decade indicate that the majority of incident cardiovascular (CV) events (CVE) occur among individuals with systolic and diastolic blood pressure (BP) ≥140/90 mm Hg. New American Guidelines suggest lower cut-point for definition and treatment threshold to <130/80 mmHg. This change would highlight the need to focus CV prevention on further BP reduction among adults with BP <140/90 mm Hg.

Purpose: We evaluated risk of incident CVE on the basis of clinical characteristics of hypertensive patients with controlled BP, focusing on follow-up (FU) BP values.

Methods: From the Campania Salute Network 3933 patients had controlled BP (average BP during FU <140/90 mmHg), and available cardiac and carotid ultrasound, to identify LV hypertrophy (LVH) and carotid plaque (CP), as target organ damage (TOD). A composite end-point of incident major and minor CVE was censored (fatal and non-fatal stroke or AMI, TIA, coronary or carotid revascularization, atrial fibrillation).

Results: During a median FU of 53 months (interquartile range: 26–102), 161 incident CVE occurred. CVE were more frequent in older men, with lower diastolic BP (DBP) and heart rate, higher prevalence of LVH and CP, and higher LDL cholesterol (all p<0.001). During FU, patients withCVE were also taking more antihypertensive meds (p<0.01). Because DBP<70 mmHg has been reported to increase CV risk, this cut point was included in the Cox regression. In Cox analy-

sis, average DBP<70 mmHg was associated with near 3-fold greater risk of CVE, independently of age and sex (Table 1).

Table 1. Cox regression model for combined CV endpoints

Variables	Sig.	HR	95,0% CI for HR	
			Lower	Upper
Age (years)	0.0001	1.06	1.04	1.08
Male sex	0.004	1.67	1.18	2.36
Baseline diastolic BP <70 mmHg (n/y)	0.95	1.03	0.44	2.39
Average diastolic BP during FU <70mmHg (n/y)	0.008	2.70	1.30	5.63
Heart Rate (bpm)	0.267	0.99	0.98	1.01
LDL cholesterol (mg/dl)	0.175	1.00	0.99	1.01
LV hypertrophy (n/y)	0.25	1.22	0.87	1.69
Carotid plaque (n/y)	0.23	1.23	0.88	1.70
Antihypertensive meds during FU (N of drugs)	0.07	1.17	0.99	0.38

Conclusions: In hypertensive patients with controlled BP during FU, risk of incident CVE is associated with DBP during FU <70 mmHg, independently of significant effect of older age and male sex, with no impact of baseline TOD.

3025
High normal blood pressure conferred higher risk for cardiovascular disease in a random population sample of 50-year-old men during 21-years follow-up

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Background: Elevated blood pressure (BP) is common and hypertension is a strong risk factor for heart failure and cardiovascular (CVD) mortality. However, the correlation between various BP categories as well as hypertension subtypes and cardiovascular diseases are inadequately studied.
Aim: To investigate the relation of different BP categories, hypertensive subtype and the risk of cardiovascular disease.
Method: As part of a longitudinal cohort study "the Study of Men Born in 1943" in Sweden, 798 men were followed from the age of 50 until the age of 71. Baseline data, including lifestyle, blood pressure, antropometric and laboratory data were collected, and a reexamination was done at 71 years of age, including echocardiography. Participants were classified according to their BP at the age of 50: 1) optimal-normal BP (SBP<130mmHg and DBP<85mmHg); 2) high normal BP (130mmHg≤SBP<140mmHg, 85mmHg≤DBP<90mmHg); 3) isolated systolic/diastolic hypertension (ISH/IDH): (SBP≥140mmHg and DBP<90mmHg/ SBP<140mmHg and DBP≥90mmHg); 4) systolic diastolic hypertension (SDH) (SBP≥140mmHg and DBP≥90mmHg). Two major end-points were applied in this study: cardiovascular disease (CVD), coronary heart disease (CHD). The criteria for defining a CVD event were the time to first occurrence of myocardial infarction, heart failure, death resulting from coronary heart disease, stroke, intermittent claudication, other cardiovascular death and revascularization procedures.
Result: During a 21 year follow up period, BP elevated from 1993 to 2014. The incidence of CVD and CHD were all lowest for those with optimal normal BP. In a multivariable Cox proportional hazards models high normal BP, ISH/IDH and SDH were associated with a higher risk for CVD and CHD compared with optimal-normal BP. The adjusted relative risk for CVD was highest for SDH (HR 1.95; 95% CI 1.37–2.79), followed by ISH/IDH (HR 1.34; 95% CI 0.93–1.95) and high-normal BP (HR 1.31; 95% CI 0.91–1.89) compared to optimal BP. The adjusted HR for CHD was also highest for SDH (HR 2.10; 95% CI 1.26–3.49), followed by ISH/IDH (HR 1.42; 95% CI 0.83–2.45) and high-normal BP (HR 1.21; 95% CI 0.70–2.11) with optimal BP as reference.
Conclusion: Over 21-year follow-up, 50-year old men with high normal blood pressure and isolated systolic/diastolic hypertension had significantly higher relative risk for CVD and CHD than those with optimal-normal BP.
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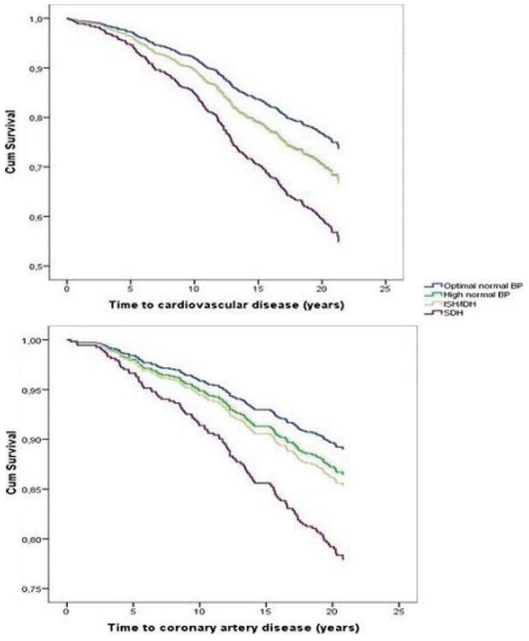

Adjusted risk for outcome of cardiovascular disease

3026
Prevalence of arterial hypotension in elderly hypertensive patients using 24hs ambulatory blood pressure monitoring

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Introduction: Arterial hypotension (AH) caused by antihypertensive drugs is one of the most undesirable side effects in elderly hypertensive patients.
Objective: The objective of the study was to evaluate the presence of AH and its relationship with the number of drugs administered in patients older than 65 years under antihypertensive treatment, using 24hs ambulatory blood pressure monitoring (ABPM). Sample and Method: We analyzed 12177 ABPM studies. Of them 327 was discarded for several reasons leaving a total sample of 10850. All the studies were carried out under the current technical criteria and abnormality values accepted by the HBP Societies. The subjects were divided into 3 groups: 65 to 69, 70 to 79 and more than 80 years and by tertiles of systolic blood pressure (SBP): up to 110, 120 and ≥130 mmHg. AH was considered in any of the four circumstances: diurnal systolic blood pressure (SBPD) or 24-hour SBP (SBP24) ≤100 mmHg. or daytime mean arterial pressure (MAPD) or 24-hr MAP (MAP24) ≤ to 73 mmHg. respectively.
Results: 1778 patients (16%) were over 65 years old. 321 were discarded for not being in treatment. The final sample was 1457 subjects (13%), 41% men, average age 73.1 years. The BP average of the 1457 patients was: SBPD 129.9, SBP24: 126.2, MAPD: 93.6 and MAP24: 90.2. Of these, 57 patients (3.91%), met the AH criteria and only 9 of them, 16%, experienced symptoms probably attributable to AH (dizziness and weakness). None of them experienced major side effects such as syncopes or falls. The BP average of the 57 AH patients was: SBPD 98.9, SBP24: 99.8, MAPD: 68.8 and MAP24: 73.6. The average number of drugs used per patient was 2.1. There were no significant differences between the age groups and the number of drugs used (p=0.766)The AII receptors antagonists, the calcium antagonists, the diuretics, the beta blockers and the ACE inhibitors were in that order the most used drugs.
Conclusions: These results show that the prevalence of AH and especially symptomatic, is scarce in elderly patients, and in agreement with the cardiovascular benefit demonstrated recently, the risk of lowering BP to lower values seems to be low and well tolerated in this age group.

3027
Changes in arterial stiffness independently predict stroke in patients with essential hypertension: Data from a Greek 8-year-follow-up study

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Background/Introduction: Although arterial stiffening is related to atherosclerosis progression, the prognostic role of its alterations in cerebrovascular events in hypertension is not fully elucidated.
Purpose: The aim of the present study was to assess the predictive role of changes in arterial stiffness for the incidence of stroke in a cohort of essential hypertensive patients.
Methods: We followed up 1082 essential hypertensives (mean age 55.9 years, 562 males, office blood pressure (BP)=145/91 mmHg) for a mean period of 8 years. All subjects had at least one annual visit and underwent blood sampling for assessment of metabolic profile, while arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method at the initial and last visit. The distribution of baseline PWV was split by the median (8.2 m/sec) and accordingly subjects were classified into those with high (n=546) and low values (n=536). Stroke was defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened confirmed by computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings.
Results: The incidence of stroke over the follow-up period was 2.2%. Hypertensives who had stroke (n=24) compared to those without stroke at follow-up (n=1058) were older at baseline (65±9 vs 56±12 years, p=0.032), had higher office BP levels (155±13 vs 145±15 mmHg, p=0.014) and prevalence of high PWV levels (67% vs 40%, p=0.021). No difference was observed between hypertensives with stroke and those without stroke with respect to baseline renal function and lipid levels (p=NS for all). By univariate Cox regression analysis it was revealed that changes in PWV levels between baseline and last visit predicted