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.

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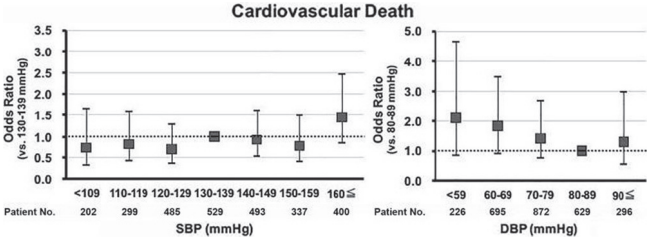
**Background:** The new 2017 ACC/AHA high blood pressure (BP) guidelines lowered the target BP for patients with diabetes mellitus (DM) to 130/80mmHg or less. However, there is a concern that extremely low BP may increase cardiovascular (CV) events in DM patients, especially in DM patients with coronary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