

### LB2.3 EIGHT BLOOD PRESSURE LOCI IDENTIFIED BY A GENOME-WIDE ASSOCIATION STUDY OF 34,433 PEOPLE OF EUROPEAN ANCESTRY

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**Objective:** High blood pressure is a common, heritable cause of cardiovascular disease worldwide. To date, the identification of common genetic variants influencing blood pressure across the population has proven challenging. To address this we established the Global BPgen consortium involving 164 people from 92 European and US centres to undertake a large-scale meta-analysis of genome-wide association scan data from 34,433 individuals drawn from 17 cohorts of European ancestry with high quality blood pressure measurements.

**Methods:** After extensive quality control checks, we conducted a meta-analysis of c.2.5m genotyped and imputed SNPs for association with systolic and diastolic blood pressure in 34,433 subjects using inverse variance weighting. We followed up the top 12 loci with direct genotyping ( $N \leq 71,225$  of European ancestry,  $N = 12,889$  of Indian Asian ancestry) and simultaneously undertook *in silico* comparison of the top 20 signals (10 for systolic blood pressure (SBP) and 10 for diastolic blood pressure (DBP) with the Cohorts for Heart and Ageing Research in Genome Epidemiology consortium ( $N = 29,136$ ). A threshold of  $P \leq 5 \times 10^{-8}$  was used to denote genome-wide significance.

**Results:** We detected and validated association between common variants in 8 regions near the *CYP17A1* ( $P = 7 \times 10^{-24}$ ), *CYP1A2* ( $P = 1 \times 10^{-23}$ ), *FGF5* ( $P = 1 \times 10^{-21}$ ), *SH2B3* ( $P = 3 \times 10^{-18}$ ), *MTHFR* ( $P = 2 \times 10^{-13}$ ), *c10orf107* ( $P = 1 \times 10^{-9}$ ), *ZNF652* ( $P = 5 \times 10^{-9}$ ) and *PLCD3* ( $P = 1 \times 10^{-6}$ ) genes. All of the variants were also associated with dichotomous hypertension.

**Conclusion:** These associations between common variants and blood pressure and hypertension offer mechanistic insights into the regulation of blood pressure and may point to novel targets for interventions to prevent cardiovascular disease.

### LB2.4 CATHETER-BASED RENAL DENERVATION REDUCES TOTAL BODY AND RENAL NORADRENALINE SPILLOVER AND BLOOD PRESSURE IN RESISTANT HYPERTENSION

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**Background:** In essential hypertension, renal noradrenaline (NA) spillover is commonly increased and in experimental hypertension renal sympathectomy abolishes the blood pressure elevation. Therapeutic renal sympathetic nerve ablation with catheter-based radiofrequency energy (Symplicity, Ardian Inc.) was tested in patients with resistant hypertension (SBP  $\geq 160$  mmHg on  $\geq 3$  anti-HTN drugs, including a diuretic).

**Methods:** Office blood pressure (BP), estimated GFR (eGFR) by MDRD and safety data were acquired prior to, and at 1, 3, 6 and 12 months post-procedure. Whole body and renal noradrenaline spillover were measured with isotope dilution in a subset of 10 patients at baseline and 30 days post denervation.

**Results:** 45 pts with a baseline mean office blood pressure of 177/101 mmHg (SD 20/15), (mean 4.7 antihypertensive medications) were studied; office blood pressures after procedure were reduced by 14/10, 21/10, 22/11, 24/11, and 27/17 mmHg at 1, 3, 6, 9, and 12 months, respectively. Thirty days after denervation, mean reduction in total renal noradrenaline spillover was 47%,  $p = 0.023$  (95% CI 28–65%), and total body NA spillover was reduced 28%,  $p = 0.043$  (95% CI 4–52%). One intra-procedural renal artery dissection occurred before radiofrequency energy delivery without further sequelae. No other renal vascular complications were identified in the 18 patients with short term repeat angiographic studies (14–30 days) or among 31 patients who underwent CTA or MRA 6 months after the ablations. Paired baseline and 6-month follow-up eGFR in 25 patients, and were 79 (SD 21) and 83 ml/min-1.73m<sup>2</sup> (SD 25).

**Conclusions:** Renal sympathetic nerve ablation, is associated with reduction of renal NA spillover indicative of disabling of renal efferent sympathetic nerves. Afferent renal sympathetic nerves from the kidney to the brain influence central sympathetic output, and the observed reduction

of total body NA spillover suggests renal sympathetic afferent traffic is reduced. If afferent nerve disabling is a significant cause of the reduction of BP, the effect is expected to be lifelong, since these nerves have little capacity for regeneration. Furthermore, the observed reduction of central sympathetic activity may facilitate LVH regression and increase insulin sensitivity. The disabling of renal sympathetic nerves is associated with a safe, significant and sustained BP reduction.

### LB2.5 ASSOCIATION BETWEEN VASCULAR RISK AND SICK LEAVE LENGTH AND COST

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**Background:** Few studies have evaluated the relationship between sick leave (SL), vascular risk factors (VRF), global cardiovascular risk (CVR) and vascular disease or diabetes (VD/D).

**Objective:** To investigate the association between SL, VRF, CVR, VD/D and other VRF in a very large nationwide database of the Spanish working population.

**Methods:** cross-sectional observational study including 1,081,184 workers (72.7% male; mean age 37.2 years for males and 35.3 years for females) who underwent Medical Check-ups (MCU) between 2004–2007. SL average length and its cost was calculated multiplying days of SL for employee contribution basis during the year following the MCU [either by common disease (CD) or labour accident (LA)]. CVR was stratified according to SCORE model for low-risk European countries as low ( $\leq 4\%$ ) and moderate/high ( $>4\%$ ). Vascular disease (VD): previous diagnosis of coronary, cerebrovascular or peripheral arterial disease. Diabetes was considered if fasting glucose  $>126$  mg/dl and/or previous diagnosis or treatment for diabetes.

**Results:** Table 1 shows the association (logistic regression: odds ratio, Confidence Interval (CI 95%) between CVR, VD/D, high blood pressure (HBP) and weight excess, average SL (CD or LA) length and cost per worker.

	OR (95% CI) CD SL-length	CD SL-cost	LA SL-length	LA SL-cost
SCORE risk $\geq 4\%$ vs $<4\%$	1.342 (1.281–1.406)	1.304 (1.245–1.366)	1.139 (1.075–1.208)	1.070 (1.009–1.134)
VD/D vs no VD/D	1.860 (1.753–1.973)	1.754 (1.653–1.861)	1.087 (0.989–1.182)	1.089 (1.001–1.184)
BP* 140/90–160/100** vs $<140/90$ mmHg	1.063 (1.034–1.093)	1.051 (1.022–1.080)	1.047 (1.013–1.083)	1.026 (0.992–1.061)
BP* $\geq 160/100$ vs $<140/90$ mmHg	1.122 (1.070–1.176)	1.075 (1.026–1.127)	1.116 (1.054–1.182)	1.078 (1.017–1.143)
BMI** 25–29.9 vs $<25$ kg/m <sup>2</sup>	1.115 (1.061–1.139)	1.159 (1.134–1.185)	1.126 (1.095–1.158)	1.163 (1.150–1.216)
BMI** $\geq 30$ vs $<25$ kg/m <sup>2</sup>	1.227 (1.194–1.262)	1.254 (1.219–1.290)	1.235 (1.193–1.278)	1.286 (1.244–1.334)

\*Adjusted for other covariates: age ( $\leq 45$  vs  $>45$  years), sex (men vs women), body mass index (BMI 25–29.9 vs  $<25$ ;  $\geq 30$  vs  $<25$ ), occupational categories (blue collar vs White collar), Labour contract (present or absent).

\*\*Adjusted for other covariates: age; sex; smoking (yes/no); glomerular filtration rate ( $<60$  ml/min/1.73m<sup>2</sup> vs  $\geq 60$  ml/min/1.73m<sup>2</sup>), occupational categories (blue collar vs White collar), Labour contract (present or absent).

**Conclusions:** Adjusted for other covariates, a high CVR, VD/D, HBP and obesity were associated with higher SL length and cost, constantly for common disease and frequently for labour accidents, which emphasize the importance of extending cardiovascular preventive strategies in the workplace both for the health and wellbeing of the workers and for reducing the economic burden of absence from work.

### LB2.6 DARUSENTAN LOWERS BLOOD PRESSURE SIGNIFICANTLY ON TOP OF MULTI-DRUG TREATMENT IN PATIENTS WITH RESISTANT HYPERTENSION

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**Objective:** Evaluate the efficacy and safety of darusentan (DAR), an oral ET<sub>A</sub>-selective endothelin receptor antagonist, in patients with resistant hypertension (RHTN) treated with full or maximally tolerated doses of  $\geq 3$  antihypertensive drugs, including a diuretic.

**Design and Methods:** In this Phase 3 randomized, double-blind, multicenter study, 379 patients with RHTN were randomized to placebo (PBO);



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# ABSTRACT BOOK

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