LATE-BREAKERS

EFFECTS OF BLOOD PRESSURE-LOWERING ON CANCER RISK: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS OF 300,000 PARTICIPANTS

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Objective: Evidence for the effects of pharmaceutical blood pressure (BP)-lowering on cancer risk is inconsistent and based on observational data. We therefore investigated the effect of BP-lowering on the risk of cancer in a large collaborative study.

Design and method: We included randomised trials participating in the Blood Pressure-Lowering Treatment Trialists’ Collaboration. Placebo-controlled trials, drug class comparison trials and trials comparing more-vs-less intensive BP-lowering that provided individual-level participant data (IPD) on cancer events were pooled. We investigated the effects of BP reduction on cancer risk by conducting one-stage IPD meta-analyses using Cox proportional hazard models, stratified by trial and accounting for competing risks. We also investigated effects stratified by age, gender, body mass index (BMI), smoking and previous antihypertensive use at baseline.

Results: This analysis included 300,098 participants (42% women) from 39 trials. At baseline, the mean age of participants was 66 (standard deviation [SD]=9), mean BMI was 28 (SD=5), 18% were current smokers and 75% were previously on BP-lowering medication. Over a median duration of 4 years, 16,748 participants were diagnosed with cancer, and 4547 cancer deaths were reported. The hazard ratio (HR) per 5mmHg reduction in systolic BP was 1.03 (95% confidence interval [CI] 0.99-1.07) for any cancer and 1.05 (95% CIs 0.98-1.12) for cancer death. We found heterogeneity in the effects of BP-lowering across age, gender, BMI and smoking groups for any cancer and cancer death, and across groups defined by previous antihypertensive use for any cancer. However, there was no evidence that BP-lowering significantly increased the risk of developing cancer in specific patient subgroups. We found no evidence for trends in increasing or decreasing risk over time for either outcome (P for trend: any cancer=0.98, cancer death=0.99).

Conclusions: This large-scale IPD meta-analysis found no evidence that BP-lowering had an important effect on cancer risk. Although we found that BP-lowering effects differed across several patient characteristics, there was no evidence for trend in cancer risk over time. We plan to further investigate the effects of BP-lowering on site-specific cancers (breast, colorectal, kidney, lung, prostate and skin) and present these results at the meeting.

THE ERYTHROCYTE MEMBRANES BETA-ADRENOREACTIVITY CHANGES AFTER RENAL DENERVATION AS A PROGNOSTIC FACTOR FOR THE LONG-TERM ANTIPHYPTENSIVE EFFICACY OF THE INTERVENTION

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Objective: To study the functional state of the sympatheodrenal system (SAS) assessed by the erythrocyte membranes beta-adrenoreactivity (beta-ARM) level, 7 days and 2 years after renal denervation (RD), to assess the prognostic capabilities of this indicator in relation to the long-term antihypertensive efficacy of the treatment.

Design and method: The study included 48 patients, 18 men and 30 women with resistant hypertension (RH) on stable antihypertensive therapy. The levels of mean daily systolic (SBP) and diastolic blood pressure (DBP), and level of beta-ARM at baseline, 7 days and 2 years after RD were studied. The beta-ARM determination based on erythrocytes hemolysis inhibition by the beta-blocker adding in hypoosmotic medium, that prevents their destruction by binding to erythrocyte membranes beta-adrenergic receptors. An increase in the beta-ARM value reflects a decrease in erythrocyte membranes beta-adrenergic receptors number on the background of prolonged sympathetic hyperactivation.

Results: The average daily blood pressure levels decreased from 160±16.088.1±14.6 mm Hg to 145±19.3/79.4±13.6 mm Hg (P=0.000) for 2 years. The beta-ARM dynamics was as follows: 43.8±19.9 conventional units (CE) initially, decreased to 40.5±17.0 CE after 7 days (P=0.05), and increased to 55.3±19.0 CE (P=0.008) after 2 years. At the same time, the beta-ARM decrease after 7 days was significant in the responders group (P=0.028), whose blood pressure after 2 years decreased by 10 mm Hg or more, and was absent in the non-responders group. There was a correlation between the dynamics of beta-ARM after 7 days and SBP and DBP in 2 years (r=0.54, p=0.05). This makes it possible to predict the RD long-term effectiveness.

Conclusions: The decrease in beta-ARM 7 after RD indicates the effectiveness of the procedure and allows us to expect a significant blood pressure decrease in the long term after surgery. Nevertheless, 2 years after RD a decrease in the erythrocyte membranes adrenergic receptors density is observed, probably through a negative feedback mechanism in response to ongoing sympathetic stimulation even against the background of a blood pressure decrease.

PROXIMAL TUBULE-SPECIFIC DELETION OF AT1A RECEPTORS ATTENUATES CIRCULATING AND INTRATUBULAR ANGIOTENSIN II-INDUCED HYPERTENSION IN MICE

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Objective: The present study used a novel mouse model with proximal tubule-specific knockout of AT1a receptors in the kidney, PT-Agr1a-/-, to test the hypothesis that intratubular angiotensin II (Ang II) and AT1a receptors in the proximal tubules are responsible for maintaining normal blood pressure and the development of Ang II-induced hypertension.

Design and method: To test our hypothesis, eight groups (n=7-15 per group) of adult male wild-type, global Agr1a-/-, and PT-Agr1a-/-, and PT-Nhe3-/- mice were infused with Ang II (1.5 mg/kg/day, i.p.), or overexpressed an intracellular Ang II fusion protein (Ad-gsp22-ECFP/Ang II) in the proximal tubules of the kidney for 2 weeks. Basal blood pressure and the pressor responses, glomerular filtration rate (GFR) and 24 h urinary natriuretic response, and the pressure-natriuresis response were determined.

Results: Basal telemetry blood pressure were ~15 ± 3 mmHg lower in PT-Agr1a-/- than wild-type mice and ~13 ± 5 mmHg higher than Agr1a-/- mice (P<0.01). Basal glomerular filtration was ~23.9% higher (P<0.01), whereas fractional proximal tubule Na+ reabsorption was lower in PT-Agr1a-/- mice (P<0.01). Deletion of AT1a receptors in the proximal tubules augmented the pressure-natriuresis response (P<0.01), and natriuretic responses to salt loading or Ang III infusion (P<0.01). Ang II induced hypertension in wild-type, PT-Agr1a-/- and PT-Nhe3-/- mice, but the pressor response was ~16 ± 2 mmHg lower in PT-Agr1a-/- and PT-Nhe3-/- mice (P<0.01). Deletion of AT1a receptors or NHE3 in the proximal tubules attenuated ~50% of Ang II-induced hypertension in wild-type mice (P<0.01), but blocked intracellular Ang II fusion protein-induced hypertension in PT-Agr1a-/- mice (P<0.01).

Conclusions: Taken together, the results of the present study provide new insights into the critical role of intratubular Ang II/AT1a/NHE3 pathways in the proximal tubules in normal blood pressure control and the development of Ang II-induced hypertension.