LONG TERM BENEFITS OF BLOOD PRESSURE TREATMENT ON THE INCIDENCE OF ATRIAL FIBRILLATION, HEART FAILURE AND CARDIOVASCULAR MORBIDITY AND MORTALITY: 20-YEARS FOLLOW-UP OF ASCOT-LEGACY

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Objective: Previously, we reported 16-year cardiovascular (CV) mortality associated with either atenolol- or amloidipine-based treatment regimen; but without data on non-fatal CV events. We now report longer morbidity and mortality including the impact of BP-treatment on the incidence of atrial fibrillation and heart failure.

Design and method: In the ASCOT-Legacy Study, 8580 hypertensive patients (4275 assigned to atenolol+-/diuretic-based and 4305 to amloidipine+/perindopril-based treatment) were followed in the UK for the maximum duration of 21 years (IQR: 9.1-19.3 years). All fatal/non-fatal CV events during the trial period and the post-trial mortality events were independently adjudicated. Post-trial morbidity events were evaluated using electronic health records. Cox proportional hazards were estimated for the first occurrence of atrial fibrillation, fatal/non-fatal HF, non-fatal/fatal stroke (stroke), non-fatal/fatal coronary heart disease (CHD), total coronary events and total CV events in two treatment arms. Analyses were adjusted for a-priori confounders (See table). Interaction, if any, with associated statin therapy was evaluated. We also did a sensitivity analysis using only post-trial data.

Results: During the in-trial period of 5.5 years, the cumulative mean SBP was marginally higher for those on atenolol-based treatment compared to those on amloidipine-based treatment (138.0 [SD,10.8] and 136.3 [9.9] mm Hg, respectively). Table 1 shows the crude and adjusted hazard ratios (HRs) associated with the two treatment regimens. Those on amloidipine-based (vs. atenolol-based) treatment had significantly reduced risk of atrial fibrillation [0.91, 95% CI, 0.83 to 0.99], total coronary events [0.92, 0.86 to 0.96], stroke [0.82, 0.72 to 0.93] and total CV events [0.93, 0.88 to 0.98]. There was no significant difference in the incidence of heart failure or CHD, although there was a nominal reduction. No evidence of interaction with statin therapy was noted. Post-trial significant differences were apparent for stroke, total coronary events and total CV events.

Conclusions: Allocation to an amloidipine-based treatment has a long-term beneficial CV effect, particularly on stroke and total coronary and CV events. Reduction in the risk new-onset atrial fibrillation may be an important mediator of this legacy effect.

SAFETY, PHARMACODYNAMICS, AND BLOOD PRESSURE EFFECTS OF ALN-AGT, AN RNA INTERFERENCE THERAPEUTIC TARGETING ANGIOTENSINOGEN, IN A RANDOMIZED SINGLE ASCENDING DOSE STUDY OF HYPERTENSIVE ADULTS

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Objective: Angiotensinogen (AGT) is the sole precursor of all angiotensin peptides and plays a key role in hypertension pathogenesis. We evaluated the effect of ALN-AGT, a subcutaneous investigational RNA interference (RNAi) therapeutic targeting hepatic AGT synthesis, on blood pressure in hypertensive patients.

Design and method: As part of a phase 1 program designed to assess the safety and tolerability of ALN-AGT, we conducted a multicenter study randomizing patients aged 18-65 years with mild to moderate hypertension (mean seated systolic blood pressure [SBP] >130 and >165 mmHg after washout of antihypertensive medication) 2:1 to ascending single doses of ALN-AGT or placebo. Change from baseline in BP at 8 weeks was measured by ambulatory BP monitoring (ABPM). We report interim results as of Oct 27, 2020.

Design and method: Eighty-four patients (mean age 53 years, 39% female, mean baseline 24 h SBP 139.7 ± 8.9 mm Hg) were enrolled in ascending dose cohorts of 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg or 800 mg. Dose-related reductions in serum AGT levels were observed (figure), with mean reductions of >90% at doses >100 mg. AGT remained durably reduced through 12 weeks after single dose administration (data pending for 800 mg cohort). Concomitant reductions in BP from baseline were observed with AGT knockdown, with mean reductions in 24-hour SBP of >10 mm Hg observed at Week 8 after single doses of 100 mg or higher. No treatment-related serious adverse events or clinically significant elevations in blood creatinine or potassium were seen. No patient required intervention for low blood pressure.

Results: Single dose administration of ALN-AGT to hypertensive patients was generally well tolerated and resulted in dose-related reductions in serum AGT and BP over 8 weeks. Durable AGT knockdown to 12 weeks supports further evaluation of once quarterly or potentially less frequent dose administration.

BLOOD PRESSURE-LOWERING, ANTHYPERTENSIVE TREATMENT AND INCIDENT DIABETES

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Objective: To investigate the effect of blood pressure lowering and specific antihypertensives on the risk of new-onset type 2 diabetes, leveraging the strengths of both genetic data and individual-level data from randomised trials of blood pressure-lowering treatments.

Design and method: We pooled individual-level data of 145,939 participants from nineteen randomised clinical trials. We used stratified Cox proportional hazard models, with fixed treatment effects, and participants as the unit of analysis. Analyses were complemented with Mendelian randomisation studies using naturally randomised genetic variants associated with systolic blood pressure and genetic variants encoding the therapeutic targets of each drug class.

Results: After a median of 4.4 years follow-up, 9,883 participants were diagnosed with new-onset diabetes in clinical trials. Blood pressure-lowering treatment was...