

## Genetic susceptibility, elevated blood pressure and risk of atrial fibrillation

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**Background:** Whether elevated blood pressure (BP) is a modifiable risk factor for atrial fibrillation (AF) is not established.

**Purpose:** We tested (1) whether the association between BP and risk of AF is causal, (2) whether it varies according to individual's genetic susceptibility for AF, and (3) the extent to which specific BP-lowering drugs are expected to reduce this risk.

**Methods:** First, causality of association was assessed through two-sample Mendelian Randomization (MR), using data from two independent genome-wide association studies that included a total of one million European population. Second, UK Biobank individual participant data of 329,237 participants at baseline was used to study the effect of BP on AF according to genetic susceptibility of developing AF. Third, a possible treatment effect with BP-lowering drug classes on AF risk was predicted through genetic variants in druggable genes that code proteins related to the function of each drug class. Estimated drug effects were compared with effects on incident coronary heart disease, for which direct trial evidence exists.

**Results:** The two-sample MR analysis indicated that on average each 10-mm Hg increment in systolic BP increased the risk of AF (odds ratio [OR]: 1.23 [1.11 to 1.36]). This association was replicated in the UK biobank using individual participant data. However, in a further genetic risk-stratified analysis, there was evidence for a linear gradient in the relative effects of systolic BP on AF; while there was no conclusive evidence of an effect in those with low genetic risk, a strong effect was observed among those with high genetic susceptibility for AF (Figure). The indirect comparison of predicted treatment effects using genetic proxies for three main drug classes (angiotensin-converting enzyme inhibitors, beta-blockers and calcium channel blockers) suggested similar average effects for prevention of atrial fibrillation and coronary heart disease.

**Conclusions:** The association between elevated BP and higher risk of AF is likely to be causal, suggesting that BP-lowering treatment may be effective in AF prevention. However, average effects masked clinically important variations, with a more pronounced effect in individuals with high genetic susceptibility.

**Figure.** Stratified Mendelian randomisation effect of genetically-predicted higher systolic blood pressure and risk of atrial fibrillation by genetic susceptibility for atrial fibrillation.

Analysis adjusted for age, sex, body mass index, genotype measurement batch, alcohol intake frequency, smoking status, genetic kinship to other participants, UK Biobank assessment center and 10 genetic principal components (population stratification adjustment). AF: atrial fibrillation; OR: odds ratio per 10 mmHg higher systolic blood pressure; CI: confidence interval.

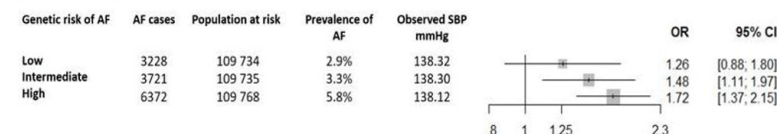


Figure 1