

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

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## Abstract

**Background:** Whether elevated blood pressure (BP) is a modifiable risk factor for atrial fibrillation (AF) is less clear. 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:** Causality of association was assessed using two-sample Mendelian Randomization (MR) framework through different statistical methods. A stratified MR approach was used to study the effect of BP on AF according to genetic susceptibility of developing AF. The effect of BP-lowering drug classes on AF risk was assessed through variants in druggable genes that code proteins related to the function of each drug class.

**Results:** Each 20-mmHg increase in genetically-determined systolic BP was associated with an approximately 60% higher odds of AF (odds ratio [OR]: 1.61 [95% CI 1.34 to 1.94]). Risk-stratified analyses further showed significant evidence for interaction in the effect of SBP on AF, with no significant effect on AF risk in those with low genetic risk (OR: 1.23 [95% CI 0.64 to 2.35]) and a strong effect among those with high genetic susceptibility for AF (OR: 2.67 [95% CI 1.77 to 4.04]). Each 10 mmHg decrease in SBP determined through genetic score for beta-blockers showed a 21% lower risk of AF (OR: 0.79 [CI 95% 0.69 to 0.91]), and when using the calcium channel blockers genetic score, a 14% lower risk of AF (OR: 0.86 [CI 95% 0.82 to 0.91]).

**Conclusions:** The association between elevated BP and increased risk of AF is likely to be unconfounded, with a more pronounced impact in individuals with high genetic susceptibility.