Background: Observational evidence indicates that patients with atrial fibrillation (AF) are at a four- to fivefold increased risk of stroke. By two-sample mendelian randomization (MR), we have shown in our previous work that specifically the cardioembolic stroke subtype is caused by AF. This risk elevation is however variable and appears to be modulated by other risk factors such as hypertension traits and coronary artery disease (CAD).

Purpose: This study seeks to determine (1) whether genetic predisposition to cardioembolic stroke by AF is independent from modulators, and (2) whether the other stroke subtypes are causally linked with different exposures.

Methods: The associations between AF, hypertension traits, and CAD as exposures and stroke subtypes as outcomes were individually tested in a two-sample mendelian randomisation (MR) analysis using genetic instruments from publicly available genome-wide association studies (GWAS) in large cohorts. For atrial fibrillation, genetic instruments were obtained from the dataset by Nielsen et al. with 60,620 atrial fibrillation cases and 970,216 controls, collected from six contributing studies including the AFGen Consortium. Associations with stroke subtypes were evaluated in the MEGASTROKE genome-wide association study data set (67,162 cases; 454,450 controls). The genetic markers for hypertension traits were taken from a GWAS by Evangelou et al. which combines data from the UK Biobank (UKB) and the International Consortium of Blood Pressure (ICBP) with a total sample size of 757,601 individuals. Genetic instruments for CAD were obtained from the CARDioGRAMplusC4D consortium (60,801 cases and 123,504 controls from 48 studies). Several MR regression methods such as MR-Egger regression and inverse-variance weighted regression as well as sensitivity analyses were applied. A multivariable MR model served to determine which of the exposures had an independent causal effect on each of the stroke subtypes.

Results: Atrial fibrillation turned out to be the sole independent causal risk factor for cardioembolic stroke with a beta coefficient of 0.75 (SE = ±0.04; P = 8.59 x 10e-100) and an OR of 2.16 (1.97-2.27) in a multivariable model adjusted for AF, CAD, systolic blood pressure (SBP) and diastolic blood pressure. In this model, SBP and CAD were non-causative for cardioembolic stroke, but exhibited significant, albeit weak causal associations with small vessel stroke (SBP: OR 1.04 (1.02-1.06); CAD: OR 1.14 (1.02-1.28)) and large artery stroke (SBP: OR 1.09 (1.06-1.11); CAD: OR 1.59 (1.40-1.79)).

Conclusions: Causality of the association between the cardioembolic stroke subtype and AF is independent from modulators such as SBP and CAD. However, SBP and CAD play a complementary role as causal exposures for small vessel and large artery stroke which in turn are not causally linked with AF.