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Genetically determined blood pressure, antihypertensive drug classes, and risk of stroke subtypes

Marios K. Georgakis, MD, PhD, Dipender Gill, MD, PhD, Alastair J.S. Webb, DPhil, et al.

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Correspondence
Dr. Dichgans
martin.dichgans@
med.uni-muenchen.de

Study objective

To explore, using Mendelian Randomization, whether the effects of blood pressure (BP) and BP lowering through different antihypertensive drug classes on stroke risk vary by stroke etiology.

What is known and what this paper adds

BP and pharmacotherapy-based BP-lowering regimens are determinants of stroke risk. This study supports a causal role of hypertension in all major stroke subtypes except lobar intracerebral hemorrhage (ICH), and identifies calcium channel blockers (CCB) as promising for prevention of cerebral small vessel disease (SVD).

Participants and setting

Genetic variants associated with BP or the BP lowering effect of antihypertensive medications were assessed in genome-wide association study (GWAS) data from 757,601 patients sourced from a meta-analysis of the International Consortium for BP and the UK Biobank. Genetic associations with stroke were determined using data from the MEGASTROKE multiethnic GWAS that included 67,162 patients with stroke and 454,450 stroke-free controls and from an International Stroke Genetics Consortium (ISGC) meta-analysis that included 1,545 patients with intracerebral hemorrhage (ICH) and 1,481 stroke-free controls.

Design, size, and duration

GWAS data were used to identify single-nucleotide polymorphisms (SNPs) associated with systolic BP (SBP) or diastolic BP (DBP), as well as a list of SBP-associated SNPs in genes that encode targets for common antihypertensive drug classes. Associations with any stroke, ischemic stroke and its subtypes, intracerebral hemorrhage (ICH, deep and lobar), and SVD and white matter hyperintensities (WMH) were examined using 2-sample Mendelian randomization.

Primary outcome measures

The primary outcome was the association of the SNPs noted above with the risk of stroke and stroke subtypes.

Table Selected associations between genetically determined BP and stroke risk

	Odds ratio (95% confidence interval) for stroke per	
Stroke type	10-mm Hg increment in SBP	5-mm Hg increment in DBP
Any stroke	1.39 (1.33–1.44)	1.27 (1.23–1.32)
Ischemic stroke	1.41 (1.35–1.47)	1.28 (1.24–1.33)
ICH	1.41 (1.11–1.79)	1.29 (1.05–1.57)

Main results and the role of chance

Genetic predisposition to higher SBP and DBP was associated with higher risk of any stroke, ischemic stroke, and ICH, as well as all ischemic stroke subtypes (with a higher risk of large artery and small vessel stroke compared to cardioembolic stroke), and deep, but not lobar ICH. Genetically determined BP and genetic proxies for calcium channel blockers, but not beta blockers, were associated with lower risk of any stroke and ischemic stroke. Proxies for CCBs showed particularly strong associations with SVD and WMH.

Bias, confounding, and other reasons for caution

Mendelian randomization analyses include the lifetime effects of genetically determined BP, which may differ from the effect of a clinical antihypertensive intervention. The present study could not provide analyses for angiotensin-converting enzyme inhibitors. Participants were all from European ancestry.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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