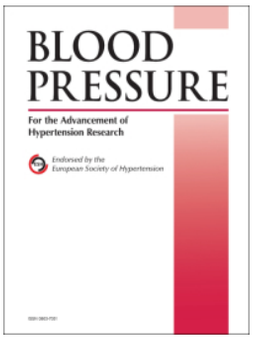

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Predictive value of new cardiovascular tools for stroke risk reclassification

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Key points

- About 30% of ischaemic strokes are of undetermined origin. A large proportion of people without prior atrial fibrillation (AF) experience embolic events.
- Novel cardiovascular morphological and functional assessment tools can be implemented in stroke risk scores.
- There is a need for an easy-to-apply transition in clinical practice from population based-scoring and traditional risk factors towards individualised stroke risk reclassification tools. This will help guide preventive and therapeutic decisions.

Plain language summary

Ischaemic stroke is one of the major underlying causes of cardiovascular disease mortality and disability.

There is some ambiguity about the meaning of "reclassification" in the literature, which has led to the definition of two main problems:

- Primary prevention - to re-stratify individuals at intermediate risk for developing ischaemic stroke into low or high-risk groups (requiring interventions for risk reduction). While stroke-related risk factors (arterial hypertension, dyslipidemia, current smoking, history of diabetes mellitus, myocardial infarction) are relatively established [1], there is a residual risk for stroke, that cannot be entirely explained by conventional cardiovascular risk or AF recurrence (Figure 1). Prevention in individuals at intermediate risk is problematic as the potential benefit of treatment should outweigh the potential harm.
- Secondary prevention - to identify the exact origin of the undetermined (unknown origin) type of ischaemic stroke - an embolic stroke of undetermined source (ESUS) (31%), followed by cardiac embolisms (29%), small-vessel occlusion (21%), large-artery atherosclerosis (15%), other determined origins (5%) [1].

In this context, we reviewed easily applicable tools that can be added to known population-based scores to improve individual stroke risk reclassification (Figure 1).

Vascular risk modifiers

Circadian rhythm of blood pressure

Current arterial hypertension treatment focuses on achieving target blood pressure (BP) levels. Even if mean BP is controlled, impaired BP variability, abnormal dipping pattern or morning surge increase the risk for unrecognised stroke. The circadian pattern of stroke incidence proved to be similar, regardless of stroke subtype [2]. Therefore, an ambulatory 24-hour BP profile yields additional prognostic value in stroke risk assessment in hypertensive patients.

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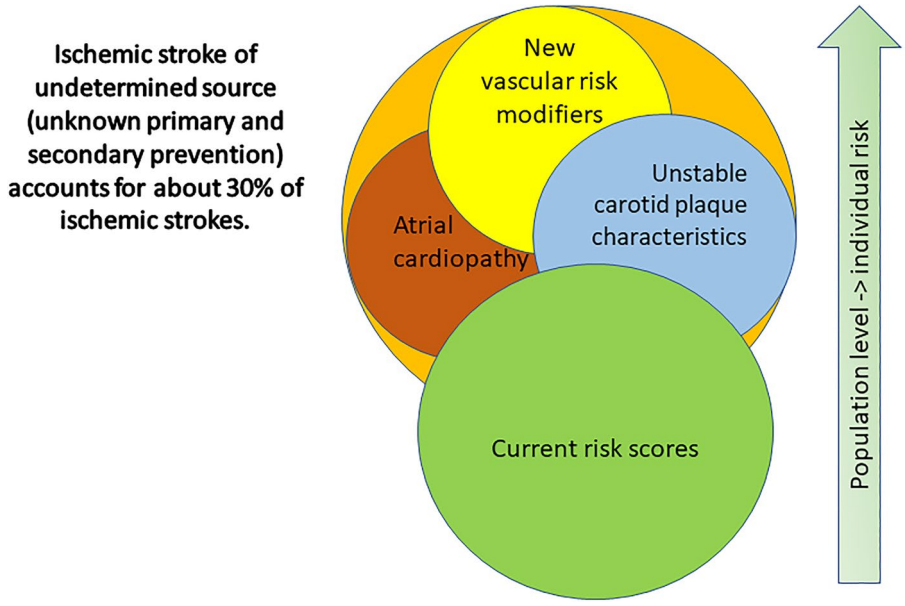

Figure 1. Visual interpretation of the need for new cardiovascular tools for stroke risk reclassification.

Arterial stiffness

Arterial stiffness is a marker of early vascular ageing (a result of the cumulative effect of risk factors) and a causative factor for developing hypertension and cardiovascular events. Increased pulse wave velocity (PWV), a direct marker of arterial stiffening, was found as an independent predictor for incident stroke and stroke recurrence in patients with lacunar infarctions [3]. The mechanisms underlying the adverse effect of elevated PWV on cerebral vasculature include (1) high pulsatile energy flow reaching the high-flow-low-resistance target organ; and the hemodynamic mismatch between aortic reverse/forward flow in the structurally modified aortic arch which may contribute to atherosclerotic embolic stroke *via* accelerated reverse/diastolic flow [4].

Atrial cardiopathy

Aortic stiffness is associated with impaired ventriculo-arterial coupling, followed by diastolic dysfunction of the left ventricle, symptoms of heart failure (with preserved ejection fraction), hemodynamic, and subsequently morphological changes in the left atrium (LA) [5]. Changes in the LA structure and function can be subclinical, but still associated with a significant risk for stroke. The Cardiovascular Health Study [6] found that among 3 723 adults ≥65 years without a history of stroke or atrial fibrillation (AF), 583 subjects had a stroke during a median of 12.9 years follow-up. The factors associated with stroke risk were atrial cardiopathy markers (i. e. P wave terminal force in V1 on ECG, NT-pProBNP, and incident AF). LA enlargement (LAE) was independently associated with an increased risk of ischaemic stroke in the absence of AF. When combined with Holter-recorded excessive atrial ectopy, LAE improves stroke risk prediction independently from CHA_2DS_2-VASc in subjects with no known AF [7]. The functional assessment of LA strain and strain rate is a further approach to stroke risk reclassification. While LA may remain normal in size and volume, and the actual hemodynamic parameters may be compensated, LA function can be impaired [8]. The presence of aortic stiffness, a marker of hypertension-mediated organ damage, is independently associated with LA function, even in the absence of overt cardiovascular disease, supporting the concept for screening and early diagnosis of atrial cardiopathy in hypertensive patients with increased PWV.

Reclassification tools

Nearly half of the patients with ESUS can be reclassified into cardio-embolic, atherogenic, or mixed between the two types. Intermediate carotid atherosclerotic plaques (<50%) may be a potential source of embolism. Furthermore, the detection of intraplaque haemorrhage (IPH) on carotid MRI is strongly associated with future risk of stroke irrespective of symptoms or carotid stenosis degree and is a stronger predictor of stroke than any known clinical risk factors [9]. IPH can reclassify up to 15% of ischaemic strokes [10]. Given that cardio-embolic strokes had an ipsilateral unstable carotid plaque, cardio-embolic

strokes can be partially reclassified into multiple aetiologies or large-artery atherosclerosis which has therapeutic and secondary preventive implications. Ipsilateral carotid plaque, aortic arch plaque, or contralateral carotid stenosis >50% may significantly increase the risk of large-artery stenosis stroke, explaining several potential ESUS origins [11]. In the NAVIGATE-ESUS trial [12] 41% of patients had multiple potential embolic sources and the recurrence rates between patients on rivaroxaban or aspirin were not significantly different. A better understanding of the pathogenesis and stroke phenotypic subtype is urgently needed to treat properly ESUS. The current multiple risk factor scores may not be the best choice for individual embolism risk assessment because their power is low, and adding specific risk factors may increase specificity. A recent meta-analysis showed that improving current scores may increase discriminatory abilities in patients with AF [13], however patients without known AF may remain at an unrecognised risk. A further promising approach in predicting atrial cardiopathy is the presence of biochemical markers for LA volume overload (BNP, galectin 3) and excessive fibrosis (Pro-collagen type III N-terminal pro-peptide (PIIINP), C-telopeptide of type I collagen (ICTP), and fibroblast growth factor 23 (FGF-23) [14].

Conclusion

A better understanding of the origin of strokes with an undetermined source is essential for appropriate treatment. Consideration of individual factors such as PWV, left atrial cardiopathy markers (i.e. electrical, imaging, and biochemical), and carotid plaque characteristics may complement current population stratification scores and minimize individual stroke risk.

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References

[1] Adams H, Jr., Bendixen B, Kappelle L, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. Stroke. 1993;24(1):1–5. doi:10.1161/01.STR.24.1.35.

[2] Fodor D, Marta M, Perju-Dumbrava L. Implications of circadian rhythm in stroke occurrence: certainties and possibilities. Brain Sci. 2021;11(7):865. doi:10.3390/brainsci11070865.

[3] Saji N, Murotani K, Shimizu H, et al. Increased pulse wave velocity in patients with acute lacunar infarction doubled the risk of future ischemic stroke. Hypertens Res. 2017;40(4):371–375. doi:10.1038/hr.2016.157.

[4] Hashimoto J, Ito S. Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta. Potential implication for retrograde embolic stroke in hypertension. Hypertension. 2013;62(3):542–549. doi:10.1161/HYPERTENSIONAHA.113.01318.

[5] Chirinos J, Sweitzer N. Ventricular-arterial coupling in chronic heart failure. Card Fail Rev. 2017;3(1):12–18. doi:10.15420/cfr.2017:4:2.

[6] Kamel H, Bartz T, Elkind M, et al. Atrial cardiopathy and the risk of ischemic stroke in the cardiovascular health study. Stoke. 2018;49(4):980–986. doi:10.1161/STROKEAHA.117.020059.

[7] Edwards J, Healey J, Fang J, et al. Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. J Am Heart Assoc. 2020;9(11):e013227. doi:10.1161/JAHA.119.013227.

[8] Habibi M, Zareian M, Venkatesh B, et al. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: insights form the MESA study. JACC Cardiovasc Imaging. 2019;12(12):2417–2427. doi:10.1016/j.jcmg.2019.02.021.

[9] Schindler A, Schinner R, Altaf N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-Analysis of individual patient data. JACC Cardiovasc Imaging. 2020;13(2):395–406. doi:10.1016/j.jcmg.2019.03.028.

[10] Kamel H, Navi BB, Merkler AE, et al. Reclassification of ischemic stroke etiological subtypes on the basis of High-Risk nonstenosing carotid plaque. Stroke. 2020;51(2):504–510. doi:10.1161/STROKEAHA.119.027970.

[11] Hoshino T, Mizuno T, Nishimura A, et al. Reclassification and risk stratification of embolic stroke of undetermined source by ASCOD phenotyping. Int J Stroke. 2023;18(3):322–330. doi:10.1177/17474930221096953.

[12] Ntaios G, Pearce L, Veltkamp R, et al. Potential embolic sources, and outcomes in embolic stroke of undetermined source in the NAVIGATE-ESUS trial. Stroke. 2020;51(6):1797–1804. doi:10.1161/STROKEAHA.119.028669.

[13] van der Endt VHW, Milders J, Penning de Vries BBL, et al. Comprehensive comparison of stroke risk score performance: a systematic review and meta-analysis among 6 267 728 patients with atrial fibrillation. Europace. 2022;24(11):1739–1753. doi:10.1093/europace/euac096.

[14] Begg G, Karim R, Oesterlein T, et al. Intra-cardiac and peripheral levels of biochemical markers of fibrosis in patients undergoing catheter ablation for atrial fibrillation. Europace. 2017;19(12):1944–1950. doi:10.1093/europace/euw315.