

Statins for all:

should patients who have migraine with aura be on a statin?

Over the past decade there has been increasing recognition of the importance of statins in preventing cardiovascular disease and, despite concerns of potential side-effects, in their use in populations who are at a lower risk.

Inflammatory conditions are known to increase cardiovascular risk, and rheumatoid arthritis is now recognised as a relevant factor in risk algorithms. Migraine is fundamentally an inflammatory problem triggered by activation of the trigeminal neurovascular complex. Should this be included in a risk analysis?

BACKGROUND

Migraine affects 7.6% of males and 18.3% of females in England.¹ Thirty per cent of patients with migraine, or 'migraineurs', have migraine with aura, a transitory motor or sensory, positive or negative, neurological phenomenon lasting <1 hour that typically precedes the headache. An aura is a wave of depolarisation that travels at 3 mm/minute across the cortex and is associated with an oligoemia that is less than the ischaemic threshold. The relationship between depolarisation, blood flow, and headache is not understood.

Although epidemiology is confounded by migraine diagnostic concerns, a recent meta-analysis of migraine and cardiovascular disease found significant risks for those who had aura, but no increased risk for migraine without aura. Ischaemic stroke was the main concern with an overall odds ratio (OR) of 2.51 [95% confidence interval (CI) = 1.52 to 4.14] with increased risks for females (OR 2.89; 95% CI = 2.43 to 3.45).² Another meta-analysis showed increased risk in patients aged <45 years (OR 2.65; 95% CI = 1.41 to 4.97), smokers (OR 9.03; 95% CI = 4.22 to 19.34), and females using combined oral contraception (OR 7.02; 95% CI = 1.51 to 32.68).³ The data on an association with ischaemic heart disease have been more variable, but recent studies have shown a doubling of risk for migraine with aura.⁴

Cardiovascular risks are higher in those who experience >12 attacks a year (OR 1.7; 95% CI = 1.1 to 2.8).⁵ Should migraine with aura be included in a formal risk assessment? If so, what should the multiplication factor be and should the frequency of migraine be taken into account?

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POSSIBLE MECHANISMS RELATING MIGRAINE WITH AURA TO VASCULAR DISEASE

Although migraine with aura is associated with increase in risk factors, such as smoking, cholesterol, and blood pressure, these cannot account for the increased vascular risk, and the relationship is likely to be independent of other risk factors.⁶ Migraineurs who have aura demonstrate progressive white-matter hyperintensities on MRI, which are related to headache load. These lesions have a similar appearance to the microvascular changes that occur in older people, although surprisingly their exact nature has not been confirmed.⁷

The underlying mechanism that gives rise to vascular risk is unknown, but possibilities include the following.

- **Endothelial dysfunction.** The endothelium is a complex organ that responds to a number of factors, including blood flow. A number of abnormal vascular biomarkers have been identified including endothelial microparticles that are thought to play a part in vascular control. However, studies on vascular reactivity have been mixed, without any formal conclusions.
- **Platelet abnormalities.** Platelets of migraineurs show high levels of 5-hydroxytryptamine, a substance known to be implicated in the migraine process. They also show increased adherence. However, population studies have not been conclusive and there is no evidence

that aspirin or clopidogrel have an impact on migraine frequency.

- **Microemboli.** Migraineurs with aura have an increased incidence of patent right-to-left cardiac shunts, and retrospective analysis of closure in migraineurs for other reasons has shown significant benefit. The suggestion was that vasoactive substances or microemboli were bypassing the pulmonary circulation, which may act as a vascular filter. However, a controversial prospective randomised controlled trial showed no evidence of benefit of foramen closure.⁸
- **Drug induced.** Triptans, widely used in migraine, have vasoconstrictive properties. However, a systematic review of observational studies showed no impact.^{8,9}

IMPLICATIONS FOR CLINICAL PRACTICE

In the UK, based on a cost-utility analysis, the National Institute for Health and Care Excellence has recommended that statins are introduced when the 10-year risk of cardiovascular disease is 10%.¹⁰ The Framingham risk assessment tool has been superseded by QRISK®2.¹¹

As studies give different estimates of risk, albeit all raised, and no definitive mechanisms or vascular biomarkers have been identified, a pragmatic approach taking an approximate average of existing studies seems indicated. Inevitably this will be a subjective judgement, but until further

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Table 1. 10-year risk of cardiovascular disease derived from QRISK®2 for migraineurs with aura versus no migraine in the absence of any other risk factors^a

Total cholesterol, ^b mmol/L	10-year risk of CVD Migraine with aura (no migraine), males, %	10-year risk of CVD Migraine with aura (no migraine), females, %
Age 35 years		
7.0	1.4 (0.9)	1.25 (0.5)
6.0	1.2 (0.8)	1.25 (0.5)
5.0	1.1 (0.7)	1.0 (0.4)
Age 45 years		
7.0	5.1 (3.4)	4.0 (1.6)
6.0	4.4 (3.0)	3.5 (1.4)
5.0	3.9 (2.6)	3.3 (1.3)
Age 55 years		
7.0	13.1 (8.7)	10.5 (4.2)
6.0	11.4 (7.6)	9.5 (3.8)
5.0	10.1 (6.7)	8.4 (3.4)

^aMales of average height and weight (177 cm, 79 kg) and average HDL 1.2 and females of average height and weight (164 cm, 69 kg) and average HDL 1.4. The 10-year risk is multiplied by 2.5 for female and 1.5 for male migraineurs with aura. ^bNon-smoker, systolic blood pressure 130 mmHg. No other risk factors. CVD = cardiovascular disease.

data are forthcoming my suggestion is that, as a basis for discussion with the patient, the 10-year risk is multiplied by 2.5 for female and 1.5 for male migraineurs with aura. Lower treatment thresholds should be considered for younger patients, and for migraineurs who experience >12 attacks a year, as risks are likely to be higher in these groups. The importance of other risk factors and in particular smoking should be emphasised.

What does this mean in practice for the 4% of the population who have migraine with aura? Examples of clinical profiles and their risks derived from QRISK®2 are shown in Table 1. This reflects the fact that

underlying vascular risk remains greater in males and increases with age, and the additional workload for GPs in patients without other risk factors is likely to be small. Due to our limited knowledge of the mechanisms through which migraine operate these calculations will be imprecise, but are a useful starting point. They alert us to the fact that, in the absence of other risk factors, age still remains the most significant consideration.

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