

## Left atrial enlargement: A cause of stroke?

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See related research article by Bouzas-Mosquera and colleagues on page E657 and at [www.cmaj.ca/lookup/doi/10.1503/cmaj.091688](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.091688).

Although there are a variety of established risk factors for ischemic stroke and its common pathophysiologies are well known, a specific cause remains undefined in 25%–40% of instances. That rate is influenced in part by the thoroughness of the poststroke evaluation.<sup>1</sup> A cause, however, can remain undetermined in up to 12% of patients having an acute event, even with a full diagnostic assessment.<sup>2</sup>

At least part of the diagnostic uncertainty can be related to the impact of relatively unrecognized risk factors. For example, the most widely used stroke risk assessment tool, the Framingham stroke risk profile, includes the following well-recognized stroke risk factors: age, systolic blood pressure, use of antihypertensive medications, diabetes mellitus, smoking, having cardiovascular disease, atrial fibrillation and left ventricular hypertrophy on electrocardiography.<sup>3</sup> Although this tool is useful, many people have strokes despite a low Framingham stroke risk profile score, which does not incorporate a variety of less established risk factors. In this week's *CMAJ*, Bouzas-Mosquera and colleagues<sup>4</sup> describe an independent, graded association between left atrial size on electrocardiography and stroke risk in women but not in men. Prior studies reported a similar relation between left atrial size and ischemic stroke risk in men, but not in women.<sup>5,6</sup>

The reason for the discrepancy among these studies is uncertain, and the findings need to be validated through replication in other patient populations. Bouzas-Mosquera and coauthors posit that the variability among reports might be a result of differences in study populations. Another possibility is that left atrial enlargement is a risk marker that only indirectly reflects one or a combination of risk factors. For example, left atrial enlargement is associated with an increased risk of atrial fibrillation,<sup>7</sup> which is a major stroke risk factor that may become apparent only with prolonged and repeated cardiac monitoring.

Left atrial enlargement also might be a marker for other conditions that could increase stroke risk. For example, left atrial dysfunction can occur in patients with a patent foramen ovale.<sup>8</sup> Patent foramen ovale (not assessed in the study

by Bouzas-Mosquera and colleagues) is found more commonly in patients with cryptogenic stroke than in those with no history of stroke or in those who have stroke of determined cause.<sup>9</sup> Paradoxical embolism through a patent foramen ovale may be important in the pathophysiology of acute stroke in patients with deep vein thrombosis, a relatively rare event.

The role of patent foramen ovale in patients without a source of embolism is less certain. There is no difference in the rate of recurrent stroke between groups of patients with otherwise cryptogenic stroke who do or do not have a patent foramen ovale, regardless of the type of medical treatment (antiplatelet medication v. anticoagulation). One randomized trial with results reported in abstract form (CLOSURE-1, 2011 International Stroke Conference) found no difference in the risk of recurrent stroke between patients treated with endovascular patent foramen ovale closure versus those receiving medical therapy. Additional clinical trials are in progress.

Studies also emphasize the important relation between lifestyle factors and stroke risk. Men and women who follow five lifestyle behaviours (not smoking, having a healthy diet, getting at least 30 min. per day of moderate or vigorous physical activity, having an optimal weight and consuming alcohol in moderation [no more than one alcoholic drink/day for women or one to two for men]) have an 80% lower risk of a first stroke as compared with those not following these behaviours, with increasing benefit depending on the number of lifestyle factors followed.<sup>10</sup> The study by Bouzas-Mosquera and colleagues adjusted for cigarette smoking, but not these other lifestyle behaviours, which also affect the risk of cardiac disease.

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Please see end of article.

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### KEY POINTS

- The cause of stroke is frequently uncertain.
- Traditional risk factors do not fully explain the cause of stroke in many people.
- Several studies report a novel association between left atrial enlargement and stroke, but vary regarding whether the relation is present in men as compared with women.
- Left atrial enlargement may be a risk marker rather than a risk factor.

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Several other novel risk factors not assessed in the study by Bouzas-Mosquera and colleagues are common to both stroke and cardiac disease. For example, a large number of studies point to a relation between both systemic inflammation and chronic infection and the risk of stroke as well as cardiac events.<sup>11</sup> Trials of antibiotics, however, have not shown benefit in lowering the risk of recurrent coronary events.<sup>12,13</sup> Similarly, treatments aimed at eliminating or controlling chronic infections have not proven to be helpful for the prevention of stroke.<sup>10</sup> Inflammatory biomarkers such as high-sensitivity C-reactive protein and lipoprotein-associated phospholipase A2 are also independently associated with cardiovascular and stroke risk. One study found that treatment of patients with high blood levels of high-sensitivity C-reactive protein with a statin led to a 44% reduction in the combined risk of cardiovascular events and stroke, with a 52% reduction in stroke risk, although the absolute rate of stroke was low.<sup>11</sup>

High levels of lipoprotein (a), a low-density lipoprotein particle, are associated with increased cardiovascular and stroke risk. Meta-analysis found that incident stroke was 22% higher in patients in the highest tertile of lipoprotein (a) compared with those in the lowest tertile.<sup>14</sup> Levels of lipoprotein (a) can be lowered with niacin, but whether doing so reduces the risk of stroke has not been determined.

High homocysteine has also been associated with an increased risk of both cardiovascular events and stroke.<sup>10</sup> Randomized trials, however, have not found that lowering homocysteine with B vitamins reduces the risk of coronary events. Similarly, two trials found no reduction in recurrent stroke among patients with high homocysteine who were treated with B-vitamin supplementation.<sup>15,16</sup> In contrast, analysis of data from another trial suggested that lowering of homocysteine was beneficial for prevention of secondary stroke.<sup>17</sup> The role of B-vitamin supplementation to prevent a first or recurrent stroke remains uncertain. Current guidelines indicate that supplementation could be considered, although its benefit is not established.<sup>10</sup>

There are numerous additional emerging potential risk factors for stroke.<sup>10</sup> Many, including several of those reviewed here, may also increase the risk of cardiac events and influence the development of left atrial enlargement. Whether left atrial enlargement represents a risk marker or a stroke risk factor, and whether interventions aimed specifically at reducing left atrial enlargement might be viable preventive interventions, requires further study.

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