Secondary stroke prevention in women

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In a meta-analysis of results from 21 randomized trials comparing antiplatelet therapy with placebo in 18,270 patients with prior stroke or transient ischemic attack, antiplatelet therapy was associated with a 28% relative odds reduction in nonfatal strokes and a 16% reduction in fatal strokes, while another trial for secondary prevention with atorvastatin 80 mg showed a 16% risk reduction in time to first occurrence of stroke (adjusted hazard ratio: 0·84, 95% CI: 0·71–0·99). However, few studies have examined the sex differences regarding the efficacy of these treatments. Specifically, recent studies have reported higher rates of perioperative complications during endarterectomy in women. Nonetheless, to date, the data on the effects of carotid artery stenting in women, coming from diverse studies and meta-analyses, have been limited owing to the small number of female patients examined. Owing to this, the evidence of the benefit for women is unclear. Peculiar pathophysiological aspects of stroke, the higher stroke risk in some specific periods in life (e.g., pregnancy, puerperium and older age) and worse documented stroke outcome in women suggest that sex does matter in stroke management. Thus, future randomized controlled trials need to be sex-balanced, in order to better understand the efficacy of appropriate secondary stroke prevention therapy in women.

Cerebrovascular disease is the second most common cause of death worldwide and all projections indicate that this will remain stable until 2020 [1]. Stroke is the most common cause of long-term disability in western society [2]. This article provides a comprehensive review of the published literature on sex differences in stroke with a focus on secondary stroke prevention.

Drug management

Antiplatelet treatment

Past clinical trials on stroke have largely ignored consideration of any sex-specific responses to treatments, even though it has been demonstrated that sex hormones have differential effects on platelet function (testosterone-promoting platelet activity and estrogen-inhibiting activity) [3,4]. Sex differences have been reported in the pharmacology of aspirin, including adsorption, bioavailability, anti-inflammatory and antiplatelet effects [5,6]. In the next sections, the sex differences of the most utilized antiplatelet drugs will be discussed.

Aspirin

Aspirin irreversibly inhibits the COX-1 enzyme through acetylating the serine residue at position 529. COX-1 catalyzes the conversion of arachidonic acid into prostaglandins G2 and H2, which are subsequently converted by tromboxane synthase into thromboxane A2 – a potent vasoconstrictor and activator of platelet aggregation.

Conversely, aspirin seems to provide similar benefits in terms of secondary stroke prevention in both men and women [8]. Despite this, some studies have found that aspirin treatment was lower at admission and at discharge in women, especially in those older than 85 years [9,10]. In a recent meta-analysis, the Antithrombotic Trialists collaboration investigated the presence of major vascular events (e.g., MI, stroke or vascular death) in six primary prevention trials and 16 secondary prevention trials that compared long-term aspirin use versus controls [8]. Secondary prevention trials demonstrated that aspirin was associated with greater absolute risk reduction in serious vascular events (6.7 vs 8.2% per year; p = 0.0001), together with a nonsignificant increase in hemorrhagic stroke. In particular, aspirin prevented a fifth of total strokes (2.08 vs 2.54% per year; p = 0.002) and coronary events (4.3 vs 5.3% per year; p = 0.0001). No significant sex differences were found in the reductions of all major vascular events, even if the rates of vascular events were lower in the female group.

Clopidogrel

Clopidogrel, an inhibitor of ADP, prevents platelet aggregation as it reduces ADP binding to its receptors. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was the largest randomized, blinded, international trial to assess the relative efficacy of clopidogrel (75 mg once daily) compared with aspirin (325 mg once daily). The objective of the study was to demonstrate a reduction in the composite outcome, including ischemic stroke, MI and vascular death. The study population

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was made up of subgroups with atherosclerotic vascular disease: recent ischemic stroke, recent MI or symptomatic peripheral arterial disease. Over 3 years, the trial recruited 19,185 patients, with more than 6300 in each clinical subgroup, with a mean follow-up of 1.91 years. The intention-to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI or vascular death compared with 5.83% in those treated with aspirin. These rates reflect a statistically significant ($p = 0.043$) relative-risk reduction of 8.7% in favor of clopidogrel (95% CI: 0.3–16.5). However, women represented only 28% of the sample population and no subanalysis on sex-related effect was performed. These limitations did not allow for a specific evaluation of sex difference for clopidogrel versus aspirin in secondary stroke prevention [11].

Dual antiplatelet therapy

Aspirin & clopidogrel

Findings of randomized controlled trials in patients with coronary manifestations of atherothrombosis [12,13] have shown a benefit from clopidogrel plus standard treatment, including aspirin [14,15]. In addition, the dual antiaggregation leads to an acceptable increase in the risk of major bleeding complications. These trials have provided the rationale to undertake the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial, whose aim was to determine whether aspirin added to clopidogrel would further reduce the risk of recurrent ischemic vascular events in high-risk patients after transient ischemic attack or previous ischemic stroke [16]. This randomized, double-blind, placebo-controlled trial compared aspirin (75 mg/day) with placebo in high-risk patients experiencing recent ischemic stroke or transient ischemic attack and at least one additional vascular risk factor. The results showed that aspirin plus clopidogrel in this high-risk population did not significantly reduce major vascular events and significantly increased the risk of major bleeding.

In the MATCH trial the percentage of female patients for each treatment arm was 37%. The study showed a greater treatment effect from dual antiplatelet therapy in men compared with women. However, the trial was not designed to study the sex-related effects of double-antiplatelet therapy and, furthermore, these limitations did not allow for a specific evaluation of sex difference for clopidogrel plus aspirin in secondary stroke prevention.

Aspirin & dipyridamole

Different randomized controlled trials have compared aspirin with or without dipyridamole (200 mg twice daily) in secondary prevention for transient ischemic attack or minor stroke of presumed arterial origin. The European Stroke Prevention Study (ESPS)-1 included 2500 patients randomized to either placebo or the combination of aspirin plus dipyridamole (225 mg/day dipyridamole and 975 mg aspirin) [17]. Combination therapy reduced the risk of the pooled end point stroke/death by 33% and the risk of stroke alone by 38%. ESPS-1 did not include an aspirin-alone arm, so it was not possible to determine the presence of any added benefit from dipyridamole. Therefore, a second trial was undertaken, ESPS-2, which randomized 6602 patients with prior stroke or transient ischemic attack using a different dipyridamole formulation and aspirin dose compared with ESPS-1. The risk of stroke was significantly reduced: 18% with aspirin alone, 16% with dipyridamole alone and 37% with a combination of aspirin plus dipyridamole. The death outcome alone was not reduced by any of the treatments. The combination of aspirin plus dipyridamole was superior to both aspirin alone (23% reduction) and dipyridamole alone (25% reduction) [18]. The uncertainty about the secondary preventive value of combining dipyridamole and aspirin was reconfirmed by a Cochrane review, showing that in patients with other types of vascular diseases, this therapy was no more effective than aspirin alone [19].

The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) was designed to resolve this uncertainty by comparing dipyridamole and aspirin with aspirin alone in transient ischemic attack patients or those with minor ischemic stroke of presumed arterial origin. In this trial, where the percentage of women in each treatment arm was low (34% for aspirin plus dipyridamole and 35% for aspirin alone), no significant difference between the sexes was observed, although women seemed to benefit less from the combination treatment without reaching statistical significance [20]. A recent Swedish study has evaluated the interindividual differences in headache incidence associated with aspirin and dipyridamole. The study used a titration regime of the combination ASA 25 mg plus dipyridamole 200 mg once daily for 5 days followed by twice daily, verifying the treatment effect in the different age and sex groups, localization of stroke and the number of days since stroke onset. There were 174 ischemic

stroke patients with a mean age of 70.3 years; 63% men and 37% women. Headache of any kind was reported in 70 patients (40.2%) and moderate/severe headache was reported in 37 patients (21.3%). In six patients medication was discontinued owing to severe headache. A statistical trend reported a higher risk of suffering from headache in younger patients and females [21].

Aspirin & dipyridamole versus clopidogrel

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study was a double-blind, randomized trial that compared the efficacy and safety of two antiplatelet regimens – aspirin plus extended-release dipyridamole (ASA–ERDP) versus clopidogrel in secondary stroke prevention [22]. The primary outcome was first recurrence of stroke. The secondary outcome was a composite end point, including stroke, MI or death secondary to vascular causes. A total of 20,332 patients were followed for a mean of 2.5 years. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA–ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio [HR]: 1.01; 95% CI: 0.92–1.11). The secondary outcome occurred in 1333 patients (13.1%) in each group (HR for ASA–ERDP: 0.99; 95% CI: 0.92–1.07). There were more major hemorrhagic events among ASA–ERDP patients (419 [4.1%]) than among those receiving clopidogrel (365 [3.6%]) (HR: 1.15; 95% CI: 1.00–1.32), including intracranial hemorrhage (HR: 1.42; 95% CI: 1.11–1.83). The net risks of recurrent stroke or major hemorrhagic event were similar in the two groups (1194 ASA–ERDP patients [11.7%] vs 1156 clopidogrel patients [11.4%]; HR: 1.03; 95% CI: 0.95–1.11). In this trial, the percentage of women in each treatment arm was 36%. The study showed a better effect for clopidogrel treatment in women compared with men. However, the trial was not designed to study the sex-related effects of double-antiplatelet therapy. As such, these results did not reach any statistical power to be used in clinical practice.

Statin treatment

Whether statins have sex-related difference in terms of stroke protection is unknown [23]; however, a recent trial of high-dose statins for secondary stroke prevention did not find any sex by treatment interactions [24], even if women tend to have more side effects from statins, such as myopathies [25].

A recent meta-analysis of 15 randomized controlled statin trials has examined the sex-specific incidence of cardiovascular events showing that statins reduced the risk of cardiovascular events in both sexes, while women on statin treatment did not show any reductions in mortality and stroke [23].

Anticoagulation therapy

Women with nonvalvular atrial fibrillation have nearly double the risk of a stroke compared with men [26]. Studies dealing with anticoagulation therapy will be discussed in another article in this issue [27].

Carotid stenosis management

Carotid endarterectomy

Carotid endarterectomy (CEA) is highly effective in preventing stroke in patients with symptomatic severe stenosis, while patients with symptomatic moderate stenosis experience fewer benefits from CEA. The risk of stroke, in the first few days and weeks after a transient ischemic attack or a minor stroke, is particularly high especially in patients with carotid stenosis. The benefit of carotid surgery decreases if surgery is not performed immediately after the symptomatic event. In fact, it has been shown that CEA performed within 2 weeks in a nondisabling hemispheric stroke is not associated with an increased operative risk [28], even if a very high operative risk in progressive syndromes treated with urgent surgery exists [29]. Indeed, in patients with >70% stenosis, the number of patients who need to undergo surgery (number needed to treat [NNT]) to prevent one ipsilateral stroke is 3, if CEA is performed within 2 weeks of the event. If CEA is performed between 2 and 4 weeks of the event, the benefit is reduced by a half (NNT = 6) and in patients operated on after 4 weeks following the event the NNT is 9 [28]. This time-dependent benefit ratio is especially true for women, as a subgroup analysis of pooled individual patient data from European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown [28]. The benefit from CEA significantly diminished with increasing time from last event to randomization in women ($p < 0.001$) but not in men ($p = 0.74$); therefore, the trend toward reducing benefit from CEA over time was sex related ($p < 0.001$). The main determinant of this sex difference was a more rapid decline over time of the stroke

risk in women in the medical arm ($p < 0.001$) compared with men ($p < 0.03$). These data are consistent with the known sex-related difference in the pathophysiology of atherothrombotic plaque inflammation since women more frequently have transient endothelial erosion than plaque rupture [30–32]. Histological analysis of CEA samples revealed that women had more stable plaques since they were less prone to rupture compared with men [33]. Moreover, another study has reported that women had significantly narrower carotid stenoses compared with men, while men had greater plaque areas. In addition, this study showed that plaque area, and not degree of stenosis, was found to be a predictor of poor outcome; supporting the epidemiological data that men are at a higher risk of stroke [33,34]. Furthermore, female sex is classified as a risk variable for surgery in patients undergoing CEA for symptomatic stenosis of 70–99%. Indeed, combined data from NASCET and ASA and Carotid Endarterectomy (ACE) trials showed that the 30-day perioperative risk of death after CEA was higher in women than in men (2.3 vs 0.8%; $p = 0.002$) [35]. This was primarily because of the higher risk of fatal stroke in women during the perioperative period. In addition, the 30-day incidence of any stroke and any death was also higher in women than in men (7.6 vs 5.9%) [36] with a significant increased risk (odds ratio: 1.31) [37]. After the perioperative period, the long-term risk of stroke or death following surgery in patients with high-grade symptomatic carotid stenosis is the same in both sexes (HR: 1.05) [38]. The reasons for the perioperative risk difference remains speculative. It may be that differences in the internal carotid artery size or anatomy of women render the surgery more difficult to perform or lead to a higher incidence of carotid thrombosis [30,39]. Regarding surgery for symptomatic moderate (50–69%) stenosis, a significant benefit is evident only in patients randomized <2 weeks after their last event, and men appear to benefit more from CEA surgery than women [28]. Indeed, women with 50–69% internal carotid artery stenosis had no benefit from CEA because they generally have a lower risk of stroke than men when they are medically treated. The 5-year absolute risk reduction of ipsilateral stroke after CEA was only 3.0% in women compared with 10% in men; corresponding to a 5-year NNT of 33 and 10, respectively [36]. Endarterectomy for moderate stenosis is not beneficial in women without other stroke risk factors (absolute risk reduction: 3.0%; $p = 0.94$ in women; absolute risk reduction: 10%; $p = 0.02$ in men).

Carotid stenting

Carotid angioplasty and stenting (CAS) was developed as a potential alternative treatment to CEA and has been evaluated in randomized trials and many nonrandomized studies involving a variety of specialists, including neurologists, radiologists, cardiologists, vascular surgeons and neurosurgeons, most of whom have already implemented the technique in their clinical practices [40]. According to the latest published stroke guidelines from American Heart Association/American Stroke Association, CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography. CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4–6% similar to those observed in trials of CEA and CAS (recommendation class IIa; level of evidence B) [41]. Published randomized controlled trials on CAS in symptomatic patients have pointed to an increased risk from CAS versus CEA in symptomatic populations, regardless of sex, while large randomized CAS trials on asymptomatic patients are ongoing. Conversely, according to recent literature, it seems that CAS may be performed with low complication rates in women; however no strong evidence is available [42]. Even more conflicting results on the risks of CAS in women have been provided by randomized controlled trials [43–46]. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial included 171 symptomatic women and 436 symptomatic men in the CAS group: it was the only randomized controlled trial that specifically analyzed outcome considering sex as a variable [43,44]. In fact, women had a slightly nonsignificant increase in the primary end point rate (ipsilateral stroke or death within 30 days) compared with men (8.2 vs 6.4%) [42]. The rate of ipsilateral stroke within 2 years plus periprocedural stroke and death was lower in women (8.3 vs 9.9%). Nevertheless, none of these differences were significant.

Very little information is available from the small number of women included in all other large CAS trials (n = 72; 28%) examining

endarterectomy versus angioplasty with symptomatic severe carotid stenosis [47]. The same issue was dealt with by the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which included only 55 women (33%).

The International Carotid Stenting Study (ICSS) [48] showed that CEA was safer than carotid stenting for symptomatic patients; indeed, stroke or death within 30 days of stenting was more than double compared with the endarterectomy group. An exploratory analysis of the composite outcome of stroke, death or procedural MI suggested that carotid stenting might have a similar risk to that of endarterectomy in women, but was more hazardous than endarterectomy in men. The difference seemed to be largely explained by a higher risk of outcome events in women assigned to endarterectomy than in men (7.6 vs 4.2%). However, the difference between the HRs comparing the risk related to stenting or to endarterectomy in men and women reached a borderline significance (p = 0.71) [48]. The prospective meta-analysis of patient data at 120 days after treatment from EVA-3S, SPACE and ICSS, performed by Carotid Stenting Trialists' Collaboration, confirmed that surgical risk was higher in women than in men, whereas risk of stenting was virtually unaffected by sex. The risk ratio of any stroke or death within 120 days between CAS and CEA was higher in men (1.68) than in women (1.22); in the CAS group, women did not have significant hazard ratios (95% CI: 0.79–1.89), while the risk of CAS in men was significantly worse with confidence interval above 1 (95% CI: 1.25–2.24). Nevertheless, there was no significant difference in treatment effects between men and women (p = 0.24) [49]. The largest randomized controlled trial on CAS versus CEA, the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) showed that carotid-artery stenting and CEA were associated with similar rates of periprocedural cumulative stroke, MI, death or ipsilateral stroke (7.2 and 6.8%, respectively; HR for stenting was 1.11 [95% CI: 0.81–1.51; p = 0.51]), among men and women with either symptomatic or asymptomatic carotid stenosis. However, the incidence of periprocedural stroke was lower in the endarterectomy group than in the stenting group (p = 0.01), whereas the incidence of periprocedural MI was lower in the stenting group (p = 0.03). Prespecified analyses did not show any modifications in the treatment effects by sex, even if women represented only 35% of all randomized patients [50]. In conclusion, women have been greatly under-represented in all carotid trials (i.e., the CEA and CAS trials) and it remains to be seen whether sufficient enrollment of women will play a decisive role in the ongoing trials analyzing CAS.

Conclusion

The major trials assessing secondary prevention have under-representated female patients, so their results can be considered principally valid for male patients. Furthermore, the complexity of pathophysiology of stroke in women, who experience different periods of high stroke risk over their lifetimes (e.g., pregnancy, puerperium and older age) and their worse stroke outcome suggests that sex matters in stroke management.

Future perspective

To date, most randomized controlled trials have greatly under-represented women. Therefore, the data that they have produced cannot be applicable in clinical routine for the secondary prevention of stroke in women. Given that women tend to be older than men, and tend to have comorbidities when they present with cerebrovascular events, future randomized controlled trials must be designed to take into account these factors. Furthermore, the greater burden of stroke deaths in women is predicted to be even higher in the future, so a better designed randomized controlled trial means that women would be better represented in the future.

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Executive summary

- Aspirin is the most studied drug for primary and secondary prevention in stroke medicine. No significant sex differences have been found considering the reductions of all major vascular events, such as myocardial infarction, stroke and major vascular events.
- Females only represent 30% of patients in trials investigating clopidogrel, combination therapy such as aspirin/dipyridamole or clopidogrel in combination with aspirin, which is too low a number in order to formulate recommendations for these treatments in secondary stroke prevention.
- Regarding statins, trials have shown a reduction in cardiovascular events for both sexes, while women on statin treatment did not show any reductions in mortality and stroke.
- Regarding carotid stenosis, for women who have had a minor stroke or transient ischemic attack and severe (≥70%) carotid stenosis, carotid endarterectomy have maximum benefit within 15 days from symptom onset. When degree of symptomatic carotid stenosis is moderate (50–69%) the risk–benefit should be evaluated in women with multiple stroke risk factors. In addition, carotid angioplasty and stenting could be indicated as an alternative to carotid endarterectomy for symptomatic women when the procedure is performed by operators with established periprocedural morbidity and mortality rates of 4–6%, similar to those observed in trials of carotid endarterectomy and carotid angioplasty and stenting.

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