Gender and stroke: acute phase treatment and prevention

Simona Sacco, MD
Davide Cerone, MD
Antonio Carolei, MD, FAHA

Department of Neurology, University of L'Aquila, Italy

Corresponding author: Antonio Carolei
Clinica Neurologica
Dipartimento di Medicina Interna e Sanità Pubblica
Università degli Studi di L'Aquila
Piazzale Salvatore Tommasi 1
67010 L'Aquila, Italy
E-mail: a_carolei@yahoo.com

Summary

Stroke is the third most common cause of death in women and a major cause of disability. Many aspects of stroke are similar in men and women, including clinical presentation, main risk factors, and distribution of the main subtypes. There are, however, some gender differences and specificities in stroke including some aspects related to treatment. Women are less likely to receive thrombolysis than men; however, in treated cases, the efficacy of intravenous thrombolysis is higher in women than in men. Hormone replacement therapy has been suggested as a possible strategy to reduce the occurrence of stroke in postmenopausal women but several clinical trials failed to show any benefit in stroke and cardiovascular disease prevention. Also in stroke prevention with antiplatelets there emerge some important gender differences: in primary prevention of stroke, aspirin was effective in women but not in men while in secondary prevention no gender differences were found with any of the available antiplatelet agents.

KEY WORDS: gender, prevention, stroke, treatment, women.

Introduction

Stroke is the third most common cause of death and a major cause of disability. Many aspects of stroke are similar in men and women, including clinical presentation, main risk factors, and distribution of stroke subtypes. There are, however, some gender differences and specificities in stroke including some aspects related to treatment. Although age-specific stroke incidence rates are higher in men than women, more strokes per year occur in women because women live longer (Fig. 1) (1). In fact, the increased lifetime risk of stroke in women may be explained in part by women's longer life expectancy. Women develop a first-ever stroke an average of four years later than men (mean age in years at stroke onset 76.7±10.6 vs 72.6±11.9) (1,2). Women also have a worse survival rate than men after stroke. Intriguingly, the proportion of deaths in women with high hematocrit values was found to be almost three times higher than that of

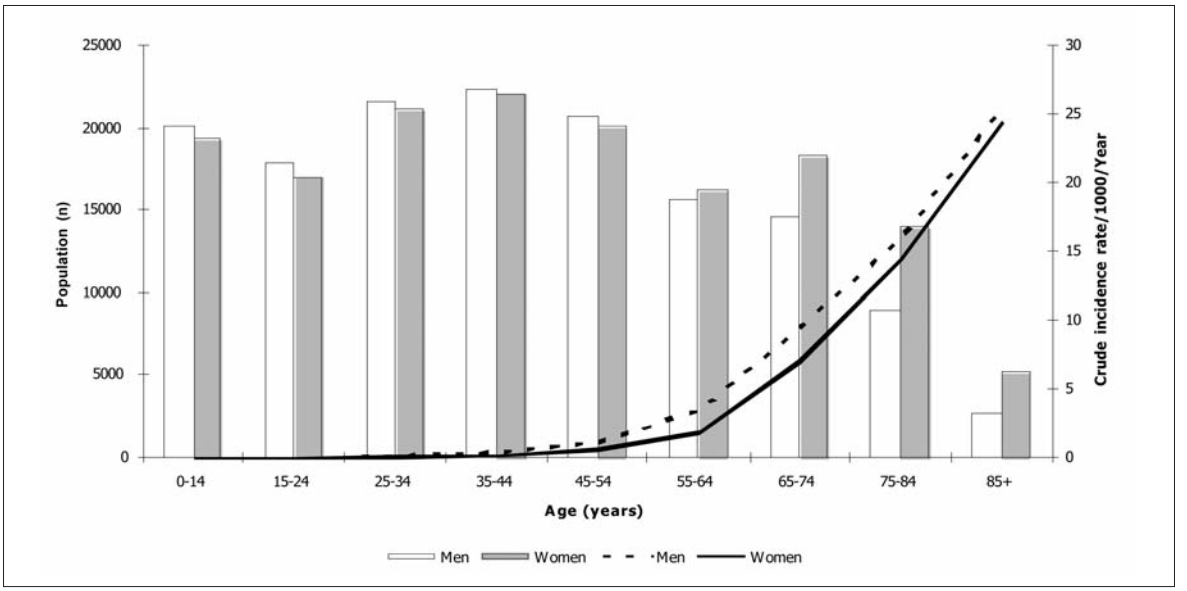

Figure 1 - First-ever stroke crude incidence rate and distribution of individuals in the resident population (2001 census data) according to age groups and gender in the L'Aquila Stroke Registry (1994-1998).

men with similar hematocrit values (3). Several studies also associated female gender with a worse functional outcome after stroke. These gender-related differences in the incidence and prognosis of stroke will become even more marked as the population ages and the proportion of older women increases.

Whereas after the menopause the main causes of stroke in women are similar to those found in men, including large artery atheroma, small vessel disease, and cardiac disease, earlier in life the causes and risk factors for stroke differ widely according to gender. In premenopausal women, stroke, although rare, remains a potentially devastating occurrence during pregnancy and the postpartum period. The risk of ischemic stroke or intracerebral hemorrhage during pregnancy and the first six weeks postpartum is 2.4 times greater than for non-pregnant women of similar age and race. The period associated with the highest risk of ischemic stroke is not pregnancy per se but rather the six weeks postpartum (8.7-fold increase). Intracerebral hemorrhage showed a small relative risk (RR) of 2.5 during pregnancy that increased dramatically to 28.3 in the six weeks after childbirth. The excess risk of stroke (all types except subarachnoid hemorrhage) attributable to the combined pregnancy/postpregnancy period was 8.1 per 100,000 pregnancies (4). Moreover, an increased number of pregnancies has been associated with an increased risk of cardiovascular disease among women.

Numerous studies dealing with oral contraceptive use and stroke have shown that oral contraceptives with a high estrogen content greatly increase the risk of stroke (RR around 4), both ischemic and hemorrhagic, whereas oral contraceptives with a low estrogen content double the risk of ischemic stroke with a low absolute risk (5). Another specific risk factor for stroke in young women is migraine with aura (6). The risk of stroke is increased in young women who, in addition to having migraine with aura, also use oral contraceptives and smoke.

Gender differences in presentation, clinical care and outcomes have been documented in multiple studies of patients with stroke. Indeed, because of the specific role played by women in society, the social and health care repercussions of stroke in this group deserve special consideration. In most countries, women are still responsible for the home and family, and should the woman of the household suffer a stroke, the illness and the recovery have a considerable impact on the family as a whole, which becomes even greater when the individual concerned is admitted to a long-term care institution. Furthermore, a third of stroke cases occur in the poorest countries where conditions, in terms of hygiene, nutrition and availability of treatments, are less favorable and where women frequently have less access to the education and resources necessary to prevent and combat this disease.

Thrombolysis in women

A meta-analysis of 18 studies that had detected gender differences in the likelihood of receiving intravenous (iv) thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) reported an odds ratio (OR) of 0.70 (95% CI 0.55-0.88), indicating that women have a 30% lower odds of receiving this treatment than men (7). However, there was substantial between-study variability. Among 13 hospital-based studies, the combined OR was 0.78 (95% CI 0.71-0.86) with no significant heterogeneity. Among the three administrative studies, the OR was 0.55 (95% CI 0.34-0.90) but there was significant heterogeneity. Among four studies that included data on the eligible subgroup, women had non-significantly lower odds of receiving the treatment (OR=0.81; 95% CI 0.58-1.13). Despite the presence of significant between-study variations, women with acute stroke were consistently less likely to receive thrombolysis treatment compared to men (7).

Moreover, gender differences in the efficacy of thrombolysis were also reported. In a pooled analysis of the National Institutes of Neurological Disorders and Stroke (NINDS) trial, the Second European Cooperative Acute Stroke Study (ECASS II), and the Alteplase Thrombolysis for Acute Non-interventional Therapy in Acute Ischemic Stroke (ATLANTIS) trial, iv thrombolysis with rt-PA was more effective in women than men, independently of other variables (8). In patients treated with rt-PA up to six hours after onset in these trials, women and men had similar outcomes [40.5% of women and 38.5% of men had a three-month modified Rankin Scale (mRS) score of ≤1], although among placebo-treated patients, women fared worse than men (30.3% of women and 36.7% of men had a three-month mRS ≤1, p=0.03). The investigators interpreted these findings as indicating that rt-PA reversed the worse post-stroke outcomes usually found in women. However, that analysis did not include data on the localization of stroke or the type of vessel occlusion.

Another study reported higher complete or partial recanalization rates (94% vs 59%, p=0.02) as determined by magnetic resonance angiography or computed tomography angiography after iv thrombolysis in women with acute large-artery anterior circulation strokes (9). This difference was also present in a smaller subset of patients who had vessel imaging at 24 hours, suggesting that very early recanalization and improvement in National Institutes of Health Stroke Scale (NIHSS) scores were more frequent in women. Women were 2.4 times more likely to show a major neurological improvement at 24 hours (≥8-point improvement of the NIHSS score or a score of 0 or 1 at 24 hours) (10). In a secondary analysis of the Glycine Antagonist in Neuroprotection (GAIN) Americas trial, a significant gender difference in outcomes was seen among patients receiving iv rt-PA. Men were more than three times as likely as women to achieve functional independence at three months, despite no evidence of a survival benefit compared with women (11). The Canadian Alteplase for Stroke Effectiveness Study (CASES), a multicenter study that collected outcomes data for patients treated with rt-PA to assess the safety and effectiveness of alteplase for stroke in the context of routine care, found no effect of gender on 90-day functional outcome (12). This was consistent with the pooled analysis of randomized controlled trials, which showed greater benefit from thrombolysis in women and nullification of the usual gender difference in outcome (8). An analysis of data from the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) showed that male gender was an independent predictor of mortality within three months (13).

There are biological reasons why women may have a less favorable response to iv thrombolysis than men; mainly, studies have found that, among stroke patients, women have higher levels of procoagulant factors such as plasminogen activator inhibitor and factor VII than men (11).

As regards intra-arterial thrombolysis, no gender-specific differences in angiographic recanalization and clinical outcome after intra-arterial thrombolysis with urokinase or rt-PA in anterior and posterior circulation ischemic stroke were reported (14). Arnold et al. studied 248 patients with acute ischemic anterior circulation stroke and found no gender difference in the angiographic recanalization rate and clinical outcome after intra-arterial thrombolysis (15). A secondary analysis of the Pro-Urokinase for Acute Cerebral Thromboembolism-2 (PROACT-2) study (16) was consistent with the previously reported gender-related modification of treatment effect on outcomes after thrombolysis for stroke (8). A gender by pro-urokinase treatment interaction was observed, with women showing a greater treatment effect (20% absolute benefit) compared with men (10% absolute benefit). The reason for this interaction is that thrombolytic treatment nullifies the worse outcome seen in untreated women compared with men: women do worse after ischemic stroke than men but this gender difference in natural history is reversed with thrombolysis. Since the PROACT-2 trial was angiographically controlled, the authors were able to establish that differences in outcome were attributable to improved recanalization at 2 hours among women.

Potential gender-dependent differences in the response to iv thrombolysis and intra-arterial thrombolysis are difficult to explain. First, a smaller diameter of the intracranial arteries in women may result in smaller clot volume and explain the higher likelihood of recanalization in women after iv thrombolysis, despite lower local concentrations of the fibrinolytic agent. Second, gender-based differences in coagulation and fibrinolysis among patients with acute ischemic stroke have been described and might have a different impact on iv thrombolysis compared with intra-arterial thrombolysis. Third, estrogens have been shown to exert a neuroprotective effect in animal models. Finally, women are less likely than men to receive iv thrombolysis, suggesting that selection bias may be a potential confounder.

Hormone replacement therapy and risk of stroke

Stroke is a major health problem particularly in postmenopausal women, which raises the question of whether its increased incidence is due to aging or to hormonal status. The observation that the risk of stroke increases in women in the postmenopausal period has led to the hypothesis that estrogens have a positive effect on cerebral circulation. Estrogens have an antiatherogenic effect which, in part, explains why, during the fertile period of a woman's life, the incidence of atherothrombotic and lacunar stroke is lower than that of males of the same age. After the menopause, the incidence of these entities increases and this is related, among other causes, to the loss of the protective effect exerted by estrogens. Furthermore, estrogens have a neuroprotective effect against ischemic cerebral damage. These observations have prompted investigations of postmenopausal hormone replacement therapy (HRT) as a possible strategy for stroke prevention.

Over the past 30 years, the majority of cohort, retrospective, and prospective observational studies have demonstrated significant reductions in cardiovascular disease in postmenopausal women receiving estrogen or combined estrogen-progestin therapy (17). Observational reports in stroke are not as clearly positive as those in the field of cardiovascular disease. Although laboratory and observational studies of postmenopausal hormone therapy have suggested that it exerts a beneficial effect for the prevention of cardiovascular disease and reduction of stroke severity, randomized trials suggest that there is no effect or even an increased risk of stroke with treatment. Among postmenopausal women who were generally healthy, the Women's Health Initiative (WHI) (18), a randomized trial of 16,608 women, 95% of whom had no pre-existing cerebrovascular disease, found that estrogen plus progestin increased ischemic stroke risk by 44%, with no effect on hemorrhagic stroke. The excess risk was apparent in all age groups, in all categories of baseline stroke risk, and in women both with and without hypertension or prior history of cerebrovascular disease. A more detailed analysis of women with stroke in the group assigned to HRT showed that there was an increased risk of ischemic stroke, but not of fatal stroke or of hemorrhagic stroke. In addition, the women in the combination group did not have a significantly worse stroke disability outcome, as measured by the mRS. A parallel WHI trial included women with previous hysterectomy who were treated with conjugated equine estrogen (19). Among the 10,739 women included, it was found that conjugated equine estrogen alone increased the risk of ischemic stroke by 55% but that there was no significant effect on hemorrhagic stroke. The excess risk of total stroke conferred by estrogen alone was 12 additional strokes per 10,000 person-years.

In postmenopausal women with known coronary artery disease, the Heart and Estrogen/Progestin Replacement Study (HERS), a secondary prevention trial, found that a combination of estrogen plus progestin hormone therapy did not reduce stroke risk as compared to placebo (20). Treated women were at higher risk of thromboembolic events relative to placebo controls [hazard ratio (HR)=2.89].

The Women's Estrogen for Stroke Trial (WEST) was designed to determine the effects of hormone therapy on the incidence of vascular events after stroke. The study found that estrogen alone (1 mg 17β-estradiol) in women with a mean age of 71 years also carried an increased risk of stroke in the first six months after randomisation (21). The 17β-estradiol group also had a nearly three-fold rate of fatal strokes compared with those on placebo (RR=2.9; 95% CI 0.9-9.0), and women with non-fatal strokes had worse neurological deficits compared with the placebo group, indicating that those who had recurrent stroke and were randomized to hormonal therapy were less likely to recover.

A meta-analysis of HRT identified 28 relevant randomized trials (with a total of 39,769 subjects) addressing this question (22). HRT use was associated with increases in total stroke (OR=1.29; 95% CI 1.13-1.47), non-fatal stroke (OR=1.23; 95% CI 1.06-1.44), fatal or disabling stroke (OR=1.56; 95% CI 1.11-2.20), and ischemic stroke (OR=1.29; 95% CI 1.06-1.56), and with a

trend toward more fatal strokes (OR=1.28; 95% CI 0.87-1.88), but with no increase in hemorrhagic strokes (OR=1.07; 95% CI 0.65-1.75).

The most probable explanation for why HRT had an overall neutral effect on stroke and a beneficial effect on coronary artery disease in observational studies is the healthy-user effect; that is, the women more likely to use hormone therapy were those with healthier lifestyles and a lower risk of stroke and heart disease. Study differences might be related to different hormone regimens (estrogen and progestinic dose and type) used in observational versus randomized studies. In addition, the time since menopause might be important. Most women in observational studies started taking hormone therapy during the perimenopause or within two years of the menopause, whereas hormone therapy was started about 10 years after the menopause in the WHI. The time since menopause might also correspond to a particular stage of atherosclerosis and therefore a differential effect of estrogen.

The American Heart Association/American Stroke Association (AHA/ASA) Guideline on Primary Prevention of Ischemic Stroke recommended that postmenopausal HRT (estrogen with or without a progestin) not be used for primary prevention of stroke (Class III, Level of Evidence A) (23). The use of HRT for other indications should be informed by the risk estimate for vascular outcomes provided by the reviewed clinical trials. There were not sufficient data to allow the formulation of recommendations about the use of other forms of therapy such as selective estrogen receptor modulators (23).

Antithrombotic treatment in women

Gender-based differences in the pathophysiology and treatment of thrombosis have been examined in a growing body of literature. Although women tend to be underrepresented in randomized clinical trials of antithrombotic therapy, most analyses indicate that men and women accrue equal therapeutic benefit in a variety of clinical settings. Unlike studies in high-risk patients, studies of aspirin for primary prevention of cardiovascular disease in healthy individuals have revealed gender-based differences in responses to therapy.

Aspirin in primary prevention

The two early randomized trials of aspirin in primary prevention, the Physicians' Health Study (PHS) and the British Male Doctors' Trial (BMD), included only men (24,25). In the Hypertension Optimal Treatment (HOT) trial (26), men and women with hypertension were randomized to aspirin or placebo. Aspirin significantly lowered the risk of myocardial infarction in men (OR=0.57; 95% CI 0.41-0.81), but had no significant effect in women (27). No reduction in stroke risk was seen in either men or women (Table I). The Primary Prevention Project (PPP) randomized over 4,400 people to aspirin or placebo with or without vitamin E (28). A non-significantly increased risk of myocardial infarction in women (OR=1.37; 95% CI 0.47-3.95) and a decreased risk of myocardial infarction in men (OR=0.50; 95% CI 0.24-1.04) were observed in this trial (27,28). For ischemic stroke, there emerged a trend toward a decreased risk in women (OR=0.68; 95% CI 0.24-1.92) but not in men (OR=1.16; 95% CI 0.42-3.22) (27) (Table I). In the largest study of aspirin in primary prevention, the Women's Health Study, 39,876 apparently healthy women ≥45 years of age were randomized to aspirin or placebo and followed up for a mean of 10 years for the major cardiovascular events of myocardial infarction, stroke, and death from cardiovascular causes (29). Unlike data from prior studies that had included mainly men, this study found a non-significant 9% reduction (RR=0.91; 95% CI 0.80-1.03; p=0.13) in the combined primary end point. Aspirin, compared to placebo, lowered the risk of stroke by 17% (RR=0.83; 95% CI 0.69-0.99; p=0.04), owing to a 24% reduction in the risk of ischemic stroke (RR=0.76; 95% CI 0.63-0.93; p=0.009) and a non-significant increase in the risk of hemorrhagic stroke (RR=1.24; 95%

Table I - Aspirin treatment in primary prevention studies in women.

Trial	Hypertension Optimal Treatment trial, 1998 (ref. 26)	Primary Prevention Project, 2001 (ref. 28)	Women's Health Study, 2005 (ref. 29)
No. of included subjects	18,790	4,495	39,876
Women (%)	47	58	100
Characteristics of included subjects	Men and women with hypertension	Men and women with ≥1 major cardiovascular risk factor	Apparently healthy female health care professionals
Aspirin dose	75 mg/day	100 mg/day	100 mg/every other day
Mean follow up (years)	4	3.6	10.1
Effects on cardiovascular events [OR (95% CI)]	0.81 (0.63-1.05)	0.66 (0.36-1.23)	0.91 (0.80-1.03)
Effects on stroke [OR (95% CI)]	0.81 (0.56-1.16)	0.56 (0.21-1.51)	0.84 (0.70-1.01)
Effects on ischemic stroke [OR (95% CI)]	-	0.68 (0.24-1.92)	0.77 (0.63-0.94)
Effects on hemorrhagic stroke [OR (95% CI)]	-	0.20 (0.01-4.23)	1.25 (0.83-1.88)
Effects on major bleedings [OR (95% CI)]	1.89 (1.16-3.08)	4.63 (1.00-21.46)	1.40 (1.07-1.83)

All numbers as reported in ref. 27.

CI 0.82-1.87; p=0.31) (Table I). Aspirin had no significant effect on the risk of fatal and non-fatal myocardial infarction (RR=1.02; 95% CI 0.84-1.25; p=0.83) in the overall study population, but decreased the risk of myocardial infarction in women over the age of 65 years (29). Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (RR=1.40; 95% CI 1.07-1.83; p=0.02). It is important to note that the dose of aspirin used in the Women's Health Study was low (100 mg every other day) and that higher doses might be required for adequate platelet inhibition.

In a meta-analysis including all the three mentioned primary prevention trials in women and involving more than 95,000 patients, aspirin had no effect on the risk of myocardial infarction (OR=1.01; 95% CI 0.84-1.21) or cardiovascular death (OR=0.90; 95% CI 0.64-1.28) in women, but lowered the risk of ischemic stroke (OR=0.76; 95% CI 0.63-0.93) (27). However, there was an increased risk of major bleeding (mostly gastrointestinal) in women taking aspirin (OR=1.68; 95% CI 1.13-2.52) in the absence of any increase in hemorrhagic stroke (OR=1.07; 95% CI 0.42-2.69).

A non-randomized observational prospective cohort study, the Nurses' Health Study (30), which followed up more than 85,000 women in the United States, also confirmed possible benefits of aspirin treatment in primary prevention. The study found that women taking 1 to 6 aspirin per week had a lower risk of myocardial infarction within the first six years of follow up (RR=0.75; 95% CI 0.58-0.99) than women who did not take aspirin. At 24 years of follow up, a significantly lower risk of death from all causes was observed among women who had used aspirin regularly versus those who had never used aspirin (RR=0.75; 95% CI 0.71-0.81) (31). The greatest risk reduction was in death from cardiovascular disease (RR=0.62; 95% CI 0.55-0.71) and stroke (RR=0.62; 95% CI 0.48-0.80). A linear relationship was seen between increasing duration of aspirin use and decreasing mortality.

The reasons for any gender-based differences in the efficacy of aspirin for primary prevention are unclear and require further exploration. Several possibilities may explain the differences observed between genders. First, there exists evidence that seems to point to a difference in aspirin metabolism. Several studies suggested a reduced pharmacological effect of aspirin among women compared with men. Differences in platelet activity induced by sex hormones have been well documented (i.e. testosterone increases platelet activity while estrogens inhibit it). Second, the event rates of stroke and myocardial infarction differ. Women have a greater proportion of strokes compared to myocardial infarctions, whereas men have a greater proportion of myocardial infarctions compared to strokes. Third, aspirin resistance (the failure of aspirin to inhibit platelet function as measured by a variety of assays) tends to be more common among women than men; this is due to the greater baseline platelet function in *ex vivo* assays in women than in men that leads to higher values after aspirin therapy (32). However, because numerous secondary prevention trials of aspirin have failed to show a gender difference for recurrent stroke and other ischemic vascular events, the reasons for this apparent gender difference remain unclear.

The AHA/ASA Guideline on Primary Prevention of Ischemic Stroke report that aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa, Level of Evidence B) (23). Moreover, the US Preventive Services Task Force, also taking into account the effects of age, concludes that for women aged 55 to 79 years whose benefit due to a reduction in ischemic stroke exceeds the harm of gastrointestinal bleeding, there is high certainty that the net benefit is substantial, for women 80 years or older, the evidence is insufficient to allow an assessment of the balance of benefits and harm, and for women aged 54 years or younger, the potential benefits of reducing ischemic stroke are small, and there is moderate certainty that the benefits fail to outweigh the harm (33).

Antithrombotics in secondary stroke prevention

In the context of stroke or transient ischemic attack, the benefits of aspirin in preventing recurrent ischemic events are similar in men and women. A recent observational study examined aspirin use and dose in relation to clinical outcomes in 8,928 postmenopausal women with known cardiovascular disease followed up for 6.5 years in the WHI (34). After controlling for potential confounders, the women who reported taking aspirin at least three times a week were found to show significant risk reductions in all-cause death (14%) and cardiovascular death (25%) compared with non-users. There was also a 10% risk reduction in composite cardiovascular events (including non-fatal myocardial infarction) that did not reach statistical significance. An aspirin dose of 81 mg was comparable to 325 mg for preventing clinical events in 2,072 women who were matched for risk factors and other potential confounders. Guidelines for the prevention of stroke do not report any advice referring to possible gender differences (35,36).

Antithrombotics in acute stroke

In the context of acute stoke, aspirin also lowers the risk of recurrent ischemic strokes to a similar degree in women and men (37,38). Among high-risk patients, women receive the same benefit from aspirin therapy as do men, including a 34% decrease in non-fatal myocardial infarction, a 25% decrease in non-fatal stroke, and a 15% decrease in vascular death (39).

Prevention of cardioembolic stroke

Atrial fibrillation is the most common arrhythmia encountered in clinical practice and it is a major risk factor for stroke. Among individuals affected by atrial fibrillation, women appear to be at higher risk of suffering a stroke than men, and women over the age of 75 years are at the highest risk. In keeping with these observations, atrial fibrillation is more frequently noted in women presenting with stroke than in men (OR=1.57; 95% CI 1.34-1.83) (40).

Warfarin therapy is at least equally effective in lowering the risk of thromboembolism in men and women, with

some studies showing more benefit in women (41). Importantly, several recent trials have disclosed similar rates of major bleeding in women and men under warfarin therapy, and, in particular, no increased risk of intracranial bleeding (41,42).

Statins and stroke prevention

Several studies provide data assessing potential gender-related differences in the effects of statins for primary stroke prevention. The Cholesterol and Recurrent Events (CARE) study found a non-significant 35% reduction of stroke with statin treatment in women but no difference between men and women (43). The Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) study found that more women in the statin group (4.4%) than in the placebo group (3.6%) had strokes, whereas in the men, statins were associated with a beneficial effect (3.6% with statin treatment versus 4.7% with placebo) (44). When the data from these two trials were pooled with data from the West of Scotland Coronary Prevention Study (WOSCOPS), there emerged no statistical interaction between gender and statin treatment on the occurrence of stroke. Therefore, there is no evidence for a gender-related difference in the effects of statins in primary stroke prevention in the setting of known coronary heart disease or in other primary prevention populations. Consistent with these results, the Prospective Pravastatin Pooling Project (PPP) and the Heart Protection Study (HPS) found that statin treatment was associated with similar reductions in the occurrence of predominantly first strokes regardless of gender (45). Meta-analysis of 14 trials of statins including more than 90,000 subjects, most of whom had coronary artery disease or major vascular risk factors, found that men and women had similar treatment-associated reductions in both major coronary events and major vascular events (46). A secondary analysis of subjects with coronary artery disease enrolled in three clinical trials of oral glycoprotein IIb/IIIa inhibitors found no significant difference in statin-associated stroke reductions between men and women (47).

The Stroke Prevention with Aggressive Reductions in Cholesterol Levels (SPARCL) trial showed that treating patients with recent stroke or transient ischemic attack and no known coronary artery disease with atorvastatin 80 mg per day reduced the combined risk of fatal and non-fatal stroke as well as other cardiovascular events (48). A post-hoc analysis of this same trial showed similar statin-related reductions in stroke and other cardiovascular events in men and women who had a recent stroke or transient ischemic attack and no known coronary artery disease at the time of study enrolment (49).

Concluding remarks

In conclusion, as shown by this review, several gender differences have been detected in both acute phase and preventive treatments for stroke. The underlying mechanisms of such differences need to be clarified and their elucidation might help to improve therapeutic results in both men and women. Furthermore, gender disparities, in favor of men, still exist in the management of stroke and even in the inclusion of men versus women in clinical trials. Every effort should be made to abolish these discrepancies.

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