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# Stroke in women: difference in risk factors and treatment compared to men

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## ABSTRACT

Stroke is one of the major public health problems and it is the leading cause of death in the world with around 6.5 million deaths per year. Age-specific mortality rates increase with age and are higher in men than in women for all age groups, except at the age of 80+ when the mortality rates in women are higher than in men. Women live longer and therefore have a higher lifetime risk of stroke than men. Women have sex-specific risk factors as well as some unrecognized risks that contribute to poor stroke outcomes. Among the traditional risk factors that have a greater impact on stroke in women are hypertension, atrial fibrillation and diabetes mellitus. Risk factors unique to women include pregnancy, gestational diabetes, hypertensive disorders of pregnancy, eclampsia and preeclampsia, changes in hormonal status, postmenopausal hormone use and oral contraceptive use. Although in both sexes stroke is most often presented by weakness of one side of the body, face or speech disorders, women may also present with more atypical symptoms of acute stroke compared to men. Women also have a longer delay to treatment, and less frequently receive acute stroke evaluation than men.

**KEYWORDS:** stroke; women; atrial fibrillation; blood pressure

## SAŽETAK:

MOŽDANI UDAR U ŽENA: RAZLIKA U RIZIKU, ČIMBENICI I LIJEČENJE U USPOREDBI S MUŠKARCIMA  
Moždani udar jedan je od najvećih javnozdravstvenih problema i vodeći je uzrok smrti u svijetu s oko 6,5 milijuna smrtnih slučajeva godišnje. Dobno specifične stope mortaliteta rastu s godinama i veće su u muškaraca nego u žena za sve dobne skupine, osim u dobi od 80+ godina kada su stope mortaliteta u žena veće nego u muškaraca. Žene žive dulje i stoga imaju veći životni rizik od moždanog udara od muškaraca. Žene imaju čimbenike rizika specifične za spol, kao i neke neprepoznate rizike koji pridonose lošijim ishodima moždanog udara. Među tradicionalnim čimbenicima rizika koji imaju veći utjecaj na moždani udar kod žena su arterijska hipertenzija, fibrilacija atrijska i dijabetes melitus. Čimbenici rizika jedinstveni za žene uključuju trudnoću, gestacijski dijabetes, hipertenzivnu bolest u trudnoći, eklampsiju i preeklampsiju, promjene u hormonskom statusu, korištenje hormonske terapije u postmenopauzi i korištenje oralnih kontraceptiva. Iako se kod oba spola moždani udar najčešće manifestira slabošću jedne strane tijela, lica ili smetnjama govora, kod žena se mogu javiti i atipični simptomi moždanog udara. Žene također dulje čekaju na obradu, procjenu i liječenje moždanog udara od muškaraca.

**KLJUČNE RIJEČI:** moždani udar; žene; fibrilacija atrijska; krvni tlak

## INTRODUCTION

Stroke is one of the major public health problems and it is the leading cause of death in the world with around 6.5 million deaths per year (1). In Europe, it is also the second cause of death, after ischemic heart disease, with around 1 million deaths per year. Also, stroke is the cause of death in 13% of deceased women and 9% of deceased men in Europe. In Croatia, stroke has been the second cause of mortality for years, with a total of 4,950 deaths in 2020. and a share of 8.7% in total mortality. In men, stroke is in third place after ischemic heart disease and COVID-19 infection, while in women it is behind ischemic heart disease and hypertension, but compared to 2019., there was no decrease in deaths (2). Patients often suffer from neurologic sequelae as well as increased likelihood of hospital readmission and complications such as infections, venous thromboembolism, falls, and fractures (3).

Age-specific mortality rates increase with age and are higher in men than in women for all age groups, except at the age of 80+ when the mortality rates in women are higher than in men (4). Although men have a higher age-adjusted incidence of stroke, women live longer and therefore have a higher lifetime risk of stroke than men (5). The social context for women experiencing stroke is also important. The age at onset of stroke is on average 4 to 6 years higher in women than in men. In addition, women are more likely to be widowed, unmarried, or living alone and to be more limited in their activities of daily living than men at the time of stroke (6). Women tend to have worse functional outcomes after stroke in terms of return to basic life activities and quality of life (3). In addition, women are at higher risk of institutionalization after stroke (5).

Men and women differ in their likelihood of having a stroke, in the importance of various risk factors, and in the effectiveness of various treatments during and after a stroke (7). The main aim of this review is to highlight current knowledge about stroke in men and women, as well as potential areas for future studies and investigations.

## RISK FACTORS

In women, there are large differences in the strength of association of stroke risk factors. In addition to nonmodifiable risk factors for stroke (age, genetics, and race), there are several modifiable risk factors, and women are more affected by certain risk factors than men. In addition, women have sex-specific risk factors as well as some unrecognized risks that contribute to poor stroke outcomes (5). Traditional risk factors that have a greater impact on stroke in women include hypertension, atrial fibrillation, and diabetes mellitus (8).

Hypertension is the most common modifiable risk factor for stroke in both men and women. Several analyses have shown that intensive blood pressure control is the most beneficial for stroke risk reduction (9). Female stroke patients are more likely

to have higher blood pressure than male stroke patients. Although women have lower blood pressure than men for most of their lives, the prevalence of hypertension increases dramatically after menopause and exceeds that of men after age 55 (7). Blood pressure control is particularly poor in older women. In a large study in 26 countries, only 29% of women aged 70-79 years had well-controlled blood pressure (10).

Atrial fibrillation is a modifiable risk factor for both women and men, with data showing that women with atrial fibrillation have a higher risk of stroke and all-cause mortality compared with men. Female sex was also included as a risk factor in the CHADS<sub>2</sub>VASc<sub>2</sub> score for anticoagulation decision making. Women > 65 years with atrial fibrillation are at particularly high risk of stroke (6). The usual therapy for atrial fibrillation is anticoagulation. There are some data showing that women are less likely to be treated with anticoagulation and that women have a higher risk of stroke despite anticoagulation with warfarin. No difference was found between men and women treated with novel anticoagulants (10).

Diabetes mellitus is more strongly associated with ischemic stroke in women than in men, with a more pronounced difference in type 1 diabetes. The risk of ischemic stroke increases in women at lower fasting blood glucose levels than in men, even after adjustment for treatment with oral hypoglycemics or insulin (6).

Women-specific risk factors include pregnancy, gestational diabetes, eclampsia and preeclampsia, changes in hormonal status, use of postmenopausal hormones, and use of oral contraceptives. In women who use oral contraceptives, obesity and hypercholesterolemia increase the risk of stroke by 4.6 and 10.8 times, respectively, compared with women who have no risk factors and do not use oral contraceptives. Early menarche and early menopause are also associated with increased stroke risk (8).

Migraine has been shown to be a risk factor for stroke in women, but not in men, with an exponentially increased risk in women who smoke cigarettes or use oral contraceptives (2).

Elevated body mass index, clinical obesity (body mass index,  $\geq 30$  kg/m<sup>2</sup>), and higher waist-to-hip ratio are associated with higher risk of ischemic stroke in both sexes, but with a stronger association in women than men (6).

Underrecognized risk factors that contribute to poor stroke outcomes in women include depression and anxiety, which are associated with an increased risk of morbidity and mortality from cardiovascular disease. Although they have not been sufficiently investigated, other risks are beginning to be recognized, for example, abuse and violence by intimate partners, socioeconomic deprivation and poor health literacy (8).

In Croatia, the public health campaign Red Dress Day was launched in 2019., and is traditionally held on the first Friday in February under the tag #wearred. The goal of this public health campaign is to raise awareness of the causes, warning signs and consequences of stroke in women (8).

### CLINICAL PRESENTATION

Although stroke is most commonly manifested by weakness of one side of the body, facial or speech disorders, women may also present with more atypical symptoms of acute stroke compared with men, which may lead to delayed diagnosis. These atypical symptoms may include altered consciousness or mental status, fatigue, drowsiness, incontinence, facial and limb pain, and general weakness. Women also experience nausea, chest pain, shortness of breath, palpitations, and hiccups (11). If emergency department physicians do not recognize these symptoms as potential signs of acute stroke, patients may be inappropriately triaged, insufficiently or incorrectly treated, which can lead to a poor outcome (3).

### STROKE TREATMENT

Women have better awareness of stroke symptoms but are less likely to call an ambulance and more likely to not know when symptoms occur. Women also have a longer delay to treatment and are less frequently receive acute stroke evaluation than men (9).

The efficacy of intravenous tissue plasminogen activator (tPA) in the treatment of acute ischemic stroke is well established (3). A meta-analysis of 24 studies published between 2008. and 2018. reported on sex-specific usage rates of use of IV r-tPA in ischemic stroke. The analysis found that women were 13% less likely to receive IV r-tPA treatment compared with men (6). In a study of 100 patients, higher recanalization rates after tPA for anterior circulation strokes were seen in women than in men. In addition, neurologic improvement within 72 hours of treatment occurred significantly more often in women.

Endovascular thrombectomy (EVT) for the treatment of acute stroke is now standard of care in patients with large vessel occlusions occurring in specific time windows with appropriate

imaging features. An analysis of data from three early EVT trials examining sex differences in thrombectomy outcomes found no difference in reperfusion rates, time to reperfusion, or adjusted rates of functional independence. However, after adjustment for age at presentation and stroke severity, women had more years of optimal life after EVT (9).

Several studies have shown that a higher rate of endovascular thrombectomy is performed in women with ischemic stroke than in men. Sex differences in the treatment of ischemic stroke were examined in an administrative database in Germany, where more than 1.11 million patients were hospitalized for a first or recurrent ischemic stroke from 2013. to 2017. During the 5-year study period, women were 26% more likely overall to receive endovascular thrombectomy. Similar findings were made in a retrospective study of more than 4 million patients in the United States, in which women were 20% more likely to be treated with endovascular thrombectomy compared with men between 2016. and 2017. The reasons for this sex disparity are unknown; one of the reasons may be that women with atrial fibrillation are less likely to be treated for stroke prevention, which may lead to more large-vessel cardioembolic strokes in women and a higher need for endovascular thrombectomy (6).

### CONCLUSION

Stroke remains a serious and growing problem, especially in women, as the population ages. Health care providers should recognize and treat important stroke risk factors such as hypertension, diabetes mellitus, atrial fibrillation, and depression. It is critical to continue to monitor gender trends and develop strategies to ensure optimal stroke care for both women and men. Better knowledge of the impact of sex and gender on stroke will improve outcomes for all affected.

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