



Review

From head to toe: Sex and gender differences in the treatment of ischemic cerebral disease



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ARTICLE INFO

Article history:

Received 8 August 2016

Received in revised form 27 March 2017

Accepted 9 May 2017

Available online 12 May 2017

Keywords:

Acute stroke

Systemic thrombolysis

Anti-platelet drugs

Risk stratification

Anti-hypertensive drugs

Gender differences

ABSTRACT

Stroke is a major cause of mortality and morbidity, particularly in the older ages. Women have a longer life expectancy and are more likely to experience stroke than men. Interestingly, the increased risk of ischemic stroke in women seems to be independent from age or classical cardiovascular risk factors. Notwithstanding the fact that stroke outcomes and survival are usually poorer in women, current evidence suggests that thrombolysis, antiplatelet and anticoagulant therapies are more beneficial in women than in men. A possible explanation of this paradox might be that females are often undertreated and they have fewer chances to be submitted to an effective and timely treatment for stroke than the male counterpart. The first step in the attempt to solve this obvious discrimination is surely to emphasize any reasons for differences in the therapeutic approach in relation to gender and then to denounce the lack of a sustainable motivation for them. In this article, we aimed to review the existing literature about gender-related differences on efficacy, administration and side effects of the most common drugs used for the treatment of ischemic stroke. The most striking result was the evidence that the therapeutic approach for stroke is often different according to patients' gender with a clear detrimental prognostic effect for women. A major effort is necessary to overcome this problem in order to ensure equal right to treatment without any sexual discrimination.

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Abbreviations: ATRIA, AnTicoagulation and Risk factors In Atrial fibrillation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; AP, acute phase; BI, Barthel index; BP, blood pressure; ATC, Antithrombotic Trialists' Collaboration; CCB, calcium channel blockers; CARAF, Canadian Registry of Atrial Fibrillation; CASE, Canadian Alteplase for Stroke Effectiveness Study; DOACs, Direct Oral Anticoagulants; ED, emergency department; GAIN, Glycine Antagonist in Neuroprotection for Patients with Acute Stroke Americas; HR, hazard ratio; HF, heart failure; HT, hypertension; IAT, intra-arterial thrombolysis; ICH, intracerebral haemorrhage; IS, ischemic stroke; MI, myocardial infarction; IVT, intra-venous thrombolysis; JUPITER, Justification for the Use of Statins in Preventionan Intervention Trial Evaluating Rosuvastatin; LMWH, low molecular weight heparin; LOS, length of stay; MACE, major cardiovascular events; MH, major haemorrhage; M, meta-analysis; mRS, modified Rankin Scale; MOSES, Morbidity and Mortality After StrokeEprosartan Compared With Nitrendipine for Secondary Prevention; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute for Neurological Disorders and Stroke; NVAf, non-valvular atrial fibrillation; OR, odds ratio; P, perspective study; PP, primary prevention; PROACT-2, Prolyse in Acute Cerebral Thromboembolism II; PROGRESS, Perindopril pROtection aGainst REcurrent Stroke Study; RR, rate ratio; r-tPA, recombinant tissue-type plasminogen activator; R, retrospective study; RCT, randomized controlled trial; SR, systematic review; SE, systemic embolism; SP, secondary prevention; SIS-16, Stroke Impact Scale-16 score; SITS-ISTR, Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register; SITS-MOST, Stroke International Stroke Thrombolysis Monitoring Study; ECASSII, Second European-Australasian Acute Stroke Study; SPAF, Stroke Prevention in Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation; TZD, thiazide diuretics; TTR, time in therapeutic range; WHS, Women's health study.

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1. Introduction

Women are 3 times more likely to survive to 90 years of age when compared to men [1]. In view of the longer life expectancy, women have a higher risk of stroke, especially in the post-menopausal period [2]. However, this increased risk does not seem limited to older women, as previously reported. In this respect, the results of the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study, confirmed that female sex significantly increase the predisposition to stroke, independently from age [3]. Many aspects of stroke are similar in men and women, including clinical presentation, neuroimaging data, main subtypes, and indication for acute treatment. Conventional risk factors are also the same [4]. However, several studies have found that sex differences in epidemiology, clinical characteristics and management of acute stroke indeed exist and they have a significant impact on clinical outcomes [5,6]. Particularly, it is worth to underline the presence of sex-specific risk factors for stroke. Indeed, oral contraceptives administration has been associated to an increased risk of stroke [7] especially when associated to smoking and hypertension [8]. An early menopause has also been associated to an increased rate of cardiovascular events and vascular death [9,10] and the risk increases further in the presence of hormone therapy [11]. Other investigations underlined that hormonal changes may represent relevant factors that can significantly influence the risk of vascular events both in women as in men [12].

Women carrying inherited prothrombotic conditions show a 2- to 20-fold increased risk of stroke [13,14]. Migraine headache carries a 2- to 4-fold increased risk of IS (ischemic stroke) among females and even in this case the predisposition to stroke is significantly influenced by the presence of an additional cardiovascular risk factor [15,16]. A recent systematic review identified in hypertensive disorders during pregnancy (gestational hypertension, preeclampsia or eclampsia) and oophorectomy the strongest female-specific risk factors for stroke, whereas hysterectomy resulted to have a protective role [12]. There is evidence that women are very often disadvantaged in aspects related to the possibility to a timely access to the emergency department (ED) and then to receive appropriate therapeutic intervention in the acute phase [17]. The understanding of the social and pathophysiological bases for these differences may eventually improve patients' care. Our aim was to provide a review of the available literature on sex- and gender-related differences in the acute treatment of IS.

2. Methods

We searched PubMed and EMBASE databases for reviews and original research articles published in English from January 1, 2000 to June 1, 2016. We used the terms "Stroke"[MeSH], "Sex"[MeSH] or "Gender Identity"[MeSH] or "Therapeutics"[MeSH] alone and in combination with the analysed classes of drugs. The choice of this time window mainly derives from the finding that the concept of

sex differences in the management of cerebrovascular diseases has been spreading over the past 16 years as demonstrated by the analysis of the scientific production showing that most of the articles on the topic have been published since 2000 (absolute number retrieved from PubMed: 2455 papers). Before that date, the very low number of reports suggests marginal interest in the subject (absolute number retrieved from PubMed: 55 papers). For this reason, we selected papers mainly from the past 16 years, although we did not exclude frequently referenced and highly regarded older reports. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant. We selected both high-quality systematic reviews and individual studies. Two independent investigators (L.F. and G.V.), blinded to each other, screened titles and abstracts of the potentially eligible studies and extracted full texts of the papers of interest. Investigators evaluated adherence of RCTs to CONSORT checklist [18], adherence of observational studies to STROBE checklist [19] and adherence of systematic reviews to PRISMA checklist [20] as measures of reporting quality. Then they evaluated methodological quality of papers with the Joanna Briggs Institute critical appraisal checklists for RCTs, observational studies and systematic reviews [21]. Each reviewer was then asked to give a positive or negative rating on each evaluated paper. Papers receiving a double negative score were discarded. Discrepancies between investigators were solved by consensus or third party arbitration (M.S.), if required.

3. Results

According to international guidelines [22], IS treatment is mainly based on two approaches: thrombolysis with recombinant tissue-type plasminogen activator (r-tPA) alone or associated to mechanic thrombectomy and early secondary prevention based on the correction of vascular risk factors and the use of anti-platelet, anticoagulant and statin drugs.

3.1. Intravenous thrombolysis

15 observational studies, 8 randomized controlled trials and 4 systematic reviews were considered acceptable after critical appraisal and included to discuss this topic, along with 2 narrative reviews, which were not scored. Intravenous thrombolysis is now widely diffused and temporal trends have shown that the rates of patients that have access to r-tPA therapy are increasing over the last years. Indeed, according to guidelines, eligible patients with acute stroke symptoms presenting to the ED within 4.5 h from symptoms' onset should be promptly considered for intravenous thrombolysis with r-tPA. Several studies have reported gender differences both in r-tPA treatment and in stroke outcome. The introduction of mechanic thrombectomy as an adjunctive treatment resource for ischemic stroke is relatively recent [23–25] and, for this reason, data are not yet sufficient to evaluate for possible sex-related differences for this approach. However, according to a

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