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Original Article

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Long-Term Survival After Stroke According to Reperfusion Therapy, Cardiovascular Therapy and Gender

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Abstract

Background: A wide variety of factors influence stroke prognosis, including age, stroke severity and comorbid conditions; but most current information about outcomes and safety is derived from patients at 3 - 12 months and mostly coming from the hospital activity. The aim of this study is to evaluate whether treatment strategies have a differential impact on long-survival after acute ischemic stroke among men versus women.

Methods: Acute ischemic stroke patients identified from the population-based register between January 1, 2011 and December 31, 2012 were included, and they were classified into: 1) Acute ischemic stroke + intravenous thrombolysis (group I); 2) Acute ischemic stroke + mechanical thrombectomy with or without intravenous thrombolysis (group II); 3) Acute ischemic stroke + medical therapy alone (no reperfusion therapies) (group III). Follow-up went through up until December 2016. The probability of survival was estimated by the Kaplan-Meier method, and the hazard ratio was obtained by using the Cox proportional hazard regression models. Mortality was interpreted as overall mortality.

Results: A total of 14,368 cases (men 50.1%), 77.1 ± 11.0 years old were included. There was higher survival among those treated with intravenous thrombolysis ($P < 0.001$); women treated with thrombectomy ($P < 0.001$); and women < 80 years old without reperfusion therapy. The most common medications were antiplatelets (52.8%), associated with lower survival ($P < 0.001$); and statins (46.5%), associated with higher survival. The regression model produced the following independent outcome variables associated to mortality: anticoagulant hazard ratio (HR) 1.53 (95% confidence interval (95% CI): 1.44 - 1.63, $P < 0.001$), diuretics HR 1.71 (95% CI: 1.63 - 1.79, $P < 0.001$), antiplatelet HR 1.49 (95% CI: 1.42 - 1.56, $P < 0.001$), statins HR 0.73 (95% CI: 0.70 - 0.77; $P < 0.001$), angiotensin II receptor antagonists HR 0.93 (95% CI: 0.89 - 0.98, $P = 0.008$) and reperfusion therapy HR 0.88 (95% CI: 0.81 - 0.97, $P = 0.009$).

Conclusions: Men and women have different prognoses after revascularization treatment for acute ischemic stroke. Under 80 years old the women appear to have a better outcome than men when treated with thrombolysis therapy and/or catheter-based thrombectomy. The chronic cardiovascular pharmacotherapy must be evaluated whether they should be included as factors in the decision to reperfusion.

Keywords: Acute ischemic stroke; Revascularization therapy; Sex; Chronic comorbidities; Long-term survival

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Introduction

A wide variety of factors influence stroke prognosis, including age, stroke severity and comorbid conditions [1-4]. In addition, interventions such as reperfusion therapy can play a major role in the outcome of ischemic stroke. Previous reports [5-10] concerning sex differences in stroke [7, 11, 12] and outcome are inconsistent [13, 14] and are sometimes difficult to interpret; and the reasons for disparities remain unclear despite adjustment for baseline differences in age, prestroke function and comorbidities. Actually most current information about outcomes and safety is derived from patients at 3 - 12 months, and mostly coming from the hospital activity that are not avail-

able in the area of primary care. There is neither study assessing the efficacy of revascularization (medical therapy alone vs. intravenous thrombolysis (IVT) vs. mechanical thrombectomy) in long-term outcome beyond hospital discharge, nor evaluation of potential effects on survival from interactions of cardiovascular chronic treatments and revascularization therapy associated with gender differences.

This work is a continuation and extension of the Ebrictus study [15-17]. The aim of our study was to evaluate whether treatment strategies have a differential impact on long-term survival after acute ischemic stroke (AIS) among men versus women.

Materials and Methods

Data collection and study procedures

This cohort study is based on AIS patients identified from the Minimum Basic Data Register (MBDR) at hospital discharge through specific International Classification of Diseases (ICD-9) codes. Access to population-based data was reached through the Public Program epidemiological analysis for Health Research and Innovation in Catalonia (PADRIS). The measures were collected by a retrospective review of medical records of consecutive stroke admissions (January 1, 2011 through December 31, 2012) in Catalonia, Spain. Eligible patients were between the ages of 15 and 90 years. The study protocol, which is available at "Long survival after ischemic stroke and thrombolysis in Catalonia", ClinicalTrials.gov number, NCT03247036, and has been certified by the Independent Ethics Committee (IEC) of University Institute for Primary Care Research Jordi Gol (IDIAP), code 4R17/017.

The primary outcome was all-causes mortality. The study complies with the Helsinki Declaration and the local ethics committee requirements for clinical research; and the Institutional Review Board Approval.

Case definition

The automated operation of the PADRIS database retrieved all patients with a diagnosis code of AIS (codes 433.x1, 434.xx, and 436) with and without any of the following procedures codes: 99.10 "Injection or infusion of thrombolytic agent", 39.74 "Endovascular removal of obstruction from head and neck vessel(s)", and 38.91 "Arterial catheterization". According to ICD-9 procedure codes, the cohort was classified into: 1) AIS + IVT (group I); 2) AIS + mechanical thrombectomy with or without IVT (group II); and 3) AIS + medical therapy alone (no reperfusion therapies) (group III). An external audit was carried out on the general information and to investigate irregularities in the inclusion criteria.

The variables collected included: date of hospital admission, date of discharge, age, gender, treatment group (I, II or III), medication dispensation from the Integral System of Electronic Prescription (ISEP) from at least 3 months before episode (anticoagulant, antiplatelets, statin, antidiabetics, diuretics, angiotensin converting enzyme inhibitor, angiotensin II receptor antagonists (A-IIRA), and beta-blocker); and patient vital status (alive/dead), and date (day/month/year) of death from the Central Register of insured people (CRA). All these registries are population-based and managed by the Health Department, Government of Catalonia.

Statistical analysis

Statistical analysis was undertaken with the following: 1) Descriptive study of basic statistics and standard deviation of key variables stratified by age and sex; 2) The probability of survival was estimated by the Kaplan-Meier method, and the hazard ratio (HR) was obtained by using the Cox proportional hazard regression models. Mortality was interpreted as overall mortality. The variables were included in a multivariate model performed with adjustment for age, sex, and type of medication. The analysis and processing of data were performed using the SPSS 11.5 statistical package for Windows.

Results

Characteristics of the study population

A total of 14,368 AIS patients were included (men 50.1%). Table 1 shows the baseline demographics and cardiovascular medication used. The average patient age was 77.1 ± 11.0 years and average follow-up was 3.1 ± 2.2 years. Men (74.2 ± 11.1) were significantly younger ($P < 0.001$) than women (80.0 ± 10.2). The most commonly medications (Table 2) were antiplatelets (52.8%) associated with lower survival outcome ($P < 0.001$), and statins (46.5%), associated with higher survival outcome, independent of gender. Between the ages of 60 and 79 years, the most prescribed medications included anticoagulants (13.5-15.3%), antidiabetics (34-37.6%), statins (54.5-55.7%), diuretics (54.8%) and antiplatelets prescriptions which increased progressively from 44.4% at < 60 years to 63.4% at > 90 years.

Mortality rates

Overall, all-causes mortality was 43.8%, increasing from 17.1% < 60 years up to 93.5% > 90 years (Fig. 1). The cumulative 5-year survival proportion was 0.30 ± 0.06 among women and 0.38 ± 0.02 among men ($P < 0.001$) after stroke. The revascularization procedure was associated to different outcome (Fig. 2). The multivariate regression model identified the following independent outcome variables: anticoagulant HR 1.53 (95% CI:1.44 - 1.63, $P < 0.001$), diuretics HR 1.71 (95% CI: 1.63 - 1.79, $P < 0.001$), antiplatelets HR 1.49 (95% CI: 1.42 - 1.56, $P < 0.001$), statins HR 0.73 (95% CI: 0.70 - 0.77, $P < 0.001$), A-IIRA HR 0.93 (95% CI: 0.89 - 0.98, $P = 0.008$) and reperfusion therapy HR 0.88 (95% CI: 0.81 - 0.97, $P = 0.009$).

There were 941 patients (471 women) received IVT (group

Table 1. Baseline Characteristics by Sex

Variable	Thrombolytic therapy				Thrombolytic therapy and/or thrombectomy				Medical therapy alone			
	Women	Men	P	All	Women	Men	P	All	Women	Men	P	All
Cases number	521 (49.2)	538 (50.8)	0.335	1,059	165 (43.9)	211 (56.1)	0.011	376	6,530 (50.0)	6,521 (50.0)		13,051
Age (average) ± SD	77.87 ± 8.4	73.12 ± 9.9	< 0.001	75.45 ± 9.5	70.48 ± 11.2	68.64 ± 11.	0.11	69.45 ± 11.1	80.3 ± 10.1	74.4 ± 11.1	< 0.001	77.4 ± 11.0
Age groups			< 0.001				0.019				< 0.001	
< 15 years old	0	0	-	0	0	1		1	0	1		1
15 - 59	20 (3.8)	54 (10.0)	< 0.001	75	27 (16.4)	34 (16.1)		61	302 (4.6)	661 (10.1)		963
60 - 69	58 (11.1)	118 (21.9)	< 0.001	176	36 (21.8)	63 (29.9)		99	532 (8.1)	1,335 (20.5)		1,867
70 - 79	176 (33.8)	214 (39.8)	< 0.001	390	64 (38.8)	90 (42.7)		154	1,655 (25.3)	2,080 (31.9)		3735
80 - 89	244 (46.8)	144 (26.8)	< 0.001	388	38 (23.0)	23 (10.9)		61	3,052 (46.7)	2,094 (32.1)		5,146
> 90 years old	23 (4.4)	8 (1.5)	< 0.001	31	-	-		-	989 (15.1)	350 (5.4)		1,339
Primary outcome (mortality at 5 years)	274 (52.6)	249 (46.3)	0.023	523 (49.4)	57 (34.5)	92 (43.6)	0.047	149 (39.6)	4,005 (61.3)	3,447 (52.9)	< 0.001	7,452 (57.1)
Cumulated proportion survival at 5 years	0.38	0.47	0.023	0.42	0.56	0.49	0.116	0.52	0.29	0.37	< 0.001	0.33
Hemorrhagic stroke post-	6	4	0.075	10	1	3	0.587	4	72	150	0.075	222 (97.7)

Table 2. Treatments by Sex

Variables	Thrombolytic therapy				Thrombolytic therapy and/or thrombectomy				Medical therapy alone			
	Women	Men	P	All	Women	Men	P	All	Women	Men	P	All
Anticoagulants (%)	34 (6.5)	35 (6.5)	0.544	69 (6.5)	33 (20.0)	28 (13.3)	0.053	61 (16.2)	949 (14.5)	782 (12.0)	< 0.001	1731 (13.3)
Antiaggregants (%)	246 (47.2)	297 (55.2)	0.006	543 (51.3)	61 (37.0)	104 (49.3)	0.011	165 (43.9)	3,216 (49.2)	3,722 (57.1)	< 0.001	6,938 (53.2)
Statins (%)	221 (42.4)	282 (52.4)	0.001	503 (47.5)	75 (45.5)	123 (58.3)	0.009	198 (52.7)	2,777 (42.5)	3,255 (49.9)	< 0.001	6,032 (46.2)
Antidiabetics (%)	98 (18.8)	141 (26.2)	0.002	239 (22.6)	33 (20.0)	52 (24.6)	0.173	85 (22.6)	1,698 (26.0)	2,138 (32.8)	< 0.001	3,836 (29.4)
Diuretics (%)	203 (39.0)	144 (26.8)	< 0.001	347 (32.8)	58 (35.2)	50 (23.7)	0.01	108 (28.7)	2,953 (45.2)	2,038 (31.3)	< 0.001	4,991 (38.2)
ACEIs (%)	176 (33.8)	172 (32.0)	0.287	348 (32.9)	57 (34.5)	74 (35.1)	0.502	131 (34.8)	2,425 (37.1)	2,652 (40.7)	< 0.001	5,077 (38.9)
AII-RA	178 (34.2)	153 (28.4)	0.026	331 (31.3)	47 (28.5)	61 (28.9)	0.511	108 (28.7)	1,975 (30.2)	1,706 (26.2)	< 0.001	3,681 (28.2)
Beta-blocker	176 (33.8)	176 (32.7)	0.381	352 (33.2)	49 (29.7)	75 (35.3)	0.139	124 (33.0)	1,798 (27.5)	1,616 (24.8)	< 0.001	3,414 (26.2)

ACEI: angiotensin converting enzyme inhibitor; AII-RA: angiotensin II receptor antagonists.

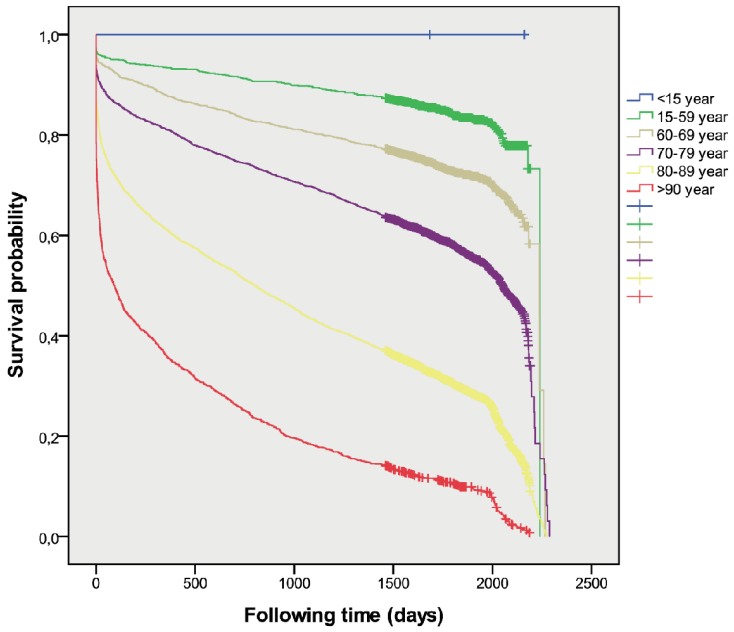

Figure 1. Overall mortality according to age (all cases).

I) and had better survival than those who did not receive it (P = 0.001) with an adjusted HR 0.83 (0.764 - 0.913) at 5-year survival, higher among men (P = 0.02) (Fig. 3). Women were older than men (78.4 ± 8.2 vs. 73.4 ± 10.0, P < 0.001). A higher mortality was shown among those treated with diuretics (P < 0.001) and/or antiplatelets (P = 0.001) independent of gender. The multivariate regression model identified the following independent outcome variables: age HR 1.08 (95% CI: 1.06 - 1.09, P = 0.001), diuretics HR 1.34 (95% CI: 1.12 - 1.61, P < 0.001), antiplatelets HR 1.34 (95% CI: 1.12 - 1.60, P<0.001), anticoagulant HR 1.43 (95% CI: 1.03 - 2.00, P = 0.03) and antidiabetics HR 1.24 (95% CI: 1.02 - 1.52, P = 0.03). Of the 376 cases who were treated with thrombolysis therapy and/or catheter-based thrombectomy (group II) the number was significantly higher among men (P = 0.01), but resulted in better survival outcomes among women (P = 0.05) (Fig. 4) than men, and got the best survival profile among women (P < 0.001) (Figs. 5, 6).

Totally, 13,051 (90.8% patients, women 50.0%) were treated with medical therapy alone (group III). They were significantly older than those with reperfusion therapy (77.4 ± 11.1 vs. 75.9 ± 9.5, P < 0.001); and women were signifi-

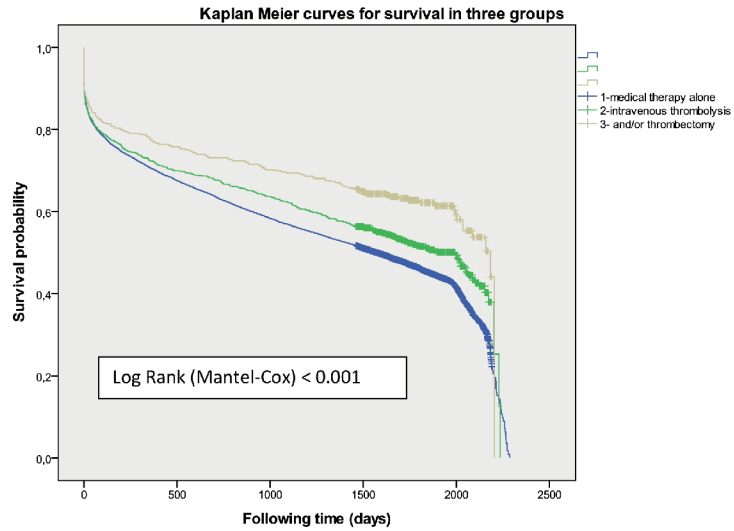

Figure 2. Overall mortality according to revascularization procedure (all cases).

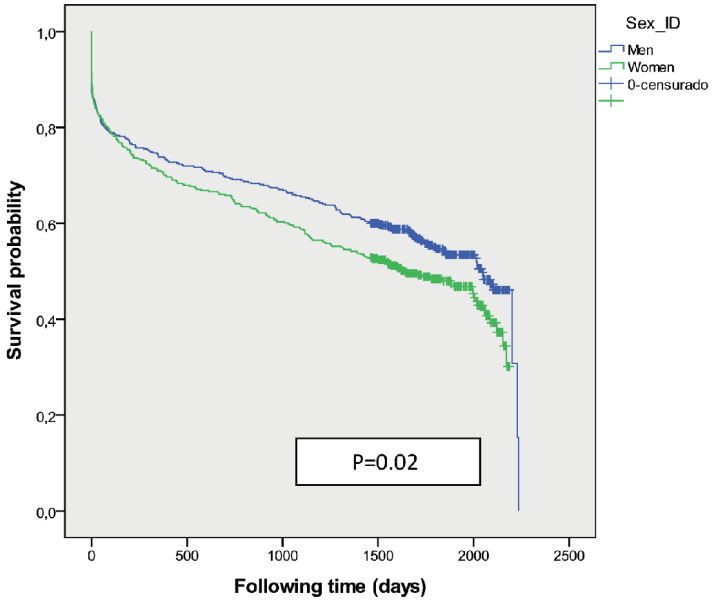

Figure 3. Survival probability for medical therapy including intravenous thrombolysis (group I) according to sex.

cantly older than men (P < 0.001) (80.3 ± 10.1 vs. 74.4 ± 11.1). Overall, there was higher survival (P < 0.001) among women under 80 years. The overall survival probability was 0.29 ± 0.08 among women and 0.37 ± 0.06 among men (P < 0.001) 5 years after stroke. Mortality was higher among those treated with anticoagulants (P < 0.001), diuretics (P < 0.001), antiplatelets (P < 0.001) and beta-blockers (P = 0.02); but the survival was significantly longer if patients were treated with A-IIRA (P < 0.001), antidiabetics (P < 0.001) and statins (P < 0.001) without differences by gender. The beta-blockers resulted in better survival outcomes in women and the antidiabetics in men (P < 0.001). The multivariate regression model identified the following independent outcome variables: A-IIRA HR 0.89 (95% CI: 0.82 - 0.96, P = 0.005), statins HR 0.90 (95% CI: 0.84 - 0.96, P = 0.003), diuretics HR 1.48 (95% CI: 1.38 - 1.59, P < 0.001), anticoagulant HR 1.32 (95% CI: 1.20 - 1.47, P < 0.001), antiplatelets HR 1.16 (95% CI: 1.08 - 1.25, P < 0.001) and age HR 1.1 (95% CI:

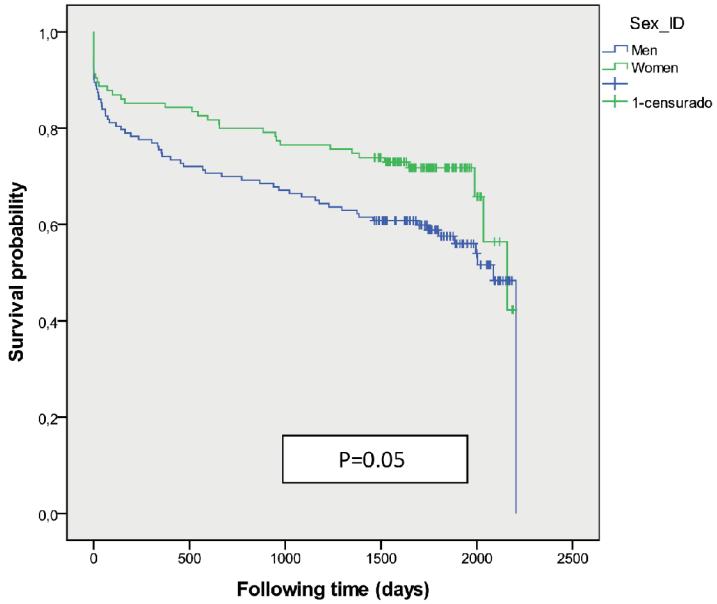

Figure 4. Survival curve for mechanical thrombectomy with or without intravenous thrombolysis (group II) according to sex.

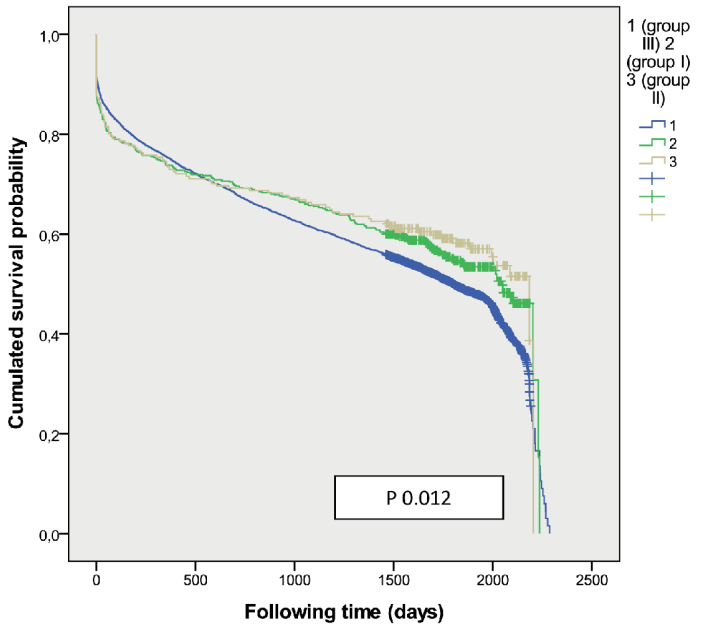

Figure 5. Overall mortality according treatment group in men.

1.06 - 1.07, P < 0.001).

Discussion

This study brings results that reperfusion therapy seems to benefit women and men differently. We observed the following key findings: 1) IVT modifies the long-term survival expected in the natural course after AIS; 2) Women were significantly older in the group treated with medical therapy alone, but their survival was better than that of men over 80 years old; 3) Some medications/drugs could be associated with a bad prognosis,

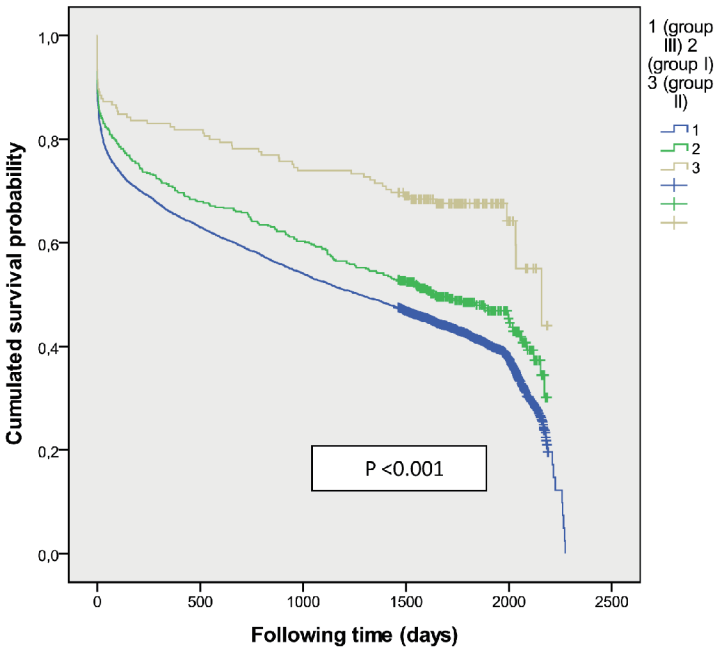

Figure 6. Overall mortality according treatment group in women.

and their use could be an indicator of that prognosis; 4) Women tend to be undertreated with medical therapies which is consistent with data from the cardiovascular outcomes literature; 5) Women in the group of mechanical thrombectomy with or without IVT showed better survival than men although our sample size was not sufficient to permit robust assessments.

Some authors [18] have suggested that these differences are multifactorial, but new data suggest that there are biological differences [19]. The challenge is whether these data can achieve better health outcomes through the selection of patients with a more favorable risk versus selection on the basis of reperfusion profile.

A greater understanding of the differences and similarities between males and females with respect to previous cardiovascular risk factors [1, 17, 18, 20], previous physical or mental condition [21, 22], response to acute stroke therapies, and recovery will hopefully lead to better outcomes in the future.

The chronic cardiovascular medications used confirm epidemiological data of stroke-related risk factors and comorbid conditions in Catalonia [4], highlighting that a higher percentage of men have been treated with antiplatelets ($P = 0.006$), statins ($P = 0.001$) and antidiabetics ($P = 0.002$), apparently for more ischemic comorbidities; and a higher percentage of women took AII-RA ($P = 0.026$) and diuretics ($P < 0.001$) possibly indicating a higher proportion of heart failure in that population. Possibly, the increase of mortality that is associated with cardiovascular pharmacotherapy is actually related to the basal comorbidities treated as diabetes mellitus, hypertension, heart failure, coronary artery diseases and/or atrial fibrillation. These comorbidities must be evaluated to determine their effects on the reperfusion therapy outcome and whether they should be included as factors in the decision to reperfusion [23].

The protective effects of statins and ARA-II are clearly independent of treatment with reperfusion therapy or the absence thereof. Statin use is widely delivered in patients who have previously suffered a stroke and were significantly more likely to survive compared with non-users [24, 25]. Aspirin given together with a thrombolytic agent may worsen the risk-to-benefit ratio [26] probably due to cerebral hemorrhagic complications, but this problem was not investigated in our study. The anticoagulant treatment often has poor quality results and has been associated with high frequency of complications and poor outcome; but in selected new oral anticoagulants (NOACs) treated patients with an acute stroke, endovascular thrombectomy is preferred if indicated and possible [27]. The use of antidiabetics was associated with higher survival in the group I, differing with results [1] that showed higher death rates among women, and higher long-term mortality in patients with diabetes [28]. Although diabetes is not a contraindication for thrombolysis therapy, patients with diabetes are often undertreated [29] and could have a sampling bias.

Previous clinical trials have largely ignored the potential for gender-specific responses to treatments [30, 31]. It may be that the beneficial impact of reperfusion therapy could be neutralized by basal comorbidities and/or their treatment, or perhaps the mortality outcome of the reperfusion therapy depends more on the comorbidities profile. The group with thrombectomy was the only one in which women had more favorable outcomes than men, but also more men than women received mechanical thrombectomy. This fact is interesting to point out for future study. The development of computerized decision tools [32, 33] that examine factors such as age, gender, cardiovascular comorbidities and their treatment may support the optimization of decision making to further improve mechanical thrombectomy effectiveness as standard care for eligible patients [34] and seamlessly support different approaches to decision-making about reperfusion therapy. Eventually, the results of controlled trials [2, 35-38] have confirmed the safety and efficacy of mechanical thrombectomy and its importance for the advancement of stroke care [39], but have not been evaluated different effects by gender and comorbidities.

There are some limitations to our study. First, it consisted of a retrospective review of medical records. Primary randomization of gender is not possible. It was not possible divide the group mechanical thrombectomy with or without IVT by reason of codification methodology. The results were limited to patients treated with reperfusion therapy and drugs for management of chronic conditions. The accessibility to procedure includes variations between different areas, and the type and quality of revascularization that patients can access often will depend on where they live particularly in the rural and remote areas.

Conclusions

Men and women have different prognoses after revascularization treatment for AIS. Under 80 years old the women appear to have a better outcome than men when treated with thrombolysis therapy and/or catheter-based thrombectomy and with medical therapy alone; whereas the men appear to have a better outcome than women when received just IVT. The chronic cardiovascular pharmacotherapy must be evaluated to determine its effects on the reperfusion therapy outcome and whether they should be included as factors in the decision to reperfusion.

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Conflict of Interest

All authors declare that they have no conflict of interest.

Author Contributions

Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

Disclosures

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Abbreviations

AIS: acute ischemic stroke; IVT: intravenous thrombolysis; MBDR: Minimum Basic Data Register at hospital discharge; ICD-9: International Classification of Diseases; PADRIS: Public Program epidemiological analysis for Health Research and Innovation in Catalonia; IEC: Independent Ethics Committee; IDIAP: University Institute for Primary Care Research Jordi Gol; ISEP: Integral System of Electronic Prescription; CRI: Central Register of insured population; HR: hazard ratio; A-IIRA: angiotensin II receptor antagonist; NOAC: new oral anticoagulant; SD: standard deviation

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