Thrombosis Research 178 (2019) 20–25

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Worse 12-month prognosis in women with non-valvular atrial fibrillation undergoing percutaneous coronary intervention

Antonia Sambola[a,*], Héctor Bueno[b,c,d], Blanca Gordon[a], María Mutubería[a], José A. Barrabés[a], Bruno García Del Blanco[a], Víctor González-Fernández[a], Núria Casamira[e], David García-Dorado[a]

[a] Department of Cardiology, Vall d'Hebron University Hospital and Research Institute, Universitat Autònoma de Barcelona, Spain
[b] Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
[c] Hospital Universitario 12 de Octubre, Madrid, Spain
[d] Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[e] Department of Pharmacy, Vall d'Hebron University Hospital and Research Institute, Barcelona, Spain

ARTICLE INFO

Keywords:
Women
Anticoagulant
Percutaneous coronary intervention
Atrial fibrillation
Prognosis

ABSTRACT

Background: Limited data exists on the impact of sex on outcomes in non-valvular atrial fibrillation (NVAF) patients undergoing percutaneous coronary intervention (PCI). We explored the impact of sex on ischemic and bleeding events in these patients within 1-year.

Methods: A prospective register included 1021 patients with NVAF undergoing PCI and 253 (24.8%) were women. The *primary end point* was a composite of cardiovascular death, stroke or systemic embolism (SSE). The *secondary end-point* was major bleeding events defined as a Bleeding Academic Research Consortium (BARC ≥ 3a).

Results: Women were older (76.8 ± 7.7 vs 71.8 ± 9.1 years, $p < 0.0001$), and presented more often CHA_2DS_2-VASc ≥ 2 (adjusted HR 1.15; 95%CI 1.13–1.18, $p < 0.0001$) and HAS-BLED ≥ 3 (adjusted HR 1.12; 95%CI 1.10–1.14, $p < 0.0001$) than men. The use of oral anticoagulant at discharge was similar in both sexes (55.9% vs 56.5%, $p = 0.45$). The time in therapeutic range (TTR ≥ 65%) was lower in women than in men (35.6 ± 24.6% vs 48.9 ± 27.2%, $p = 0.002$). The incidence of adverse events was higher in women (39.9% vs 28.9%, $p = 0.01$). After adjusting for confounder variables, cardiovascular death or SSE rate (16.6% vs 10.4%; adjusted HR 1.58; 95%CI 1.07–2.31; $p = 0.01$) and major bleeding (11.5% vs 5.0%; adjusted HR 2.17; 95%CI 1.31–3.59; $p = 0.003$) were higher in women, as was cardiovascular death (adjusted HR 1.71; 95%CI, 1.18–2.46, $p = 0.004$). TTR was negatively correlated with any bleeding event in women ($r = -0.41$; $p = 0.03$).

Conclusions: Female with NVAF undergoing PCI showed a lower TTR than men and TTR was associated with bleeding events. Female sex was an independent risk factor for cardiovascular death and major bleeding.

1. Introduction

Non-valvular atrial fibrillation (NVAF) is the most common sustained arrhythmia in women and men worldwide. It confers a substantial risk of mortality and morbidity and it is associated with high rates of hospitalization related to needs for its management, or secondary to heart failure, myocardial infarction, and stroke or thromboembolism, so NVAF represents a major healthcare burden in Europe [1].

Women generally have a lower age-adjusted incidence and prevalence of NVAF than men; however, given the greater longevity of women, the absolute number of women exceeds the number of men with NVAF in octogenarians [2]. Although women and men differ in risk factors; women are, on average, older at diagnosis and have a higher prevalence of hypertension, both sexes have similar rates of anticoagulation and remain similar time in therapeutic range (TTR) [3,5]. However, it could be modified when patients undergoing PCI and t need combination with other antithrombotic.

Abbreviations: NVAF, non-valvular atrial fibrillation; PCI, percutaneous coronary intervention; SSE, stroke or systemic embolism; TTR, time in therapeutic range; OAC, oral anticoagulation; DAPT, dual antiplatelet therapy; DAT, dual antitherapy; TT, triple therapy; BMS, bare metal stent; DES, drug eluting stent; MACE, major adverse cardiovascular events

* Corresponding author at: Department of Cardiology, Vall d'Hebron University Hospital and Research Institute, Universitat Autònoma de Barcelona, P. Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail address: asambola@vhebron.net (A. Sambola).

https://doi.org/10.1016/j.thromres.2019.03.017
Received 17 December 2018; Received in revised form 13 March 2019; Accepted 27 March 2019
Available online 28 March 2019
0049-3848/

Contradictory results have been published regarding the influence of sex on prognosis. Some studies reported that women have increased risk of NVAF-related stroke or thromboembolism, myocardial infarction and mortality [2] compared with men, others reported higher stroke rates but similar or lower risk-adjusted all-cause mortality and cardiovascular death in women [4], and other studies found similar rates of cardiovascular death, stroke and systemic embolism with a lower risk of major bleeding events in females [5].

However, whether there are sex differences regarding prognosis in patients with NVFA undergoing PCI, where multiple antithrombotic therapies may be balancing risks and benefits [5–11]. We sought to assess whether there are differences between sexes in patients with NVAF undergoing PCI regarding: 1) thromboembolic profile 2) received antithrombotic treatment and 3) prognosis.

2. Methods

2.1. Study population and design

We performed a "post-hoc" analysis of a prospective cohort study of 1021 consecutive patients with NVAF who underwent PCI. Our cohort was enrolled at University Hospital Vall d'Hebron between 2008 and 2016, where 1200 PCI procedures are performed per year.

Patients ≥18 years old with a pre-existing diagnosis of paroxysmal, persistent or permanent NVAF and those who developed new-onset NVAF during their index admission were included in this analysis. Exclusion criteria were significant valvular heart diseases or lack of 1-year follow-up. The risk of stroke or systemic embolism of patients with NVAF was assessed using the CHA_2DS_2-VASc score. Bleeding risk in patients with NVAF was estimated with the HAS-BLED score. The cohort was divided into two groups: 1) patients at low bleeding risk, defined as HAS-BLED score 0–2 and 2) patients at high bleeding risk defined as HAS-BLED score ≥ 3. We analyzed the impact of sex on cardiovascular death, stroke or systemic embolism, and bleeding outcomes at 12 months.

2.2. Choice and duration of antithrombotic therapy at discharge

Since this was an observational study, decisions as the type of revascularization performed or the type of stent used or choice and duration of antithrombotic therapies at discharge were left to the discretion of the attending cardiologists. The pattern of antithrombotic therapy at discharge was defined as: OAC alone, dual antiplatelet therapy (DAPT, aspirin 100 mg once a day and clopidogrel 75 mg once a day or Ticagrelor 90 mg bid a day), dual therapy (DAT, OAC plus a single antiplatelet) and triple therapy (TT): OAC plus DAPT.

In all patients, the exact duration of the treatment was collected; in patients discharged with DAPT (alone or plus OAC), this treatment lasted for at least 1 month following PCI when a bare metal stent (BMS) was used, and between 3 and 12 months when a drug eluting stent (DES) was used. All patients received vitamin K antagonists or direct-acting OAC plus DAPT (aspirin and clopidogrel, ticagrelor or prasugrel) or plus clopidogrel alone following the regime described previously. Thereafter, patients were followed as part of the routine clinical practice at the hospital. Clinical and demographic characteristics, risk factors for thromboembolism, cardiologic history (previous MI, previous PCI, number of injured vessels, complete revascularization, number of stents and length of stents), as well as the use of antithrombotic therapy before PCI and at discharge were collected. Clinical follow-up was performed by telephone interviews at 1, 6 and 12 months by a predefined questionnaire asking about outcomes collected and review of clinical records of patients with hospital readmissions and/or outpatient clinic visits to confirm the ongoing antithrombotic regimen followed after discharge, and to ascertain the occurrence of adverse events. Bleeding, death from any cause, myocardial infarction, target vessel revascularization, stent thrombosis and thromboembolic events that occurred during the first year after PCI were collected by a predefined questionnaire. In all cases, the medication at the time of the index adverse event was recorded. In addition, all readmissions to hospital were carefully reviewed to obtain the maximum information on any possible events and to validate our own database.

TTR was calculated by Rosendaal Method for % INR in range, by incorporating the frequency of INR measurements and their values, and assuming that changes between consecutive INR measurements are linear over time. TTR was determined over 6 months.

2.3. End-points and definitions

The *primary end point* was a composite of cardiovascular death and stroke or systemic embolic events (SSE) within 1 year. The *secondary end-point* was major bleeding events defined as a Bleeding Academic Research Consortium (BARC) ≥ 3a: 3a, overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding; 3b, overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring intravenous vasoactive agents; 3c, Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision; 4, coronary artery bypass grafting-related bleeding within 48 h; 5a, probable fatal bleeding; 5b, definite fatal bleeding [12].

2.4. Definitions of adverse events

All outcomes were adjudicated to two independent cardiologists. Stroke was defined as the sudden onset of a neurologic deficit in an area consistent with the territory of a major cerebral artery, and was categorized as ischemic, hemorrhagic or unspecified. Hemorrhagic transformation was not considered as a hemorrhagic stroke. Intracranial hemorrhage was defined as a hemorrhagic stroke or a subarachnoid or subdural hemorrhage. Stroke could be diagnosed by techniques such as brain computed tomography or magnetic resonance imaging [13]. Systemic embolism was an acute vascular occlusion of the limbs or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and had to be documented by angiography, surgery, scintigraphy or autopsy. Acute myocardial infarction was defined following the criteria of the ESC/ACCF/AHA/WHF [14]. Stent thrombosis was defined according to the criteria for "definite or probable" of the Academic Research Consortium [15]. Deaths were classified as cardiovascular, non-cardiovascular due to other specified causes (e.g. malignancy) or of unknown etiology according to the final diagnosis of clinical records or those registered in Statistics National Institute [16].

The study complies with the 1975 Declaration of Helsinki of 1975 and was approved by the Vall d'Hebron University Institutional Review Board and patients gave their written informed consent.

2.5. Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) and range and categorical variables as absolute and relative frequencies of patients in each category. Comparison of continuous variables between both sexes were made by Student's *t*-tests and comparisons for categorical variables were made by chi-square tests. The probability of adverse events during follow-up for each sex was calculated by Kaplan-Meier analysis, and survival curves were compared by the log-rank test. To assess the independent effect of sex on 12-month outcomes, a Cox proportional hazard model analysis was performed, considering the following outcomes: 1) a combined outcome: cardiovascular death and stroke or SSE 2) singles outcomes: cardiovascular death, SSE, and major bleeding (BARC ≥ 3a). The effects of women relative to men for the individual endpoints were expressed as hazard ratios (HR) and their 95% confidence intervals (CI). In addition, we

Table 1
Baseline characteristics of the study population.

	Women (N = 253)	Men (N = 768)	*p* value
Age, mean (SD)	76.8 ± 7.7	71.8 ± 9.1	0.0001
Medical history			
Smoking, n (%)	37 (14.7)	487 (63.4)	< 0.0001
Hypertension, n (%)	216 (85.4)	577 (75.1)	0.001
Diabetes, n (%)	112 (44.3)	283 (36.8)	0.02
Dyslipidemia, n (%)	146 (57.7)	423 (55.1)	0.26
Chronic renal disease, n (%)	47 (18.6)	137 (17.8)	0.43
Peripheral arterial disease, n (%)	27 (10.7)	103 (13.4)	0.15
History of stroke, n (%)	36 (14.2)	95 (12.4)	0.63
Previous MI, n (%)	62 (24.5)	240 (31.3)	0.02
History of heart failure, n (%)	67 (26.5)	246 (32)	0.05
Ejection fraction ≤ 40%, n (%)	68 (21.6)	179 (25.5)	0.14
Previous PCI, n (%)	80 (31.6)	239 (31.1)	0.47
Previous CABG, n (%)	13 (5.1)	81 (10.5)	0.005
Number of injured vessels disease, mean (SD)	1.79 ± 0.73	1.83 ± 0.76	0.52
CHA2DS2-VASc score mean (SD)	4.47 ± 1.73	3.04 ± 1.64	< 0.0001
CHA2DS2-VASc score ≥ 2, n (%)	237 (93.7)	603 (78.5)	< 0.0001
HAS-BLED score	3.19 ± 0.86	2.99 ± 1.06	0.003
Mean (SD)			
HAS-BLED score ≥ 3, n (%)	211 (83.4)	524 (68.2)	< 0.0001
Index episode (ACS), n (%)	187 (75.7)	566 (73.4)	0.58
Drug eluting stent, n (%)	96 (37.9)	283 (36.8)	0.48
Total stent length, mm	27 (17–27.5)	29 (18–48)	0.49
Antithrombotic therapy			
Oral anticoagulation at discharge, n (%)	138 (55.9)	436 (56.5)	0.45
Antithrombotic pattern at discharge, n, (%)			0.48
Triple therapy, n (%)	117 (46.2)	381 (49.6)	
Dual antiplatelet therapy, n (%)	114 (45.1)	336 (43.8)	
Acenocumarol + clopidogrel, n (%)	22 (6.6)	51 (8.7)	
TTR (patients on AVK)	35.6 ± 24.6	48.9 ± 27.5	0.002

Abbreviations: MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting HAS-BLED score: hypertension, renal/liver failure, stroke, bleeding history of predisposition, INR lability, age > 65, concomitant drugs or alcohol; CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75, diabetes, previous stroke/TIA, vascular disease, age 65–74, female sex; ACS: acute coronary syndrome.

performed Cox proportional hazard regression analyses for each individual outcome, adjusting for confounding clinical variables. Temporal trends for in-hospital mortality during the observed period were modeled using Poisson regression analysis with year as the only independent variable. In all models, incidence of TAT and their 95% confidence intervals (95%CI) were calculated.

These included demographic, clinical, or procedural variables with a $p \leq 0.15$ in Cox bivariate analysis. All *p*-values were two-sided and $p < 0.05$ considered statistically significant including demographic, clinical, or procedural variables that were potentially not well-balanced (i.e. $p \leq 0.15$ for comparison between sex). Statistical analysis was performed using the statistical package SPSS 23.0.

3. Results

3.1. Baseline and treatment characteristics

We included 1021 patients (253 women, 24.7%), 73 ± 9 years old. Compared with men, women were older, more frequently hypertensive and diabetic, and presented less often with smoking habit, and prior history of myocardial infarction or CABG (Table 1). Women had a higher thromboembolic risk and more frequently a high thromboembolic risk (CHA_2DS_2-VASc ≥ 2: 93.7% vs 78.5%, $p < 0.0001$, of whom 90% had CHA_2DS_2-VASc ≥ 3) and a higher bleeding risk (HAS-BLED ≥ 3: 83.4% vs 68.2%, $p < 0.0001$) than men, even though after adjusting for age (CHA_2DS_2-VASc ≥ 2: HR adjusted 1.15 95% CI 1.13 to 1.18, $p < 0.0001$; HAS-BLED ≥ 3 HR adjusted 1.12 95% CI 1.10 to 1.14, $p < 0.0001$, respectively).

The use of OAC was similar in both sexes (53.0% vs 58.7%, $p = 0.45$), although DOACs were used less frequently in women (50 men and 8 women). Treatment rates with OAC did not significantly improved over time (before 2010 compared to after 2010) in males (46.9% vs 53.1, nor in females 47.0 vs 53.0%, $p = 0.53$), However, treatment rates with OAC improved when we compared before and after 2014, (54% vs 68.7%, $p < 0.001$) in males and almost was significant in females (53.4% vs 67.4% in females, $p = 0.06$). Although, the risk for female not receiving OAC was maintained through the whole study period (lower OR: 1.12 in 2014; higher OR: 1.27 in 2008).

The pattern of antithrombotic therapy at discharge was also similar in women compared with men: TT 46.4% vs 49.6%, DAPT: 45.1% vs 43.8%, DAT with OAC plus clopidogrel: 6.6% vs 8.7%, $p = 0.48$. However, in the 571 patients treated with OAC (TT or DAT), the time in therapeutic range (TTR) was lower in women than in men (35.6 ± 24.6% vs 48.9 ± 27.2%, $p = 0.002$; median, 28%; IQR 8.7 to 80% vs IQR, 5.5 to 99%).

3.2. Adverse events

The incidence of adverse events at 12 months was higher in women than in men (Table 2). The primary end-point, cardiovascular death or SSE, was 17.8% in women and 10.4% in men ($p = 0.003$), with higher cardiovascular mortality (14.2% vs 9.5%, $p = 0.025$) and no significant differences in SSE (4.9% vs 2.9%, $p = 0.09$), but with a trend to a higher stroke rate (4.0% vs 2.0%, $p = 0.06$). Other ischemic events: major cardiac adverse events (MACE), stent thrombosis, myocardial infarction and target vessel revascularization did not show any difference between both sexes (Table 2). The secondary end-point was also higher in women, driven by an increased rate of major bleeding (11.5% vs 5.0%, $p < 0.001$).

The Cox regression adjusted models showed that female sex was an independent predictor of cardiovascular death and SSE (HR, 1.58; 95%CI, 1.07–2.31; $p = 0.01$) and individually of cardiovascular death (HR, 1.71; 95%CI 1.18–2.46; $p = 0.004$) (Fig. 1A–C). Although, female sex was not an independent predictor of SSE, there was a trend to a higher SSE trend (HR 1.80, 95% CI 0.89-3.61, $p = 0.09$). Treatment on TT at discharge was a protective factor (Supplementary Table 1). When the Cox regression adjusted models were analyzed considering only the use of anticoagulation treatment TT vs DAT the results were similar; female sex was not an independent factor for cardiovascular death and SSE (HR, 1.88 95% CI 1.14-3-10, $p = 0.01$) and for cardiovascular death (HR, 1.66; 95%CI 0.97–2.85, $p = 0.05$).

After adjusting, female sex was also an independent predictor of major bleeding (HR 2.17; 95% CI, 1.31–3.59; $p = 0.003$), as well as renal failure (HR 2.16; 95% CI 1.26–3.71; $p = 0.01$) and treatment on TT at discharge (HR 2.08; 95% CI 1.22–3.54; $p = 0.006$). (Supplementary Table 1, Fig. 1D). When the Cox regression adjusted model was analyzed considering only the use of anticoagulation treatment TT vs DAT the results was similar: (HR 1.98; 95% CI 1.22–2.54; $p = 0.03$).

TTR was associated with major bleeding events in patients on OAC. Therefore, TTR was negatively correlated with any bleeding event in women ($r = -0.41$; $p = 0.03$) and men ($r = -0.44$; $p = 0.03$), (TTR < 65%: females 17.9% versus males 12.0%; while none were observed when TTR ≥ 65%: females 4.8% versus males 8.9%).

4. Discussion

Our study shows that women with NVAF who undergo PCI have a higher baseline thromboembolic and haemorrhagic risk than men, and present a higher 12-month incidence of cardiovascular death or SSE, cardiovascular death alone, and major bleeding events. After adjustment for confounders, female sex remains as an independent predictor

Table 2
Crude and adjusted associations between sex and outcomes. The control group is men.

	Women N = 253	Men N = 768	HR (95% CI)	*p* value	Adjusted HR (95% CI)	Adjusted *p* value
All adverse events	101 (39.9)	222 (28.9)	1.69 (1.25–2.28)	0.001	1.60 (1.17–2.18)	0.003
Primary end-point						
Cardiovascular death or SSE rate[a]	49 (17.0)	97 (9.9)	178 (1.19–2.67)	0.005	1.58 (1.07–2.31)	0.01
Cardiovascular death[b]	36 (14.2)	73 (9.5)	1.54 (0.98–0.43)	0.05	1.71 (1.18–2.46)	0.004
Stroke or systemic embolism[c]	22 (4.0)	12 (2.9)	1.73 (0.84–3.50)	0.13	1.80 (0.89–3.61)	0.09
					1.91 (0.75–4.86)	0.17
Other ischemic events						
Major adverse cardiac events	58 (28.3)	139 (18.1)	1.31 (0.92–1.86)	0.13	0.89 (0.50–1.62)	0.72
All-cause death	41 (16.3)	98 (12.8)	1.34 (0–89-1.99)	0.15	1.29 (0.82–2.03)	0.26
Stent thrombosis	2 (0.8)	19 (2.5)	0.32 (0.07–1.40)	0.13	0.14 (0.02–0.84)	0.03
Myocardial infarction	19 (7.7)	58 (7.6)	1.02 (0.59–1.75)	0.93	0.89 (0.49–1.62)	0.72
Secondary end point						
Major bleeding (BARC ≥ 3)[d]	29 (11.5)	38 (5.0)	2.32 (1.40–3.86)	0.001	2.17 (1.31–3.55)	0.003
Other bleeding events						
Total bleeding	47 (18.6)	106 (13.9)	1.52 (1.04–2.21)	0.02	1.22 (0.63–2.38)	0.55
Minor bleeding	20 (7.9)	63 (8.2)	1.00 (0.59–1.69)	0.99	1.50 (0.64–3.50)	0.34

SSE indicates: stroke or systemic embolism. BARC indicates: Bleeding Academic Research Consortium.
[a] Adjusted by age, gender, diabetes mellitus, renal failure, history of heart failure, number of injured vessels, use of DES and triple therapy at discharge.
[b] Adjusted by age, sex, hypertension, diabetes mellitus, renal failure, history of heart failure, use of DES and triple therapy.
[c] Adjusted by age, hypertension, access vascular radial and oral anticoagulation.
[d] Adjusted by age, sex, hypertension, renal failure, use of DES and triple therapy at discharge.

of adverse ischemic and bleeding outcomes.

In our series only there were 24.7% of females, but this rate is similar to other previous studies on patients with AF undergoing PCI, such as cohort studies or RCTS (21% to 28%) [11,17,18,19]. Although NVAF is associated with an increased risk of stroke and death in men and women, a growing body of literature suggests that women and men experience risk factors for cardiovascular disease differently [20–23]. In our cohort, women were older and were more frequently hypertensive

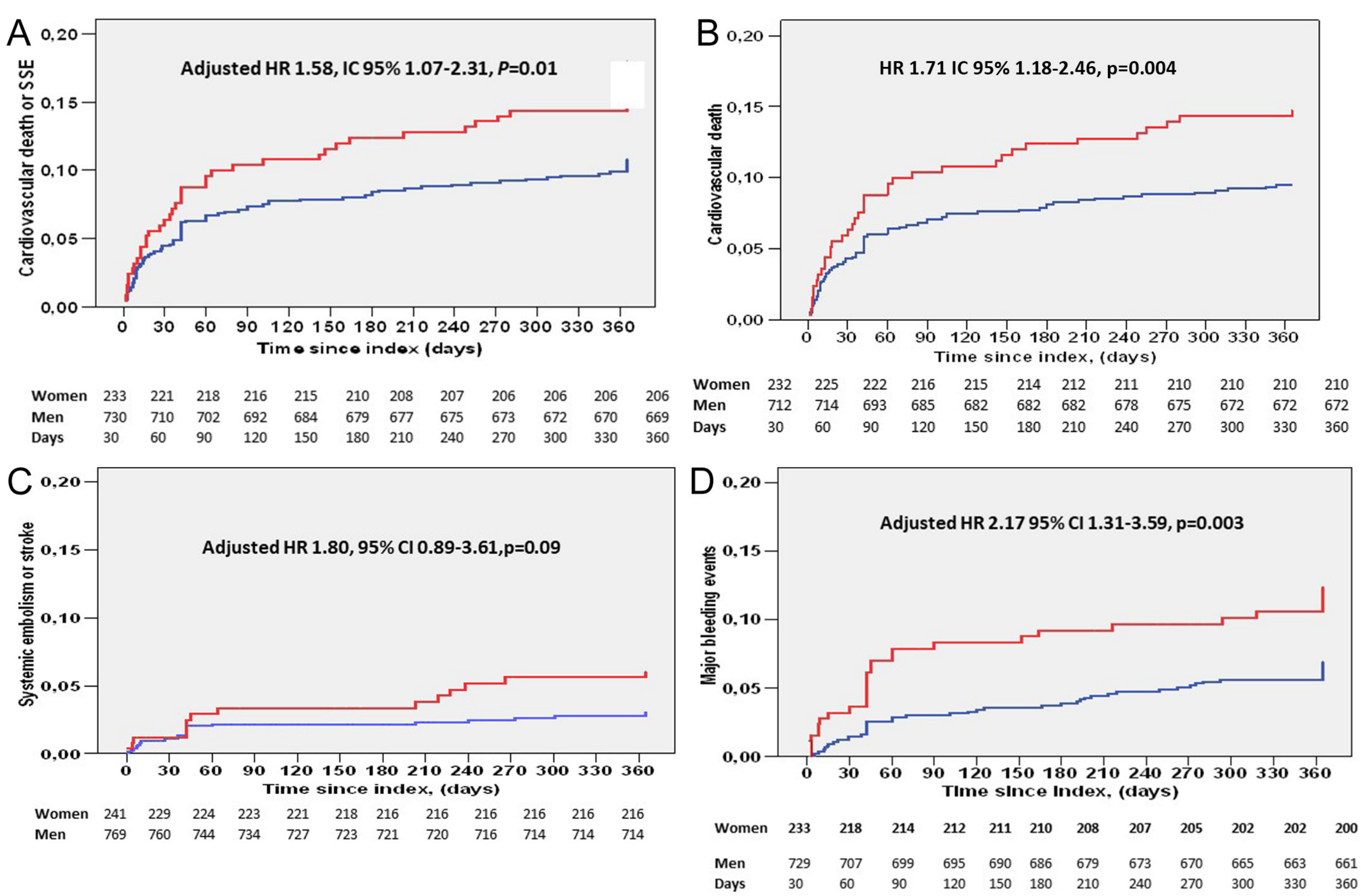

Fig. 1. Kaplan–Meier curves relating to differences between both sexes in patients with AF undergoing PCI. Number of patients followed up: Women n = 253; Men n = 758. 1. Cardiovascular death and stroke or systemic embolism 2. Cardiovascular death 3. Stroke or systemic embolism. 4. Major bleeding (BARC ≥ 3). Line in red is women. Line in blue is men. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

or diabetic than men. The finding that women are older than men in patients with NVAF is consistent with the incidence of ischemic heart disease, a condition for which women are, on average, 10 years older than men at the time of presentation [24]. This profile conferred an extremely high thrombotic risk to women, with up to 90% of patients with CHA_2DS_2-VASc ≥ 2, and a higher thromboembolic risk in women than in women. Furthermore, 68% of women had a CHADSVASC > 3 compared to 36% of men, and these differences persisted after adjusting for age. An excess of thromboembolic risk for women was especially evident among those with ≥2 non sex-related stroke risk factors, indicating a risk modification by being female, according to other authors [23]. In other words, female sex is a stroke risk modifier that increases the risk of AF related stroke in the presence of other conventional stroke risk factors.

In our cohort, despite a high thromboembolic risk, only 54% of patients received OAC but, although there were no differences between sexes in the use of OAC. Under treatment with OAC in women with NVAF has been described in a recent, large registry [25]. Our study really documents the real world scenario rather than guideline-conform treatment strategies. Although the recommendations of ESC with the introduction of the use of the CHA_2DS_2-VASc score instead of the $CHADS_2$ score in 2010, encouraged the introduction of the OAC in patients with NAVF with high thromboembolic risk, its impact was not reflected in our cohort significantly, but it was the introduction of 2014 ESC guidelines, reinforcing the idea of guidelines implementation is slow in clinical practice [26].

Similar to other studies [25,27,28], in our cohort, the proportion of women under a TTR ≥ 65% was higher than in men, as reflected a poorer anticoagulation control observed in a previous study, which could result in having a higher incidence of adverse events, specially bleeding. This fact could be favored by the combination with other antithrombotic drugs. Anticoagulation with warfarin may be less well controlled in female AF patients compared with males, thus affecting the effectiveness of warfarin in female patient; moreover, females with AF have a greater residual stroke risk even with well-controlled VKAs.

Advanced age and comorbidities are not only risk factor for thromboembolic events but also for bleeding events. Concerns about bleeding might have led to less frequent adherence to warfarin in women. These differences may have played a role in the higher ischemic risk found in women in our group. It should be noted the low proportion of patients of both sexes who received DAT in our series (6% vs 8%) may be explained to the elevated number of patients in our series diagnosed with ACS (76%), in contrast with those described in randomized trials (WOEST, Pioneer-AF and RE-DUAL, with proportions of ACS of 26%, 51.5% and 51.9%, respectively) [10,17,18]. However, the use of TT compared to DAT did not affect to the results. Therefore, the Cox regression adjusted models analyzed considering only the use of anticoagulation treatment TT vs DAT found that female sex was an independent factor for cardiovascular death and SSE, as well as for cardiovascular death.

On the other hand, use of DES was lower in our series compared with others, most likely related to the high bleeding risk of our patients (HAS-BLED ≥3, 71.7%) in a time when it was believed that BMS were safer for these patients. The choice of DES versus BMS in patients requiring long-term anticoagulation has been controversial until recently, when the European Society of Cardiology guidelines recommended the use of the newer DES generation in patients at high bleeding risk [29].

Women in our study showed a higher risk bleeding than men, which together with age, renal failure and use of TT at discharge, were independent predictors of major bleeding during follow-up. Remarkably, in our study TTR was inversely correlated with the incidence of any bleeding event in women and males, but we observed a higher number of bleeding events in women than in males; while we did not observe it when TTR ≥ 65%. The observational nature of our study does not facilitate finding an explanation for the pathophysiological relationship between sex and bleeding outcomes. One possible reason may be that the impact of anticoagulation control on bleeding risk differ by sex. With a TTR < 65% (deficient control), women have numerically more hemorrhagic events and more thromboembolic events. Because of the low number of events, we were limited in power to detect differences between females and males for the TTR < 65% and TTR ≥ 65% subgroups in a multivariant analysis, as other previous observational and randomized studies (IMPACT TRIAL) [30].

Some pre-existing studies have shown varying results on the influence of sex on the mortality of patients with NVAF. While some studies found no differences in cardiovascular morbidity and mortality between males and females [5,31], even though others found lower all-cause and cardiovascular mortality in females compared with males [16]. Finally, other studies found higher mortality or incidence of stroke in females compared with males [21,22,31,32]. These discrepant findings might be explained by differences between studied populations. In our cohort, we must take into account that the female group had a higher cardiovascular risk profile and, therefore, scored higher in the thrombotic and hemorrhagic risk scales and presented more adverse events as a whole. Remarkably, even there were no differences in stroke rate, women showed a trend to have a higher incidence than men (4% vs 2%, $p = 0.06$) as well other studies have shown. [5]. In a recent meta-analysis, NVAF was associated with a higher relative risk of cardiac events, in women compared with men [27]. In consonance with these results, we found a higher cardiovascular mortality as well as a higher incidence of major cardiovascular adverse events in women with NVAF undergoing PCI.

The presence of hypertension, reduced renal reserve, and poorer quality anticoagulation control as reflected by time in the therapeutic range were associated to cardiovascular mortality in our cohort. In other series, those factors have been investigated by other authors [4,22,28,33], as potential predictors but none have conclusively explained the dependency of the observed risk difference in thromboembolic and bleeding risk between both sexes. Aspirin should not be used for stroke prevention in females and males with AF, since aspirin is essentially ineffective and associated to similar risk of bleeding compared with DOACs or VKAs. The response to OACs could also differ between sexes. For this particular mechanism, the use of DOACs may reduce the higher risk of irregular anticoagulation control observed more frequently in women [34].

Even though multiple studies have been conducted in NVAF, few analyses have focused on sex differences in outcomes in patients undergoing PCI as our study. However, there are limitations that should be considered. Issues inherent to the observational nature of the study, such as confounding or bias cannot be fully ruled out. The relatively small sample size should be mentioned. However, the results seem to be robust enough as suggested for the concordance with recent studies focused in sex differences in patients with AF. The observational design may not correct for possible confounders or jatrogenic/treatment biases related to gender.

In summary, our results reveal sex differences in the prevention of thromboembolic risk in patients who present with NVAF underwent PCI with the consequent adverse outcomes in terms of cardiovascular death and major bleeding for women. Important efforts must be made to eliminate these differences between sexes in the management of these patients, following the recommendations that are included in the consensus document of the European Heart Rhythm Association [35].

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.03.017.

Funding

CIBERCARDIOVASCULAR and cofinanced by the European Regional Development Fund (ERDF-FEDER).

Conflict of interest

None author has nothing to declare outside the submitted work.

References

[1] P. Kirchhof, S. Benussi, D. Kotecha, et al., 2016 ESC guidelines for the management of atrial fibrillation. The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (2016) 2893–2962.

[2] D. Ko, F. Rahman, R.B. Schnabel, et al., Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis, Nat. Rev. Cardiol. 13 (2016) 312–332.

[3] G.Y.H. Lip, C. Laroche, C. Boriani, et al., Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation, Europace 17 (2015) 24–31.

[4] J.P. Piccini, D.N. Simon, A. Benjamin, et al., Differences in clinical and functional outcomes of atrial fibrillation in women and men two-year results from the ORBIT-AF registry, JAMA Cardiol. 1 (2016) 282–291.

[5] K. Senoo, G.H.Y. Lip, Female sex, time in therapeutic range, and clinical outcomes in atrial fibrillation patients taking warfarin, Stroke 47 (2016) 1665–1668.

[6] G.Y.H. Lip, J.P. Collet, M. Haude, et al., 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA), Europace 21 (2019) 192–193.

[7] A. Schlitt, A. Rubboli, G.H.Y. Lip, et al., The management of patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation: in-hospital-data from the atrial fibrillation undergoing coronary artery stenting study, Catheter. Cardiovasc. Interv. 82 (2013) E864–E870.

[8] D.H. Lam, S.M. Bell, R.S. Hira, Concomitant use of antiplatelets and anticoagulants in patients with coronary heart disease and atrial fibrillation: what do recent clinical trials teach us? Curr. Atheroscler. Rep. (2018) 20–24.

[9] F. Marin, K. Huber, G.Y. Lip, Antithrombotic therapy in atrial fibrillation and stent implantation: treatment or threats by the use of triple or dual antithrombotic therapy, Thromb. Haemost. 110 (2013) 623–625.

[10] L. Azoulay, S. Dell'Aniello, T. Simon, et al., The concurrent use of antithrombotic therapies and the risk of bleeding in patients with atrial fibrillation, Thromb. Haemost. 109 (2013) 431–439.

[11] W.J. Dewilde, T. Oirbans, F.W. Verheugt, et al., The Woest study. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial, Lancet 381 (2013) 1107–1115.

[12] R. Mehran, S.V. Rao, D.K. Bhatt, et al., Standarized bleeding definitions for cardiovascular clinical trials, Circulation 123 (2011) 2736–2747.

[13] W.N. Whiteley, K.B. Slot, P. Fernandes, et al., Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies, Stroke 43 (2012) 2904–2909.

[14] K. Thygesen, J.S. Alpert, A.S. Jaffe, et al., Third universal definition of myocardial infarction, Circulation 126 (2012) 2020–2035.

[15] D.E. Cutlip, S. Windecker, R. Mehran, Academic Research Consortium, Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (2007) 2344–2351.

[16] A. Sambola, I. Ferreira-Gonzalez, J. Angel, et al., Therapeutic strategies after coronary stenting in chronically anticoagulated patients: the MUSICA study, Heart 95 (2009) 1483–1488.

[17] C.M. Gibson, R. Mehran, C. Bode, et al., Prevention of bleeding in patients with atrial fibrillation undergoing PCI, N. Engl. J. Med. 375 (2016) 2423–2434.

[18] C.P. Cannon, D.L. Bhatt, J. Oldgren, RE-DUAL PCI Steering Committee and Investigators, Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation, N. Engl. J. Med. 377 (2017) 1513–1524.

[19] L. Fauchier, C. Lecoq, Y. Ancedy, et al., Evaluation of 5 prognostic scores for prediction of stroke, thromboembolic and coronary events, all-cause mortality, and major adverse cardiac events in patients with atrial fibrillation and coronary stenting, Am. J. Cardiol. 118 (2016) 700–707.

[20] P.B. Nielsen, F. Skjøth, T.F. Overvad, et al., Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation 137 (2018) 832–840.

[21] R. Huxley, F. Barzi, M. Woodward, Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies, BMJ 332 (2006) 73–78.

[22] N. Dagres, R. Nieuwlaat, P.E. Vardas, et al., Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the EuroHeart Survey on Atrial Fibrillation, J. Am. Coll. Cardiol. 49 (2007) 572–577.

[23] M. Rienstra, D.J. Van Veldhuisen, V.E. Hagens, et al., Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the rate control versus electrical cardioversion (race) study, JACC 46 (2005) 1298–1306.

[24] N. Wenger, Coronary heart disease: an older woman's major health risk, BMJ 351 (1997) 1085–1090.

[25] L.E. Thompson, T.M. Maddox, L. Lei, G.K. Grunwald, et al., Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR®) PINNACLE registry, J. Am. Heart Assoc. 6 (2017) (pii: e005801).

[26] Y. Ancedy, C. Lecoq, C. Saint Etienne, F. Ivanes, D. Angoulvant, D. Babuty, G.Y. Lip, L. Fauchier, Antithrombotic management in patients with atrial fibrillation undergoing coronary stent implantation: what is the impact of guideline adherence? Int. J. Cardiol. 203 (2016) 987–994.

[27] G.Y. Lip, A.L. Waldo, J. Lp, et al., Determinants of time in therapeutic range in patients receiving Oral anticoagulants (a substudy of IMPACT), Am. J. Cardiol. 118 (2016) 1680–1684.

[28] J. Carmo, J. Ferreira, F. Costa, P. Carmo, D. Cavaco, S. Carvalho, F. Morgado, P. Adragão, M. Mendes, Non-vitamin K antagonist oral anticoagulants compared with warfarin at different levels of INR control in atrial fibrillation: a meta-analysis of randomized trials, Int. J. Cardiol. 244 (2017) 196–201.

[29] M. Valgimigli, H. Bueno, R.A. Byrne, et al., 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS), Eur. Heart J. 39 (2018) 213–260.

[30] J.L. Cox, R. Parkash, S.S. Abidi, L. Thabane, F. Xie, J. MacKillop, S.R. Abidi, A. Ciaccia, S.H. Choudhri, A. Abusharekh, J. Nemis-White, IMPACT-AF Investigators, Optimizing primary care management of atrial fibrillation: the rationale and methods of the Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF) study, Am. Heart J. 201 (2018) 149–157.

[31] J. Friberg, H. Scharling, N. Gadsboll, et al., Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (the Copenhagen city heart study), Am. J. Cardiol. 94 (2004) 889–894.

[32] Connor A. Emdin, Ch. Wong, J. Allan, Wong Ch, et al., Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies E atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies, BMJ 352 (2016) h701.

[33] K. Szummer, A. Gasparini, Staffan Eliasson, Johan Ärnlöv, et al., Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction, J. Am. Heart Assoc. 6 (2017) e00.

[34] D. Vinereanu, S.R. Stevens, J.H. Alexander, et al., Clinical outcomes in patients with atrial fibrillation according to sex during anticoagulation with apixaban or warfarin: a secondary analysis of a randomized controlled trial, Eur. Heart J. 36 (2015) 3268–3275.

[35] C. Linde, M.G. Bongiorni, U. Birgersdotter-Green, et al., Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society, EP Europace 20 (2018) 1565.