Effect of Sex on Outcomes of Coronary Rotational Atherectomy Percutaneous Coronary Intervention (From the European Multicenter Euro4C Registry)

Frédéric Bouisset, MD[a,*], Flavio Ribichini, MD, PhD[b], Vincent Bataille, PhD[a], Krzysztof Reczuch, MD, PhD[c], Slawomir Dobrzycki, MD, PhD[d], Markus Meyer-Gessner, MD[e], Erwan Bressollette, MD[f], Wojciech Zajdel, MD, PhD[g], Benjamin Faurie, MD[h], Nikolaos Mezilis, MD[i], Jorge Palazuelos, MD, PhD[j], Leonardo Spedicato, MD[k], Mariano Valdés, MD, PhD[l], Beatriz Vaquerizo, MD[m], Miroslaw Ferenc, MD, PhD[n], Guillaume Cayla, MD, PhD[o], Emanuele Barbato, MD, Ph[p], and Didier Carrié, MD, PhD[a], On Behalf of the Euro4C Registry Investigators

Data regarding the potential influence of gender on outcomes of rotational atherectomy (RA) percutaneous coronary intervention (PCI) are scarce and conflicting. Using the Euro4C registry, an international prospective multicentric registry of RA PCI, we evaluated the influence of gender on clinical outcomes of RA PCI. Between October 2016 and July 2018, 966 patients were included. In them, 267 (27.6%) were females. Female patients were older than males (77.7 years old ± 9.8 vs 73.3 ± 9.5 years old respectively, $p < 0.001$) had a poorer renal function (43,1% of females had a GFR < 60 ml/min:1.73m^2 vs 30.4% of males, $p < 0.001$) and were more frequently admitted for an acute coronary syndrome (32.2% vs 22.3% $p = 0.002$). During RA procedure, women were less likely to be treated by radial approach (65.0% vs 74.4%, $p = 0.004$). In-hospital major adverse cardiac event rate—defined as cardiovascular death, myocardial infarction, stroke/transient ischemic attack, target lesion revascularization, and coronary artery bypass grafting surgery—was higher in the female group (7.1% vs 3.7%, $p = 0.043$). However, coronary perforation, dissection, slow/low flow and tamponade did not significantly differ in gender, neither did cardiovascular medications at discharge. At 1 year follow-up, rate of major adverse cardiac event was 18.4% in the female group vs 11.2% in the male group (adjusted Hazard Ratio 1.82 [1.24 to 2.67], $p = 0.002$). No significant bleeding differences were observed in gender, neither in hospital, nor during follow-up. In conclusion women had worse clinical outcomes following RA PCI during hospitalization and at 1 year follow-up than did men **(Am J Cardiol 2021;143:29−36)**

Female gender is associated with poorer outcomes after percutaneous coronary intervention (PCI), showing a higher risk of death, myocardial infarction (MI) and target vessel and target lesion failure.[1-3] Women presenting with coronary disease are older with a greater prevalence of comorbid conditions, which contribute to gender differences in outcomes after PCI.[4-6] However, beside comorbid conditions, recent large studies report that female gender is independently associated with poorer prognosis following PCI.[7−10] Rotational atherectomy (RA) has been commonly used for over 3 decades in interventional cardiology to address complex calcified coronary lesions. Its utilization varies widely in countries and centers but represents, in average, 0.8 to 3.1% of PCI procedures[11] and tends to increase with the extension of PCI indication toward more complex anatomies. However, little is known about potential gender differences in clinical outcomes following RA PCI. Only 2 retrospective monocentric studies with

[a]Department of Cardiology, Rangueil Toulouse University Hospital, University Paul Sabatier, Toulouse, France; [b]Division of Cardiology, University of Verona, Italy; [c]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; [d]Department of Invasive Cardiology, State Teaching Hospital, Medical University of Bialystok, Bialystok, Poland; [e]Augusta Krankenhaus, Düsseldorf, Germany; [f]Nouvelles cliniques Nantaises, Nantes, France; [g]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland; [h]Cardiovascular Institute, Groupe Hospitalier Mutualiste, Grenoble, France; [i]Department of Cardiology, St Luke's Hospital, Thessaloniki, Greece; [j]Department of Cardiology, Hospital Universitario Central de la Defensa Gómez Ulla, Madrid, Spain; [k]Division of Cardiology, Udine University Hospital, Udine, Italy; [l]Department of Cardiology, University Hospital Virgen Arrtixaca, Murcia, Spain; [m]Unidad de Cardiología Intervencionista, Hospital del Mar, Universidad Autónoma de Barcelona, Barcelona, Spain; [n]Department of Cardiology and Angiology II, University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany; [o]Department of Cardiology, Centre Hospitalier Universitaire de Nîmes, Université de Montpellier, Nimes, France; and [p]Division of Cardiology, Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy. Manuscript received October 20, 2020; revised manuscript received and accepted December 1, 2020.

The study was conducted with the financial support of BOSTON SCIENTIFIC.

See page 35 for disclosure information.

*Corresponding author: Tel: + 33 05 61 32 21 10; fax:+ 33 05 61 32 33 18
E-mail address: bouisset.f@chu-toulouse.fr (F. Bouisset).

0002-9149/© 2020 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2020.12.040

conflicting results have been reported to date.[12,13] The aim of the present analysis was to assess the potential influence of gender on clinical outcomes after RA PCI using the international multicentric prospective Euro4C registry.[14]

Methods

The Euro4C registry is a prospective European multicenter registry that included, between October 2016 and July 2018, all-comers patients who underwent RA PCI. The choice to use the RA was left at the discretion of the operators. The study protocol was approved by the institutional review board of each participating center and all patients gave their written consent to participate to the study. Data were collected through an e-CRF. The list of participating centers is shown in appendix (**Supplementary Table 1)** and the complete protocol has been previously reported.[14]

RA procedures were performed using the Boston Scientific Rotablator system. Characteristics of the RA procedure were recorded, and included: the access site (radial or femoral) and maximum external sheath size, the number of lesions, the nature of the vessel treated with RA and the type of lesion (bifurcation lesion, CTO). The technical parameters of rotablation were also recorded in details (size of burr, number of runs, and maximal burr speed). Patients were exclusively treated with drug eluting stents in 98.2% of cases.

The primary end point of the present study was the comparison in gender of the occurrence of major adverse cardiac events (MACE)—defined as the combination of cardio-vascular death, MI, target lesion revascularization (TLR), stroke and coronary artery bypass grafting (CABG)—in hospitalization and at 1 year following the procedure.

The secondary end points were comparisons in gender of the clinical success rate of the procedure—defined as a successful revascularization of all treated lesions (residual stenosis < 50%) and no peri-procedural complications - and the incidence of in-hospital complications including coronary perforation, coronary dissection, coronary low flow or no-flow, emergency CABG, tamponade, MI, stroke or transient ischemic attack (TIA), bleeding events (according to the BARC classification[15]), and death. Detailed definitions of these end points have been previously published.[14]

Statistical analysis was performed on STATA statistical software, release 14.1 (Stata Corporation, College Station, Texas). Continuous variables were summarized as means and standard deviations for normal distributions, and as medians and interquartile ranges when distributions were not normally distributed. Categorical variables are presented as proportions. In univariate analysis, categorical variables were compared with Chi-square test (or Fischer's exact test when necessary). *Student's t test* was used to compare the distribution of continuous normally distributed data according to categorical variables. *Mann-Whitney* was used to compare ranges of continuous non-normally distributed variables according to categorical variables. A p-value < 0.05 was considered as statistically significant.

Cumulative MACE-free and bleeding-free survival of patients according to gender was determined by the Kaplan-Meier method and compared using the *Log-rank test.*

A multiple regression multivariate analysis with a backward procedure was conducted to identify factors that significantly differ between gender (**Supplementary Table 2**). The initial full model was built including variables related to gender in univariate analysis with a p-value cut-off of 0.20. These factors were: age, creatinine clearance, left ventricular ejection fraction, radial approach, RCA lesion treated with RA, sheath caliber and burr diameter and were thus used for adjustment in survival analysis in order to perform a complete adjustment on potential confounding factors. The proportional-hazard assumption was tested for each covariate by the "log-log" method, plotting (-ln[-ln {survival}]) for each category of a nominal covariate, versus ln(analysis time).

In-hospital outcomes according to gender were compared in a logistic regression analysis presenting a crude p-value and an adjusted p-value after adjustment on potential confounding factors listed above. One-year outcomes according to gender were compared in a survival analysis (Cox model) presenting a crude Hazard Ratio (HR) and p-value and an adjusted Hazard Ratio and p-value after adjustment on potential confounding factors listed above.

Results

Between October 2016 and July 2018, 1,016 patients were prospectively included. Fifty patients were excluded due to of missing data, 966 patients were thus kept in the final analysis. Two hundred and sixty-seven patients (27.6%) were females, and 699 (72.4%) were males. One-year follow-up was complete for 891 patients (92.2%).

Female patients were significantly older (77.8 ± 9.8 vs 73.3 ± 9.5, $p<0.001$). Except for tobacco consumption, more frequent in males (22.2% vs 11.3%, $p<0.001$, age-adjusted $p = 0.02$), no statistically significant differences were observed regarding cardio-vascular risk factors between gender. Renal function was significantly worse in women ($p < 0.001$, age-adjusted $p = 0.004$). In the female group, clinical presentation was significantly more frequently unstable (i.e., STEMI, non-STEMI or unstable angina) ($p = 0.002$, age-adjusted $p = 0.04$), but left ventricular ejection fraction was better in this group ($p = 0,01$, age-adjusted $p = 0.003$). Detailed patients characteristics according to their gender are summarized in **Table 1**.

Distribution of lesions (1-, 2-, 3-vessel disease and left main disease) was similar in genders except for CTO, more frequent in men (30.9% vs 24% $p = 0.034$). Angiographic characteristics of the coronary lesions, according to gender, are presented in **Table 2**.

Radial access was used less frequently in women (74.4 vs 65%, $p < 0.004$), although the sheath diameter and the burr diameters were significantly smaller in women ($p = 0.015$ and $p < 0.001$, respectively). Technical characteristics of the RA procedure are shown in details in **Table 3**.

Dual anti platelet therapy was prescribed at discharge in 903 patients (96.6%) and 188 (20.1%) received an oral anticoagulant therapy. No significant gender differences were observed regarding cardiovascular medications. Treatments at discharge are listed in **Table 4**.

Table 1
Baseline clinical characteristics of the population according to sex

Baseline characteristics		All (n = 966)	Male (n = 699)	Female (n = 267)	p-value
Age (years)*		74.5 ± 9.8	73.3 ± 9.5	77.7 +/- 9.8	< 0.001
Diabetes Mellitus		415/956 (43.4%)	290/691 (42.0%)	125/265 (47.2%)	0.146
Hypertension		792/965 (82.1%)	561/698 (80.4%)	231/267 (86.5%)	0.026
Dyslipidemia		689/962 (71.6%)	497/697 (71.3%)	192/265 (72.5%)	0.724
Active tobacco		162/846 (19.2%)	135/608 (22.2%)	27/238 (11.3%)	< 0.001
BMI > 30 kg/m^2		217/953 (22.8%)	159/693 (22.9%)	58/260 (22.3%)	0.835
Peripheral vascular disease		219/966 (22.7%)	161/699 (23.0%)	58/267 (21.7%)	0.664
Previous stroke/TIA		128/958 (13.4%)	86/693 (12.4%)	42/265 (15.9%)	0.162
Previous MI		276/959 (28.8%)	201/694 (29.0%)	75/265 (28.3%)	0.840
Previous PCI		408/964 (42.3%)	299/697 (42.9%)	109/267 (40.8%)	0.560
Previous CABG		139/965 (14.4%)	110/698 (15.8%)	29/267 (10.9%)	0.053
MDRD creatinine clearance (ml/min/1,73 m^2)	< 30	70 (7.4%)	54 (7.9%)	16 (6.2%)	< 0.001
	30-59	258 (27.3%)	159 (23.2%)	99 (38.4%)	
	≥ 60	616 (65.3%)	473 (68.9%)	143 (55.4%)	
Killip class	I - II	700 (96.7%)	504 (96.4%)	196 (97.5%)	0.441
	III - IV	24 (3.3%)	19 (3.6%)	5 (2.5%)	
Clinical presentation	STEMI	40 (4.2%)	23 (3.3%)	17 (6.4%)	0.002
	NSTEMI	202 (20.9%)	133 (19.1%)	69 (25.8%)	
	Unstable angina	104 (10.8%)	70 (10.0%)	34 (12.7%)	
	Stable angina or silent ischemia	619 (64.1%)	472 (67.6%)	147 (55.1%)	
LVEF (%)	≤ 35	139 (16.5%)	114 (18.8%)	25 (10.7%)	0.015
	35-49	213 (25.3%)	154 (25.3%)	59 (25.3%)	
	≥ 50	489 (58.2%)	340 (55.9%)	149 (64.0%)	

BMI = Body Mass Index; CABG = Coronary Artery Bypass Grafting; LVEF = Left Ventricular Ejection Fraction; MDRD = Modification of Diet in Renal Disease; MI = Myocardial Infarction; NSTEMI = Non-ST Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; SD = Standard Deviation; STEMI = ST Elevation Myocardial Infarction; TIA = Transient Ischemic Attack.
* : Mean +/- SD.

Rate of angiographic success—defined as a success of revascularisation of all treated lesions (residual stenosis < 50%) and no per-procedure complications did not differ in genders (98.1% for female vs 97.9 for male, p = 0.791). However, clinical success—defined as an angiographic success without any complications within 24 hours following the procedure—was observed significantly less frequently in female patients (93.3% vs 89.1% p = 0.032), however this difference becomes nonsignificant after adjustment on potential confounding factors (p = 0.062).

Coronary complications during the RA procedure (coronary dissection, coronary perforation, tamponade, and low flow/no flow) did not significantly differ in gender, neither did the rate of significant bleeding (BARC ≥ 3) (p = 0,687).

In hospital MACE were more frequent in the female group, even after adjustment, (7.1% vs 3.7% p = 0.04). The components of MACE studied individually (cardio-vascular death, MI, stroke/TIA, CABG, and TLR) did not differ in gender during in-hospital period. It should be noted that all deaths that occurred during hospitalization were of cardio-vascular origin, and that no TLR was observed. In-hospital outcomes are summarized in **Table 5**.

At 1-year follow-up, the rate of MACE was 11.2% in the male group vs 18;4% in the female group; after complete adjustment on potential confounding factors, this difference in disfavor of female patients remained significant (HR:1.82 [1.24 to 2.67] p =0.002) (**Figure 1**). The probability of occurrence of cardio-vascular death and stroke or TIA were significantly higher in the female group (HR: 1.96 [1.08 to 3.58], p = 0.028 and HR: 6.27 [1.12 to 35.03], p = 0.036, respectively). The rates of MI and all-cause death were also higher—although not significantly—in the female group (6.4% vs 4.0%, p = 0.053 and 12.7% vs 8.6% p = 0.052, respectively).

Significant bleeding (BARC ≥ 3) did not differ in gender during follow-up (HR: 1.34 [0.59 to 3.06] p = 0.481) (**Figure 2**). One-year results are presented in **Table 6**.

Table 2
Baseline angiographic characteristics of the population according to sex

Angiographic characteristics		All (n = 966)	Male (n = 699)	Female (n = 267)	p-value
Left main coronary artery stenosis		241 (25.0%)	172 (24.6%)	69 (25.8%)	0.691
Number of diseased vessels	1	229 (23.7%)	161 (23.0%)	68 (25.5%)	0.663
	2	369 (38.2%)	272 (38.9%)	97 (36.3%)	
	3	368 (38.1%)	266 (38.1%)	102 (38.2%)	
Calcified bifurcation		359/965 (37.2%)	270 (38.6%)	89/266 (33.5%)	0.138
Chronic total occlusion		280 (29.0%)	216 (30.9%)	64 (24.0%)	0.034

Table 3
Rotational atherectomy procedural characteristics according to sex

RA procedure		All (n = 966)	Male (n = 699)	Female (n = 267)	p-value
Radial approach		692/964 (71.8)	519/698 (74.4)	173/266 (65.0)	0.004
Number of lesions treated with RA	1	725 (75.0)	537 (76.8)	188 (70.4)	0.119
	2	191 (19.8)	128 (18.3)	63 (23.6)	
	≥ 3	50 (5.2)	34 (4.9)	16 (6.0)	
Lesion treated with RA	Left main coronary artery	171 (17.7)	124 (17.7)	47 (17.6)	0.960
	Left descendant artery	468 (48.5)	341 (48.8)	127 (47.6)	0.735
	Circumflex artery	149 (15.4)	120 (17.2)	29 (10.9)	0.015
	Right coronary artery	316 (32.7)	205 (29.3)	111 (41.6)	< 0.001
Calcified bifurcation lesion treated with RA		312/965 (32.3)	245 (35.1)	67/266 (25.2)	0.003
Chronic total occlusion treated with RA		78/964 (8.1)	57/697 (8.2)	21 (7.9)	0.873
Sheath diameter	≤ 6 Fr	722 (75.2)	505 (72.7)	217 (81.6)	0.015
	7 or 7.5 Fr	196 (20.4)	157 (22.6)	39 (14.7)	
	8 Fr	43 (4.5)	33 (4.7)	10 (3.8)	
Mean number of burr runs for each lesion	< 2	165 (17.6)	118 (17.3)	47 (18.2)	0.728
	2 or 3	406 (43.2)	290 (42.6)	116 (44.8)	
	4	143 (15.5)	109 (16.0)	34 (13.1)	
	≥ 5	226 (24.0)	164 (24.1)	62 (23.9)	
Maximal burr diameter (mm)	1.25	266 (27.6)	175 (25.1)	91 (34.3)	< 0.001
	1.50	498 (51.7)	357 (51.2)	141 (53.2)	
	≥ 1.75	199 (20.7)	166 (23.8)	33 (12.5)	
Maximal burr speed (rpm)	< 160.000	261 (27.3)	202 (29.2)	59 (22.3)	0.107
	160.000−180.000	535 (55.9)	378 (54.5)	157 (59.5)	
	> 180.000	161 (16.8)	113 (16.3)	48 (18.2)	
Mean RA duration (sec) for each lesion	< 30	253 (27.5)	176 (26.4)	77 (30.4)	0.446
	30−59	281 (30.5)	205 (30.7)	76 (30.0)	
	≥ 60	386 (42.0)	286 (42.9)	100 (39.5)	
Type of stent	DES	940/958 (98.2)	683/695 (98.3)	257/263 (97.7)	0.573
	BMS	15/958 (1.6)	8/695 (1.2)	7/263 (2.7)	0.093
	DES + BMS	5/958 (0.5)	3/695 (0.4)	2/263 (0.8)	0.528
	DES + BRS	2/958 (0.2)	1/695 (0.1)	1/263 (0.4)	0.474
Total number of stents		1.77 ± 0.90	1.73 ± 0.91	1.86 ± 0.96	0.063
Total stent length. mm*		47 ± 27	46 ± 27	49 ± 29	0.075
IVUS or OCT use		66/698 (6.9)	53/698 (7.6)	13/266 (4.9)	0.137

BMS = Bare Metal Stent; BRS = Bioresorbable Scaffold; DES = Drug Eluting Stent; IVUS = Intra-Vascular Ultra-Sound; OCT = Optical Coherence Tomography; RA = Rotational Atherectomy.
* : Mean +/- SD.

Table 4
Medical therapy at discharge according to sex

Drugs	All (n = 966)	male (n = 699)	female (n = 267)	p-value
Aspirin	913/935 (97.7)	661/679 (97.4)	252/256 (98.4)	0.328
P2Y12 inhibitor (any type)	924/935 (98.8)	669/679 (98.5)	255/256 (99.6)	0.306
Clopidogrel	729/935 (78.0)	527/679 (77.6)	202/256 (78.9)	0.671
Ticagrelor	213/935 (22.8)	156/679 (23.0)	57/256 (22.3)	0.818
Prasugrel	23/935 (2.5)	17/679 (2.5)	6/256 (2.3)	0.888
Oral anticoagulation (any type)	188/935 (6.8)	140/679 (20.6)	48/256 (18.8)	0.525
Vitamin K antagonist	64/935 (6.8)	47/679 (6.9)	17/256 (6.6)	0.879
New oral anticoagulant	124/935 (13.3)	93/679 (13.7)	31/256 (12.1)	0.523
DAPT (Aspirin + any P2Y12 inhibitor)	903/935 (96.6)	652/679 (96.0)	251/256 (98.1)	0.129
TAT (Aspirin + any P2Y12 inhibitor + any oral anticoagulation)	175/935 (18.7)	129/679 (19.0)	46/256 (18.0)	0.719
Betablockers	764/935 (81.7)	547/679 (80.6)	217/256 (84.8)	0.138
Statin	827/935 (88.5)	607/679 (89.4)	220/256 (85.9)	0.140
ACE inhibitors	584/935 (62.5)	429/679 (63.2)	155/256 (60.6)	0.458
ARB	117/935 (12.5)	80/679 (11.8)	37/256 (14.5)	0.271

ACE = Angiotensin Converting Enzyme; ARB = Angiotensin II Receptors Blockers; DAPT = Dual Anti-Platelets Therapy; TAT = Triple Anti-Thrombotic Therapy.

Table 5
In-hospital clinical outcomes according to sex

In-hospital outcomes	All (n = 966)	male (n = 699)	female (n = 267)	p-value	adjusted p *
Angiographic success	943/963 (97.9%)	682/697 (97,8%)	261/266 (98,1%)	0,791	0,220
Clinical success	887/965 (91.9)	650 (93.3)	237/266 (89.1)	0.032	0.062
MACE †	45/965 (4.7)	26/698 (3.7)	19 (7.1)	0.025	0.043
Death	15/965 (1.6)	8/698 (1.2)	7 (2.6)	0.141	0.347
Myocardial Infarction	28/965 (2.7)	17/698 (2.4)	11 (4.1)	0.163	0.068
Stroke or TIA	3.965 (0.3)	2/698 (0.3)	1 (0.4)	1.000	NA
Emergency CABG	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Perforation	16/965 (1.7)	9/698 (1.3)	7 (2.6)	0.162	0.246
Dissection	38/965 (3.9)	25/698 (3.6)	13 (4.9)	0.358	0.341
Tamponade	5/965 (0.5)	2/698 (0.3)	3 (1.1)	0.133	NA
Bleeding (BARC ≥ 3)	12/965 (1.2)	7/698 (1.0)	5 (1.9)	0.329	0.687

CABG = Coronary Artery Bypass Grafting; MACE = Major Adverse Cardiac Events; NA = Non-Applicable; TIA = Transient Ischemic Attack.
* adjusted for age, MDRD creatinine clearance, LVEF, radial approach, RCA lesion treated with RA, sheath caliber and burr diameter.
† : Cardio-vascular death, myocardial infarction, Stroke/TIA and target lesion revascularization.

Discussion

The main findings of the present study focusing on gender differences in clinical outcomes after RA PCI are the following: (1) Female gender is independently associated with a higher rate of in-hospital MACE although female patients did not encounter significantly more RA procedural complications; (2) Female gender is, at 1-year follow-up, independently associated with a higher rate of cardiovascular death, MI, and MACE despite identical medication to male patients at discharge.

At baseline, differences observed in our population between male and female, namely an older age, a tendency to a greater prevalence of cardio-vascular risk factors (except tobacco), and a worse renal function are found classically and consistently in studies comparing female and male with coronary artery disease. However, women typically presented a less diffuse coronary disease in these studies,[7,16] which is not the case in our cohort. Indeed, except for chronic total occlusion, more prevalent in the male group, the severity of coronary disease did not significantly differ in gender in the present study (**Table 2**): this may be explained by complex patients, all requiring RA, were selected and included in our study.

Although 81.6% of women were treated using a sheath caliber ≤ 6 Fr, they were less likely to be treated by radial

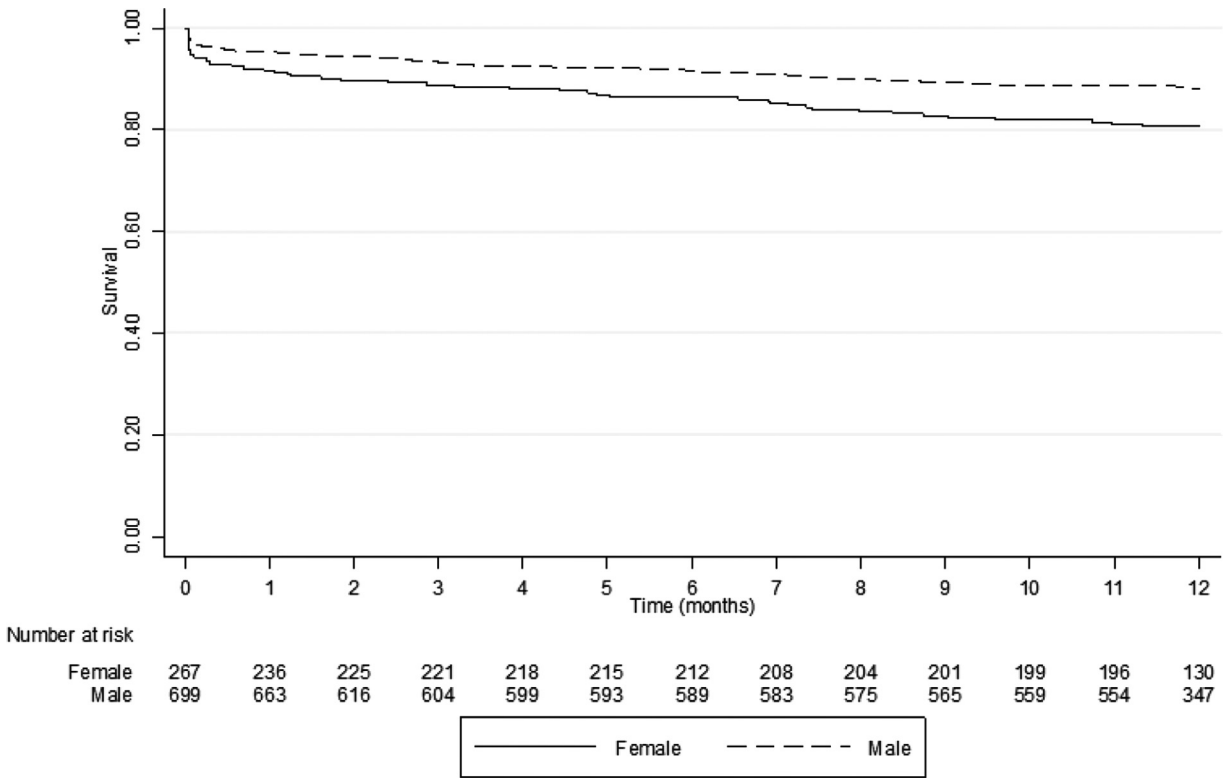

Figure 1. One-year MACE-free survival according to sex (log rank test p=0.003).

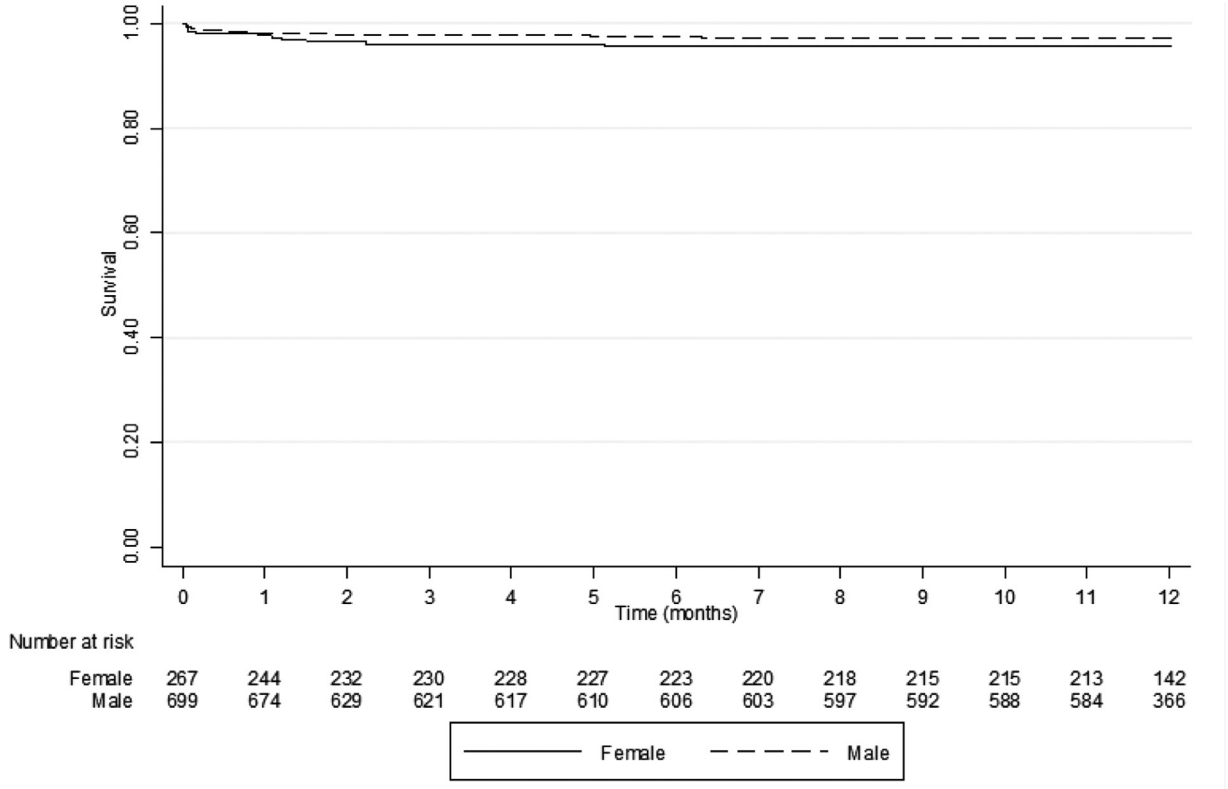

Figure 2. One-year bleeding-free survival (BARC ≥ 3) according to sex (log rank test p=0.195).

approach (p = 0.004). However, despite an inferior proportion of radial access in the female group, this route was used to treat 65% of women from our cohort (vs 74.4% in the male group). In a recent report that pooled contemporary data from the BCIS and SCAAR registries, the rate of radial approach in female patients for PCI was in the range of 40%.[3] Thus, the rate of 65% observed in the female group of our cohort, although lower than in the male group, remained relatively high and probably explains that no gender differences in bleeding were observed in our study (**Table 5**, **Table 6**, and **Figure 2**), although females usually present a higher risk of peri-procedural bleeding.[3,8-9,17] Indeed, previous reports showed that radial access significantly reduces the risk of bleeding in RA PCI,[18] and that women benefit the most from this bleeding reduction.[19]

In our cohort, we observed a higher, but not significant, rate of coronary RA complications in the female group, whereas previous reports showed significant differences regarding perforations and tamponades in female patients.[20] However, in a large study including more than 13,000 cases of RA PCI from the Japan national PCI database, Sakakura et al. identified the determinants of complications (defined as death, emergent surgery, perforations, and tamponade) and noticed no significant differences in gender for procedural complication. Our results are thus in line with this previous study.

Table 6
One-year clinical outcomes according to sex

1 year follow-up	All (n = 966)	Male (n = 699)	Female (n = 267)	Unadjusted HR (95% CI)	p value	Adjusted* HR (95% CI)	p value
Death	94 (9.7)	60 (8.6)	34 (12.7)	1.52 [0.99 - 2.31]	0.052	1.58 [0.99 - 2.51)	0.052
MACE†	127 (13.2)	78 (11.2)	49 (18.4)	1.71 [1.20 - 2.45]	0.003	1.82 [1.24 - 2.67]	0.002
CV death	55 (5.7)	33 (4.7)	22 (8.2)	1.78 [1.04 - 3.06]	0.036	1.96 [1.08 - 3.58]	0.028
Myocardial Infarction	45 (4.7)	28 (4.0)	17 (6.4)	1.63 [0.89 - 2.98]	0.112	1.86 [0.99 - 3.49]	0.053
Stroke or TIA	8 (0.8)	2 (0.3)	6 (2.3)	8.00 [1.62 - 39.66]	0.011	6.27 [1.12 - 35.03]	0.036
CABG	5 (0.5)	5 (0.7)	0 (0.0)	NA	NA	NA	NA
TLR	23 (2.4)	16 (2.3)	7 (2.6)	1.17 [0.48 - 2.85]	0.728	1.02 [0.40 - 2.59]	0.970
Bleeding (BARC ≥ 3)	29 (3.0)	18 (2.6)	11 (4.1)	1.63 [0.77 - 3.46]	0.200	1.34 [0.59 - 3.06]	0.481

CABG = Coronary Artery Bypass Grafting; CV = Cardiovascular; MACE = Major Adverse Cardiac Events; NA = Non-Applicable; TIA = Transient Ischemic Attack; TLR = Target Lesion Revascularization.

* adjusted for age, MDRD creatinine clearance, LVEF, radial approach, RCA lesion treated with RA, sheath caliber and burr diameter.

† : Cardio-vascular death, myocardial infarction, Stroke/TIA and target lesion revascularization.

At 1 year follow-up, after complete adjustment on potential confounding factors, significant differences in disfavor of female patients were observed on cardio-vascular death (HR = 1, 96 [1.08 to 3.58] p = 0.028), stroke or TIA (6.27 [1.12 to 35.03] p = 0.036). Regarding MI, the difference was not significant, but a clear tendency could be observed (HR: 1.86 [0.99 to 3.49], p = 0.053). As a result, MACE were 1.8 times more likely to occur in female patient at 1 year. It is interesting to emphasize that this significant gender difference in MACE is driven by hard end points (death, stroke/TIA, MI) and not by TLR, which clearly does not differ between gender (1.02 [0.40 to 2.59] p = 0.97). Indeed, since women are more likely to report chest pain and functional disability related to angina,[21] it could be suggested that differences in outcomes after PCI could be explained by more frequent repeated revascularization procedures in females: it is not the case in the present report. Another factor frequently more pejorative in female patients is the delay of presentation at hospital in context of ACS. However, although female patients presented more frequently with an acute coronary syndrome, the impact of this parameter is particularly important for ST elevation acute coronary syndrome, which only concerned a minority of patients in the present study (40 subjects, 4.2%). The reasons for this persistent difference in gender remain unclear. Although potential unmeasured confounders cannot be excluded, these results underline the need to pursue work on this topic.

This study is mainly limited by its observational design. As the decision of using RA was left at each centre discretion, no central corelab analyzed the procedures for end point definition or complications. Moreover, no pre- and post-procedural systematic QCA analysis was performed. Data regarding the global anatomical complexity of the coronary disease and the level of risk of the patients in our population were not available. Finally, 50 patients (4.9%) were excluded from our initial cohort for missing data, and 75 patients (7.8%) were lost during follow-up, which may lead to potential bias.

In conclusion, our study demonstrates that female gender is independently associated with poorer immediate and mid-term clinical outcomes following rotational coronary atherectomy.

Disclosures

Dr. **Bouisset** reports grants from BOSTON SCIENTIFIC, during the conduct of the study; personal fees from MSD, ABBOTT, BAYER, and AMGEN, outside the submitted work.

Dr. **Reczuch** reports personal fees from BOSTON SCIENTIFIC, outside the submitted work.

Dr. **Ferenc** reports personal fees from BOSTON SCIENTIFIC, MEDTRONIC, TERUMO, TELEFLEX, BIOTRONIK, and ORBUS NEICHE, outside the submitted work.

Dr. **Cayla** reports personal fees from Amgen, personal fees from Astra Zeneca, personal fees from Bayer, personal fees from Biotronik, personal fees from Bristol Myers Squibb, grants and personal fees from Medtronic, personal fees from MSD, personal fees from Pfizer, personal fees from Sanofi, outside the submitted work.

Dr. **Barbato** reports personal fees from ABBOTT VASCULAR and BOSTON SCIENTIFIC, outside the submitted work.

Dr. **Carrie** reports grants from BOSTON SCIENTIFIC, during the conduct of the study; personal fees from ALVIMEDICA, outside the submitted work.

All other authors have nothing to disclose

Authors contribution

Frédéric **Bouisset**: Investigation; Writing - Original Draft; Writing - Review & Editing.

Flavio **Ribichini:** Investigation; Writing - Review & Editing.

Vincent **Bataille:** Data Curation; Formal analysis.

Krzysztof **Reczuch** Investigation; Writing - Review & Editing.

Slawomir **Dobrzycki** Investigation; Writing - Review & Editing.

Markus **Meyer-Gessner** Investigation; Writing - Review & Editing.

Erwan **Bressollette** Investigation; Writing - Review & Editing.

Wojciech **Zajdel**, Investigation; Writing - Review & Editing.

Benjamin **Faurie**, Investigation; Writing - Review & Editing.

Nikolaos **Mezilis** Investigation; Writing - Review & Editing.

Jorge **Palazuelos** Investigation; Writing - Review & Editing.

Leonardo **Spedicato** Investigation; Writing - Review & Editing.

Mariano **Valdés** Investigation; Writing - Review & Editing.

Beatriz **Vaquerizo** Investigation; Writing - Review & Editing.

Miroslaw **Ferenc** Investigation; Writing - Review & Editing.

Guillaume **Cayla** Investigation; Writing - Review & Editing.

Emanuele **Barbato** Investigation; Writing - Review & Editing.

Didier **Carrié** Conceptualization; Investigation; Project administration; Funding acquisition; Supervision; Writing - Review & Editing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Acknowledgements

The authors acknowledge all the physicians and their teams in the participating centers across Europe.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.040.

1. Epps KC, Holper EM, Selzer F, Vlachos HA, Gualano SK, Abbott JD, Jacobs AK, Marroquin OC, Naidu SS, Groeneveld PW, Wilensky RL. Sex Differences in outcomes following percutaneous coronary intervention according to age. *Circ Cardiovasc Qual Outcomes* 2016;9:S16–S25.
2. Iantorno M, Torguson R, Kolm P, Gajanana D, Suddath WO, Rogers T, Bernardo NL, Ben-Dor I, Gai J, Satler LF, Garcia-Garcia HM, WS Weintraub, Waksman R. Relation of sex and race to outcomes in patients undergoing percutaneous intervention with drug-eluting stents. *Am J Cardiol* 2019;123:913–918.
3. Kunadian V, Qiu W, Lagerqvist B, Johnston N, Sinclair H, Tan Y, Ludman P, James S, Sarno G. National Institute for Cardiovascular Outcomes R. Swedish Coronary A and Angioplasty R. Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from United Kingdom and Sweden). *Am J Cardiol* 2017;119:210–216.
4. Kenkre TS, Malhotra P, Johnson BD, Handberg EM, Thompson DV, Marroquin OC, Rogers WJ, Pepine CJ, Bairey Merz CN, Kelsey SF. Ten-year mortality in the WISE study (women's ischemia syndrome evaluation). *Circ Cardiovasc Qual Outcomes* 2017;10:e003863.
5. Kovacic JC, Mehran R, Karajgikar R, Baber U, Suleman J, Kim MC, Krishnan P, Dangas G, Sharma SK, Kini A. Female gender and mortality after percutaneous coronary intervention: results from a large registry. *Catheter Cardiovasc Interv* 2012;80:514–521.
6. Parvand M, Rayner-Hartley E, Sedlak T. Recent developments in sex-related differences in presentation, prognosis, and management of coronary artery disease. *Can J Cardiol* 2018;34:390–399.
7. Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, Ben-Yehuda O, Redfors B, Madhavan MV, Maehara A, Mehran R, Stone GW. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol* 2020;75:1631–1640.
8. Heer T, Hochadel M, Schmidt K, Mehilli J, Zahn R, Kuck KH, Hamm C, Bohm M, Ertl G, Hoffmeister HM, Sack S, Senges J, Massberg S, Gitt AK, Zeymer U. Sex differences in percutaneous coronary intervention-insights from the coronary angiography and PCI Registry of the German Society of Cardiology. *J Am Heart Assoc* 2017;6:e004972.
9. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, Kwok CS, Ensor J, Burke DL, Riley RD, Holmvang L, Mamas MA. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: Insights from 6.6 million PCI procedures in the United States. *PLoS One* 2018;13:e0203325.
10. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Stahle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012;33:3105–3113.
11. Barbato E, Carrie D, Dardas P, Fajadet J, Gaul G, Haude M, Khashaba A, Koch K, Meyer-Gessner M, Palazuelos J, Reczuch K, Ribichini FL, Sharma S, Sipotz J, Sjogren I, Suetsch G, Szabo G, Valdes-Chavarri M, Vaquerizo B, Wijns W, Windecker S, de Belder A, Valgimigli M, Byrne RA, Colombo A, Di Mario C, Latib A, Hamm C and European Association of Percutaneous Cardiovascular I. European expert consensus on rotational atherectomy. *EuroIntervention* 2015;11:30–36.
12. Ford TJ, Khan A, Docherty KF, Jackson A, Morrow A, Sidik N, Rocchiccioli P, Good R, Eteiba H, Watkins S, Shaukat A, Lindsay M, Robertson K, Petrie M, Berry C, Oldroyd KG, McEntegart M. Sex differences in procedural and clinical outcomes following rotational atherectomy. *Catheter Cardiovasc Interv* 2020;95:232–241.
13. Januszek R, Pawlik A, Staszczak B, Jedrychowska M, Bartus J, Legutko J, Dudek D, Surdacki A, Bartus S. Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy. *Adv Clin Exp Med* 2020;29:225–233.
14. Bouisset F, Barbato E, Reczuch K, Dobrzycki S, Meyer-Gessner M, Bressollette E, Cayla G, Lhermusier T, Zajdel W, Palazuelos Molinero J, Ferenc M, Ribichini FL, Carrie D. Clinical outcomes of PCI with rotational atherectomy: the European multicentre Euro4C registry. *EuroIntervention* 2020;16:e305–e312.
15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–2747.
16. Gudnadottir GS, Andersen K, Thrainsdottir IS, James SK, Lagerqvist B, Gudnason T. Gender differences in coronary angiography, subsequent interventions, and outcomes among patients with acute coronary syndromes. *Am Heart J* 2017;191:65–74.
17. Ndrepepa G, Schulz S, Neumann FJ, Byrne RA, Hoppmann P, Cassese S, Ott I, Fusaro M, Ibrahim T, Tada T, Richardt G, Laugwitz KL, Schunkert H, Kastrati A. Bleeding after percutaneous coronary intervention in women and men matched for age, body mass index, and type of antithrombotic therapy. *Am Heart J* 2013;166:534–540.
18. Watt J, Austin D, Mackay D, Nolan J, Oldroyd KG. Radial versus femoral access for rotational atherectomy: a UK observational study of 8622 patients. *Circ Cardiovasc Interv* 2017;10:e005311.
19. Kwok CS, Kontopantelis E, Kunadian V, Anderson S, Ratib K, Sperrin M, Zaman A, Ludman PF, de Belder MA, Nolan J, Mamas MA, British Cardiovascular Intervention S and National Institute for Cardiovascular Outcomes R. Effect of access site, gender, and indication on clinical outcomes after percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society (BCIS). *Am Heart J* 2015;170:164–172. , 172 e1-5.
20. Kinnaird T, Kwok CS, Kontopantelis E, Ossei-Gerning N, Ludman P, deBelder M, Anderson R, Mamas MA, British Cardiovascular Intervention S and the National Institute for Cardiovascular Outcomes R. Incidence, determinants, and outcomes of coronary perforation during percutaneous coronary intervention in the United Kingdom between 2006 and 2013: an analysis of 527 121 cases from the British cardiovascular intervention society database. *Circ Cardiovasc Interv* 2016;9:e003449.
21. Sheps DS, Kaufmann PG, Sheffield D, Light KC, McMahon RP, Bonsall R, Maixner W, Carney RM, Freedland KE, Cohen JD, Goldberg AD, Ketterer MW, Raczynski JM, Pepine CJ. Sex differences in chest pain in patients with documented coronary artery disease and exercise-induced ischemia: results from the PIMI study. *Am Heart J* 2001;142:864–871.