

Impact of female gender and transradial coronary stenting with maximal antiplatelet therapy on bleeding and ischemic outcomes

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Background Female gender has been associated with poorer outcomes after percutaneous coronary intervention (PCI) and femoral approach. However, no data are available on the impact of gender and transradial PCI with maximal antiplatelet therapy on bleeding and ischemic outcomes.

Methods In the EARly discharge after Stenting of coronarY arteries (EASY) trial, 1,348 patients with acute coronary syndrome underwent transradial PCI. All patients were pretreated with aspirin and clopidogrel. After sheath insertion, 70 U/kg heparin was administered and a bolus of abciximab was given before first balloon inflation. Major adverse cardiac events including death, myocardial infarction, and target vessel revascularization; major bleeding; and local hematomas were evaluated at 30 days, 6 months, and 12 months.

Results Women (n = 298, 22%) were older, had more hypertension, more family history, and less previous PCI than men. Weight, baseline hemoglobin, and creatinine clearance were significantly lower in women. The number of dilated sites, complex lesions, and procedure duration was similar, but 5F sheath size was more frequent in women. Major adverse cardiac events remained similar at 30 days (3.4% vs 3.9%, $P = .86$), at 6 months (11.5% vs 7.8%, $P = .06$), and at 1 year (14.1% vs 12.6%) in both groups. There was no significant difference in the incidence of major bleeding between the 2 groups, but female gender was the only independent predictor of hematomas (odds ratio 4.40, 95% confidence interval 2.49-7.81, $P < .0001$).

Conclusion Despite more comorbidities, female gender was not a predictor of adverse clinical outcomes after transradial PCI with maximal antiplatelet therapy. Still, female gender remained associated with a higher risk of local hematomas. Efforts should continue to identify modifiable factors to reduce procedural bleeding in women, regardless of the access site. (*Am Heart J* 2009;157:740-5.)

Coronary artery disease, particularly acute coronary syndrome, is the main cause of mortality for men and women in Western countries. Gender differences still exist in symptoms, presentation, and referral to angiography.¹⁻³ Previous studies have reported worse in-hospital and long-term mortality of women undergoing percutaneous revascularization.^{4,6} However, many of these studies have been performed before recognition of the importance of dual antiplatelet therapy, advances in antithrombotic therapy and the

introduction of drug-eluting stents. Nowadays, modern percutaneous coronary intervention (PCI) studies show a trend to at least equalize the differences in terms of mortality, myocardial infarction (MI), and urgent revascularization between men and women once baseline comorbidities have been taken into account.⁷ Nevertheless, with the femoral approach, there is still a higher risk of bleeding and vascular complications that penalizes women's early outcomes.^{8,9} Radial approach, which has been associated with lower entry site complications and lower major bleeding, may decrease access site-related bleeding in women undergoing PCI and treated with glycoproteins IIb/IIIa receptor inhibitors (GPIs).¹⁰

The objective of this study is to compare early and late outcomes of women and men who underwent transradial PCI and were treated with maximal antiplatelet therapy in the EARly discharge after Stenting of coronarY arteries (EASY) trial.

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Methods

Study population and study design

The details of the EASY trial have been previously described.¹¹ Briefly, patients were enrolled from October 2003 to April 2005. Patients were excluded if they had presented with ST-elevation MI within 72 hours or had a history of left ventricular ejection fraction $\leq 30\%$. Except for a secondary branch in bifurcation lesions or redilatation for in-stent restenosis (ie, brachytherapy), all lesions had to be stented. The protocol was approved by Health Canada and the Laval Hospital Ethics Review Board. All patients signed an informed consent form for participation in the trial.

The study was a randomized controlled, open-label study comparing same-day home discharge and bolus-only abciximab to overnight hospitalization and bolus followed by 12-hour infusion of abciximab after uncomplicated transradial coronary stenting. In case of suboptimal results or clinical complications, patients were excluded from same-day discharge after PCI and received abciximab bolus and infusion. Abciximab was administered as a 0.25 mg/kg bolus before first balloon angioplasty, and infusion was given for a total of 12 hours at 0.125 $\mu\text{g}/\text{kg}$ per minute to a maximum of 10 $\mu\text{g}/\text{min}$. All patients were pretreated with aspirin and clopidogrel before diagnostic angiography. After radial or ulnar sheath insertion, a bolus of 70 U/kg heparin was given intravenously.¹² Vascular sheaths were removed at the end of the procedure and a bracelet (Hemostop, Zoom Inc, Piedmont, Qc, Canada) remained in place until hemostasis was completed, usually within 2 hours. Study personnel contacted all patients the day after PCI, at 30 days, at 180 days, and at 365 days. Outcomes in the randomized and registry groups at 1 year have been reported previously.^{13,14}

This study was designed as investigator-initiated trial and funded by unrestricted grants from Eli-Lilly (Indianapolis, IN), Bristol-Myers-Squibb (New York, NY)/Sanofi-Aventis (Paris, France), Régie Régionale de Québec (Québec City, Québec, Canada), and Corporation de l'Institut de cardiologie de Québec (Québec City, Québec, Canada). The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final content.

Study end points

Major cardiac adverse event (MACE) rate including death, MI, and target vessel revascularization was calculated at 30 days, 6 months, and 12 months after the index procedure. For non-Q-wave MI, pre-procedural MI was classified when any post-PCI creatine kinase-muscle-brain (CK-MB) value was $\geq 3\times$ upper limit of normal, that is, 30 $\mu\text{g}/\text{mL}$ in our laboratory. After hospital discharge, non-Q-wave MI was classified using the American College of Cardiology (ACC)/European Society of Cardiology (ESC) nomenclature, that is, using any troponin I or troponin T value or CK/CK-MB values above upper limits of normal.¹⁵ Major bleeding was graded using REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2 trial) classification.¹⁶ Briefly, these include intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss with a decrease in hemoglobin >3 g/dL; any decrease in hemoglobin >4 g/dL without overt bleeding; or transfusion of ≥ 2 units of blood products.

Table I. Baseline characteristics

	Gender		P
	Women (n = 298; 22%)	Men (n = 1050; 78%)	
Age (y)	62.5 \pm 11.0	59.7 \pm 10.0	<.0001
Diabetes	59 (20%)	174 (17%)	.19
Dyslipidemia	248 (83%)	904 (86%)	.23
Hypertension	175 (59%)	516 (49%)	.004
Family history	231 (78%)	729 (69%)	.007
Tobacco use	106 (36%)	333 (32%)	.23
Previous MI	122 (41%)	477 (45%)	.19
Previous PCI	43 (14%)	218 (21%)	.016
ACS: unstable angina	205 (69%)	698 (66%)	.49
ACS: non-ST-elevation MI	67 (23%)	266 (25%)	.36
Previous CABG	19 (6.4%)	66 (6.3%)	1.00
LMWH prior PCI	69 (23%)	254 (24%)	.76
GPI prior PCI	14 (4.7%)	53 (5.1%)	.88
Hemoglobin (g/L)	129 \pm 12	143 \pm 12	<.0001
Platelet ($10^9/\text{L}$)	263 \pm 67	232 \pm 56	<.0001
Creatinine clearance (mL/min)	78 \pm 28	95 \pm 40	<.0001
Weight (kg)	72 \pm 18	84 \pm 15	<.0001

Data are expressed as mean \pm standard deviation or number (percentage of total). Creatinine clearance was calculated according to Cockcroft formula. ACS, Acute coronary syndrome; CABG, coronary artery bypass grafting; LMWH, low-molecular-weight heparin.

Local hematoma was graded according to a specific scale: type I, ≤ 5 cm diameter (nonsignificant); type II, >5 to ≤ 10 cm diameter (mild); type III, >10 cm but distal to the elbow (moderate); type IV, extending above the elbow (severe); type V, anywhere with ischemic threat of the hand (compartment syndrome).

Statistical analysis

Categorical variables were expressed as numbers and percentages and continuous variables as mean \pm standard deviation. Baseline and procedural characteristics were compared between groups using Fisher exact test or χ^2 test for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables. Survival curves were constructed using Kaplan-Meier techniques, and comparisons were made using log-rank test. Stepwise logistic regression analysis was performed to assess the relationship of female gender with clinical outcomes. Because of differences in several baseline characteristics between men and women, the model was adjusted for variables, which differed by univariate analysis at $P < .20$. For hematoma, the following variables were tested as independent predictors: age, diabetes, hypertension, family history, previous MI, previous PCI, body mass index, waist circumference, creatinine clearance, number of dilated sites, sheath size, final activated clotting time (ACT), and gender. A probability value $<.05$ was considered significant. Statistical tests were performed using JMP 7.0 (SAS institute, Cary, NC).

Results

Women were older ($P < .0001$), more commonly had hypertension ($P < .004$), had more frequent family history

Table II. Procedural characteristics

	Gender		P
	Women (n = 298; 22%)	Men (n = 1050; 78%)	
1-Vessel	194 (65%)	606 (58%)	.066
2-Vessel	82 (28%)	341 (32%)	
3-Vessel	22 (7.4%)	103 (9.8%)	
≥B2/C lesion	171 (57%)	623 (59%)	.55
1 Dilated site	197 (66%)	646 (62%)	.084
2 Dilated sites	67 (22%)	303 (29%)	
≥3 Dilated sites	34 (11%)	101 (9.6%)	
Catheter sheath			
5F	169 (57%)	459 (44%)	.0003
6F	128 (43%)	582 (55%)	
7F	1 (0.3%)	9 (0.9%)	
Final ACT (s)	322 ± 71	308 ± 64	.003
Duration (min)	49 ± 28	48 ± 25	.54

Data are expressed as mean ± standard deviation or number (percentage of total).

Table III. Thirty-day events

	Gender		P
	Women (n = 298; 22%)	Men (n = 1050; 78%)	
Death	0 (0%)	2 (0.2%)	1.00
MI	9 (3.0%)	37 (3.5%)	.86
Urgent revascularization	1 (0.3%)	13 (1.2%)	.33
PCI	1	6	
CABG	0	7	
Major bleeding	7 (2.4%)	12 (1.1%)	.16
GI bleeding	2 (0.7%)	4 (0.4%)	
Hemoglobin drop	5 (1.7%)	4 (0.4%)	.059
CABG related	0 (0.0%)	4 (0.4%)	
Thrombocytopenia			
<100 000/μL	2 (0.7%)	17 (1.6%)	.28
<50 000/μL	1 (0.3%)	7 (0.7%)	1.00
Any transfusion	5 (1.7%)	10 (1.0%)	.34
Repeat hospitalization	17 (5.7%)	47 (4.5%)	.36
Hematoma	67 (22%)	61 (5.8%)	<.0001
Grade I	35 (12%)	37 (3.5%)	
Grade II	19 (6.4%)	14 (1.3%)	
Grade III	12 (4.0%)	9 (0.9%)	
Grade IV	1 (0.3%)	1 (0.1%)	

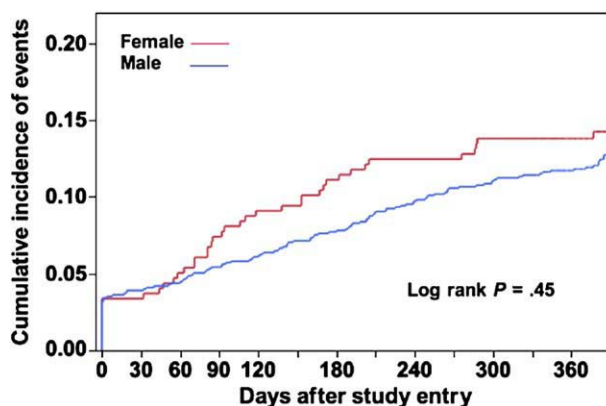
Events are expressed as numbers of patients (percentage of total). Hematoma grade I indicates ≤5 cm; grade II, ≤10 cm; grade III, >10 cm but distal to elbow; grade IV, extending above elbow. GI, Gastrointestinal.

of coronary heart disease ($P < .007$), and had less previous PCI ($P < .016$) (Table I). The weight, baseline hemoglobin, and creatinine clearance were significantly lower in females ($P < .0001$ for all). The number of dilated sites, type B2/C lesions, and procedure duration were similar, but sheath size ≥6F was less frequent in females (43% vs 56%, $P < .0001$) (Table II). Although the mean duration of the procedure was similar in women and in men, the final ACT was significantly longer in women compared to men (322 vs 308 seconds, $P = .003$).

Table IV. Major adverse cardiac events

	Gender		P
	Women (n = 298; 22%)	Men (n = 1050; 78%)	
MACE			
30 d	10 (3.4%)	41 (3.9%)	.86
6 m	34 (11.5%)	82 (7.8%)	.06
1 y	42 (14.1%)	132 (12.6%)	.49
Death			
6 m	2 (0.7%)	2 (0.2%)	.21
1 y	3 (1.0%)	8 (0.8%)	.72
MI			
6 m	12 (4.0%)	38 (3.6%)	.73
1 y	13 (4.4%)	44 (4.2%)	.87
TVR			
6 m	23 (7.7%)	49 (4.7%)	.056
1 y	31 (10.4%)	89 (8.5%)	.30

Events are expressed as numbers of patients (percentage of total). Composite end points: death, MI, or target vessel revascularization. TVR, Target vessel revascularization.

Figure 1

Major adverse cardiac event rate at 1 year. Kaplan-Meier estimates of MACE in women and men. Observe that the 2 curves remained juxtaposed until 60 days post-PCI before slightly diverging due to slightly more target vessel revascularization in women at 6 months. At 1 year, the MACE rate was similar in women and men.

At 30 days, ischemic events and rehospitalization rate were similar in both groups (Table III). There was a trend for more major bleeding in women compared to men (2.4% vs 1.1%, $P = .16$), and this resulted from a slightly higher incidence of significant hemoglobin drop (Table III). Hematoma was more frequent in women (22% vs 5.0038%, $P < .0001$), although most were mild or moderate and these were unrelated to the risk of major bleeding. There was no other access site complication than hematoma. None required surgical intervention. By multivariate analysis, female gender remained the only independent predictor for

Table V. Clinical outcomes according to gender

Author	Study period	No. of women (% total)	Early mortality	Major bleeding	Vascular complications	1-y mortality
Alfonso et al. ¹⁸	1990-1997	158 (16%)	6.0% vs 2.0%	–	7.0% vs 2.0%	–
Cho et al. ²¹	1991-1995	1771 (27%)	–	M: 2.7% placebo-1.3% abc. W: 2.9% placebo-3.0% abc.	–	M: 2.7% placebo-1.9% abc. W: 4% placebo-2.5% abc.
Mehilli et al. ²⁷	1992-1998	1,001 (23%)	1.7% vs 0.8%	–	–	4.0% vs 4.1%
Trabattoni et al. ²⁸	1992-1998	160 (14%)	1.0% vs 0.7%	9.3% vs 3.5%	9.4% vs 3.5%	–
Chiu et al. ²⁰	1992-2002	5301 (29%)	–	–	5.6% vs 2.3%	7% vs 5%
Peterson et al. ⁶	1994-1998	35,571 (32%)	1.8% vs 1.0%	–	5.4% vs 2.7%	–
Chauhan et al. ¹⁹	1995-1999	1908 (31%)	0.4% vs 0.1%	–	3.1% vs 0.6%	2.7% vs 1.6%
Iakovou et al. ²³	1996-2000	322 (26%)	1.9 vs 1.45%	0.0% vs 0.3%	1.2% vs 0.67%	–
Watanabe et al. ²⁹	1997	29,277 (35%)	1.2% vs 0.6%	–	–	–
Jacobs et al. ²⁴	1997-1998	895 (35%)	2.2% vs 1.3%	3.2% vs 1.1%	5.0% vs 2.6%	6.5% vs 4.3%
Malenka et al. ²⁶	1998-1999	3983 (33%)	1.43% vs 0.79%	–	–	–
Berger et al. ⁷	1998-1999	1331 (31%)	0.5% vs 0.5%	–	0.3% vs 0.0%	3 y: 10% vs 8.9%
Fernandes et al. ²²	1999-2000	562 (27%)	0.53% vs 0.47%	M: 0.3% placebo- 0.99% Eptif. W: 0.79% placebo-2.36% Eptif. 4.8% vs 2.7%	5.5% vs 2.6%	–
Chacko et al. ⁸	2001-2002	1537 (26%)	0.59% vs 0.22%	–	2.9% vs 1.2%	3.0% vs 1.8%
Abbott et al. ¹⁷	2001-2004	1117 (35%)	BMS: 1.3% vs 1.0% DES: 0.2% vs 0.6%	–	BMS: 4.1% vs 1.2% DES: 5.1% vs 0.3%	BMS: 5.1% vs 3.8% DES: 3.8% vs 3.6%
Lansky et al. ²⁵	2003-2005	2090 (27%)	–	–	–	3.7% vs 3.5%
This study	2003-2005	298 (22%)	0.0% vs 0.2%	2.4% vs 1.1%	–	1.0% vs 0.8%

Eptif., eptifibatide; Abc., abciximab; M, Men; W, women; BMS, bare metal stent; DES, drug-eluting stent.

mild or moderate hematoma (odds ratio 4.40, 95% confidence interval 2.49-7.81, $P < .0001$).

At 6 and 12 months of follow-up, the incidence of MACE was similar in both women and men (Table IV). At 1 year, female gender was not an independent predictor of MACE (odds ratio 1.26, 95% confidence interval 0.84-1.85) (Figure 1).

Discussion

We showed that women who underwent transradial PCI with maximal antiplatelet therapy had no difference in MACE at 30 days, 6 months, and 1 year compared to men. However, female gender was still associated with a higher risk of local hematoma despite the use of transradial approach and smaller sheath size.

Differences in early and late clinical outcomes between women and men have been debated for many years^{6-8,11,17-29} (Table V). Several confounding factors between women and men complicate this issue. In studies with acute coronary syndromes, there might be a referral bias as clinical presentation and initial management for women can be different, the so-called Yentl syndrome.³ Another frequent bias is related to the number of women referred for angiography with nonsignificant coronary artery disease. Important strengths of this study were the uniformity in clinical presentation, the systematic use of coronary stents and

abciximab, and the pretreatment with aspirin and clopidogrel (≥ 12 hours in 90% of the cases).

Studies in the early days of balloon angioplasty showed worse acute and late outcomes in women compared to men.³⁰ As expected, studies with coronary stents have shown a significant improvement in the incidence of MACE, both in women and in men. Still, a number of studies reported a higher rate of early and late MACE in women.^{8,19,20,31} More recently, whereas unadjusted ischemic events have remained unfavorable for women, statistical adjustment for baseline differences has usually greatly neutralized the gender impact.^{7,24,27} As previously noted in other studies, women in our study had several higher risk baseline characteristics. Despite these differences, our study demonstrates a similar crude incidence of ischemic events at 30 days, 6 months, and 1 year after PCI in women compared to men. Pooled analysis of trials using abciximab has suggested a similar treatment effect in women as compared to men.²¹ In our study, all patients received maximal antiplatelet therapy, and early and late outcomes compare favorably, irrespective of the gender, with recent trials.

Another important issue relates to the incidence of peri-procedural bleeding. Before the GPI era, several studies have reported an increased incidence of bleeding among women.^{8,21} Even with weight-adjusted heparin dosage, women undergoing PCI with abciximab and femoral approach have a higher incidence of major and minor bleeding compared to men.²¹ More

recently, female gender has remained an independent risk factor for bleeding even with bivalirudin use in everyday practice.³² Although it remains unclear why women have more PCI-related bleeding than men, it is worth noting that in our study there was no difference in major bleeding using the REPLACE-2 classification, and the absolute rate remained extremely low in women and men despite GPI use. In the REPLACE-2 study, however, there was a similar reduction in the bleeding risk with bivalirudin compared to heparin + GPI in women (5.9% vs 3.7%, $P = .04$) and in men (3.5% vs 1.9%, $P = .001$).¹⁶

Vascular complications and access site-related bleeding remain a serious issue with femoral PCI today, even with closure devices.^{9,33,34} Access site hematoma requiring transfusion confers a 4.5-fold increase in 1-year mortality after PCI performed by femoral approach.³⁵ Several previous PCI studies have shown an increased risk of vascular complications and access site-related bleeding in women.^{9,34-36} In the REPLACE-2 trial, the access site complication rate in women was 4.1% in the heparin arm and 1.6% in the bivalirudin arm compared with 1.9% and 0.6% in men.⁸ In univariate analysis, female gender was significantly associated with in-hospital major bleeding, minor bleeding, access site bleeding, retroperitoneal bleeding, and transfusion.⁸ Retroperitoneal bleeding, in particular, is more frequent with female gender and bears significant worse prognosis.³⁴ Our findings are consistent with prior experience and confirm the absence of serious access site-related complications and bleeding with transradial approach. Overall, our results suggest that systematic transradial approach is more important than the choice of antiplatelet or antithrombin drug regimen in modern PCI. Indeed, Pristipino et al³⁷ compared access site-related major and minor bleeding in women compared to men using femoral and transradial approach.³⁷ In their femoral experience, women had more major and minor access site-related bleeding, whereas no major bleeding occurred in women using transradial approach. Interestingly, women had still higher incidence of minor bleeding with transradial approach than men. Using femoral access, Chiu et al²⁰ showed that female gender was an independent predictor of local hematoma. This is in accordance with our results, which showed that female gender remained an independent predictor of local hematoma despite the increased use of smaller catheter size compared to men. Because ACT values at the end of the procedure were higher in women and higher than 300 seconds, it remains possible that heparin dose reduction with or without abciximab would further reduce this complication.³⁸ It should be noted that most hematomas were classified as grade I or II (ie, directly resulting from puncture site bleeding), whereas few grade III or IV hematoma (ie, resulting from wire-induced vessel injury) occurred. There was a low rate of

transfusion similar to that reported in real-world experience with transradial approach.³⁹

Limitations

This is a post hoc analysis and, therefore, our findings should be viewed primarily as hypothesis-generating and ultimately should be confirmed in a randomized trial.

Conclusion

Over the last decade, there has been remarkable decrease in the gender gap in PCI-related complications.^{20,24,40} Several improvements in PCI techniques, peri-procedural anticoagulation, and management of cardiovascular risk factors suggest that similar early and late outcomes are achievable in women and in men after PCI in stable angina and acute coronary syndromes. Still, our results suggest that systematic transradial PCI confers a significant benefit in the invasive management of women, especially in complex procedures.⁴¹ Further studies in women using small catheters, transradial approach, and new antithrombotic pharmacologic compound such as bivalirudin are required to assess optimal management of access site in providing rapid and uncomplicated hemostasis.

Disclosures

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