

Evidence for a “gender paradox” in diabetic patients undergoing percutaneous coronary intervention: adverse preprocedural risk but favorable long-term clinical outcome in women

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intervention.

Background. The aim of this study was to assess the impact of gender on procedural and late clinical outcome in a large cohort of consecutive diabetic patients undergoing percutaneous coronary intervention (PCI) in a single center.

Methods. The study included a cohort of 542 consecutive diabetic patients (414 men, 128 women), undergoing PCI for stable and unstable angina. Clinical events were assessed every 6 months for a mean follow-up period of 24 months.

Results. Compared to men, women were older and less often smokers. Insulin requirement was present in a substantially higher percentage of women than men (27 vs 18%, $p = 0.03$). Presentation with stable angina was more frequent in women, whereas silent ischemia was more prevalent in men. Adverse baseline clinical and angiographic characteristics in women (smaller vessels and longer lesion lengths) were associated with a more frequent need for multiple coronary stenting (23 vs 15% women vs men, $p < 0.001$) and a higher incidence of peripheral complications (3.2 vs 1.2%, $p = 0.049$). However, there were no statistically significant gender-related differences in major in-hospital events. Long-term clinical outcome was similar with equivalent incidence of death (4.9 vs 5.3%, $p = 0.8$), non-fatal myocardial infarction (2.4 vs 4.5%, $p = 0.1$), need for surgical or repeat percutaneous revascularization between women and men.

Conclusions. Diabetic patients show an increased rate of major adverse cardiac events and target vessel revascularization after PCI. In these patients, female gender is associated with higher procedural complexity and peripheral complications; however, long-term clinical outcome of diabetic women is similar to that of men.

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Background

Coronary atherosclerosis generally affects older women than men¹. Several studies show that women undergo coronary revascularization with percutaneous coronary intervention (PCI) later in the course of the disease and present with more comorbidities and complex anatomy with smaller vessels^{2,3}. In general, PCI in women is associated with a gender-related higher periprocedural hazard, controlled by contemporary widespread coronary stenting. Increased in-hospital morbidity and mortality^{4,5}, but unexpectedly similar long-term results⁶⁻¹¹ (the so-called “gender paradox” of restenosis)^{12,13} have been reported. Diabetes is a well recognized predictor of higher major adverse cardiac events and

restenosis rates after PCI¹⁴. A significantly worse outcome in diabetic women compared with diabetic men has been described in some series³ but not confirmed in other studies^{14,15}. To further explore this issue, we analyzed the impact of gender on procedural and long-term clinical events in a consecutive series of diabetic patients undergoing PCI at our Institution.

Methods

Patient population. Clinical and procedural data of patients undergoing PCI at the Istituto Clinico Humanitas (Rozzano-MI, Italy) are entered in the Invasive Cardiology database, which includes clinical, laboratory and procedural characteristics together

with clinical or angiographic follow-up information as it becomes available. An analysis was performed in diabetic patients treated electively with PCI from July 1, 1999 to October 30, 2003. Procedural data, in-hospital complications and clinical and angiographic outcome at follow-up were analyzed. Patients who presented with acute transmural myocardial infarction were excluded. Diabetes was defined according to the criteria of the World Health Organization as documented fasting plasma glucose ≥ 126 mg/dl, 2-hour plasma glucose ≥ 200 mg/dl at the oral glucose tolerance test or both.

Percutaneous coronary intervention and adjunct pharmacological therapy. PCI was performed according to standard clinical practice. Lesions were treated with balloon dilation; stents were used to optimize the angiographic results or to cover coronary dissections. Rotational atherectomy was used in a minority of cases for heavily calcified lesions.

All patients received 100 mg of aspirin and 500 mg of ticlopidine started at least 48 hours before the procedure. Ticlopidine was maintained for 4 weeks and aspirin indefinitely. Intravenous heparin (100 IU/kg, maximum 10 000 IU) was administered with supplemental doses to achieve an activated clotting time (ACT) > 250 -300 s. Glycoprotein IIb/IIIa inhibitors (with lower concomitant heparin of 70 U/kg and ACT maintained at 200-250 s) were administered periprocedurally either because of unstable symptoms or angiographic evidence of thrombus. Sheath removal occurred 2-6 hours after the procedure when the ACT was < 180 s. The procedure was considered successful in the presence of residual stenosis $< 30\%$ and Thrombolysis in Myocardial Infarction flow grade 2 or 3.

Definitions. Angiographic restenosis was defined as $\geq 50\%$ diameter stenosis by quantitative coronary angiography observed at follow-up at the lesion site. Angiographic complications included: subocclusive or occlusive dissections, thrombosis, distal embolization, and vessel perforation or rupture. Peripheral complications included: hematoma requiring transfusion, pseudoaneurysm and arteriovenous fistulae requiring vascular surgical repair. The diagnosis of myocardial infarction was based on the findings of typical chest pain accompanied by either new ST-segment changes or an increase in the creatine kinase activity of at least 3 times the upper limit of normal in at least two consecutive samples, or was defined by the presence of new Q waves on the follow-up electrocardiogram.

Angiographic evaluation. Type B2 and C lesions, according to the modified classification of the American College of Cardiology/American Heart Association¹⁶, were considered complex lesions. All procedural and follow-up angiograms were analyzed off-line with an automated edge-detection system (Philips, Quantitative Cardiac System). Multiple matched projections were

obtained in each patient after intracoronary injection of 200 mg of nitroglycerin. Matching "worst views" were analyzed with the contrast-filled guiding catheter used as reference for calibration.

Follow-up. Clinical follow-up included a phone interview at 3 months, exercise stress test at 6 months and an outpatient visit at 6 and 12 months and then yearly thereafter. Repeat coronary angiography was performed because of recurrence of symptoms, silent ischemia or as part of different research protocols that included routine angiographic follow-up.

Statistical analysis. Baseline characteristics of the population were analyzed using summary statistical measures. Frequencies and percentages were used for categorical data while mean \pm SD were chosen for the continuous data. Overall survival rates were calculated with the Kaplan-Meier method. The relationship between the vital status of the patients and the parameters considered as possible prognostic factors was analyzed using a Cox univariate logistic model. All statistics were made using the Stata 6 program.

Results

A total of 2697 patients (2195 men, 502 women) had PCI at the Humanitas hospital from July 1, 1999 to October 30, 2003. Among these, 542 patients (20%), 128 women (25% of the female population) and 414 men (19%) had documented diabetes mellitus and represent the study cohort. Baseline clinical and angiographic characteristics are outlined in tables I and II, respectively. As reported, women were older and insulin require-

Table I. Baseline clinical characteristics of diabetic women and men undergoing percutaneous coronary intervention.

	Women	Men	p
No. patients	128	414	
Age (years)	67 \pm 8	63 \pm 8	< 0.0001
Hypertension	83 (65%)	265 (64%)	0.2
Dyslipidemia	74 (58%)	244 (59%)	0.2
Smoking	29 (23%)	310 (75%)	< 0.001
Angina	100 (79%)	261 (63%)	< 0.001
Stable angina	52 (41%)	128 (31%)	0.03
Unstable angina	48 (38%)	133 (32%)	0.1
Silent ischemia	4 (3%)	62 (15%)	< 0.001
Prior MI	56 (44%)	203 (49%)	0.4
Prior PTCA	22 (17%)	70 (17%)	0.99
Prior CABG	27 (21%)	108 (26%)	0.3
Treatment for diabetes			
Diet-controlled	6 (5%)	29 (7%)	0.7
Insulin	35 (27%)	74 (18%)	0.03
Oral hypoglycemic agents	87 (68%)	311 (75%)	0.1

CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table II. Baseline angiographic and procedural characteristics of diabetic women and men undergoing percutaneous coronary intervention.

	Women (n=128)	Men (n=414)	p
Multivessel disease	85 (67%)	264 (64%)	0.6
Vessel diameter (mm)	2.78 ± 0.53	2.89 ± 0.66	0.004
Lesion length (mm)	17.3 ± 10.07	14.35 ± 7.77	< 0.001
Total occlusion	12 (9.8%)	40 (9.6%)	0.9
Stent per lesion (%)			
0	26	28	0.2
1	51	57	0.3
> 1	23	15	< 0.001
Vessel per procedure (%)			
1	69	77	0.3
> 1	31	23	0.06
Stent	92 (72%)	290 (70%)	0.6
Rotablator	4 (3%)	16 (4%)	0.4
Glycoprotein IIb/IIIa inhibitors	15 (12%)	74 (18%)	0.08
Procedural success	123 (96%)	389 (94%)	0.3

ment was present in a substantially higher percentage than men (27 vs 18%, respectively, $p = 0.03$). A higher percentage of female patients presented with symptoms of stable angina (41 vs 31%, $p = 0.03$), with silent ischemia more prevalent in men (15 vs 3%, $p < 0.001$). Hypertension, dyslipidemia, prior history of myocardial infarction or previous revascularization did not differ significantly by gender, whereas current smoking was more prevalent among men. Adverse angiographic characteristics of women at baseline included significantly smaller vessels and longer lesion lengths (Table II). Procedural success rates were similar (96% in women, 94% in men), with stenting in over 70% of patients in both groups. In order to achieve adequate immediate angiographic results, however, a significantly higher number of stents were implanted and more vessels treated in women than men (Table II). Multiple stenting was necessary in 23% of women vs 15% of men ($p < 0.001$), with more than one vessel treated in 31% of women but only in 23% of men ($p = 0.06$). Use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. In our laboratory, at that time (from the year 1999 to mid 2003) only high-risk patients received IIb/IIIa inhibitors (mostly for cost-containment issues), resulting in a low use even in diabetic patients (12% women vs 18% men, $p = 0.08$). Table III shows the major acute periprocedural and in-hospital events.

During the in-hospital period, there were no significant differences between women and men with respect to death (0.8 vs 0.5%, $p = 0.9$), myocardial infarction (1.6 vs 0.5%, $p = 0.2$) and coronary artery bypass graft (0.8 vs 0.5%, $p = 0.9$). Only the incidence of peripheral vascular complications was significantly higher in female patients (3.2 vs 1.2%, $p = 0.049$).

Mean clinical follow-up was 26 months, with at least one contact at 6 months in 95% of patients. An-

Table III. In-hospital outcomes of diabetic women and men undergoing percutaneous coronary intervention.

	Women	Men	p
MACE	4 (3.2%)	6 (1.5%)	0.2
Death	1 (0.8%)	2 (0.5%)	0.9
CABG	1 (0.8%)	2 (0.5%)	0.9
Myocardial infarction	2 (1.6%)	2 (0.5%)	0.2
Peripheral complications	4 (3.2%)	5 (1.2%)	0.049
Angiographic complications	6 (4.6%)	17 (4.2%)	0.9

CABG = coronary artery bypass graft; MACE = major adverse cardiac events (deaths, recurrent myocardial infarction).

giographic follow-up was obtained in 48% of women and 40% of men ($p < 0.01$), mostly for recurrence of anginal symptoms or inducible ischemia. Restenosis occurred in 45% of women vs 44% of men that were restudied. At follow-up the slight excess of adverse events, observed during the first month after intervention among women, was no longer present. Overall mortality was 4.9% among women and 5.3% among men ($p = 0.9$) and the incidence of non-fatal myocardial infarction was 2.4% among women and 4.5% among men ($p = 0.1$). The combined incidence of death, non-fatal myocardial infarction, target lesion revascularization and bypass revascularization was 30.3% in women and 31.5% in men ($p = 0.4$). The incidence of clinical restenosis (target vessel revascularization due to restenosis) in the whole population was 14.7 vs 13.9%, respectively ($p = 0.6$), and 38 vs 40% in the group who underwent repeat angiography. At follow-up, anginal complaint was present in 26.2% of women and 15.2% of men ($p = 0.002$) (Table IV; Fig. 1). Kaplan-Meier curves for the cumulative probability of death did not differ significantly by gender (Fig. 2).

Discussion

Our study shows that in a consecutive series of diabetic patients treated with PCI (with coronary stenting in over 70% of cases), adverse baseline clinical charac-

Table IV. Clinical and angiographic outcomes at follow-up.

	Women	Men	p
MACE	37 (30.3%)	124 (31.5%)	0.4
Death	6 (4.9%)	21 (5.3%)	0.8
CABG	10 (8.1%)	30 (7.6%)	0.9
Myocardial infarction	3 (2.4%)	18 (4.5%)	0.1
TLR	18 (14.7%)	55 (13.9%)	0.6
Angina	32 (26.2%)	61 (15.2%)	0.002

CABG = coronary artery bypass graft; MACE = major adverse cardiac events (deaths, myocardial infarction); TLR = target lesion revascularization.

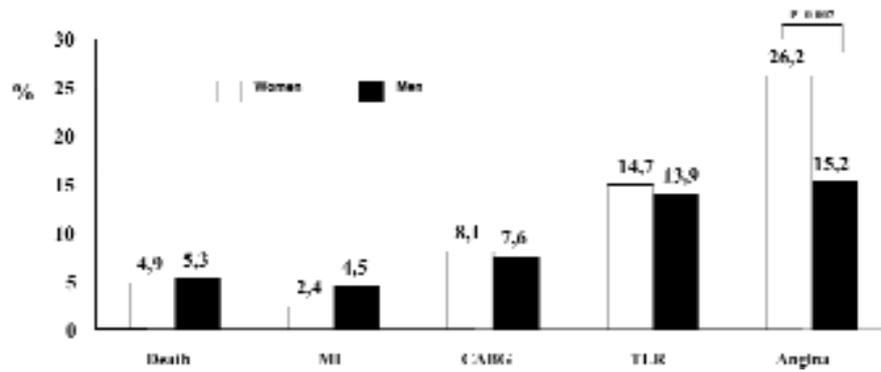


Figure 1. Long-term outcome (percentage of events) according to gender. CABG = coronary artery bypass graft; MI = myocardial infarction; TLR = target lesion revascularization.

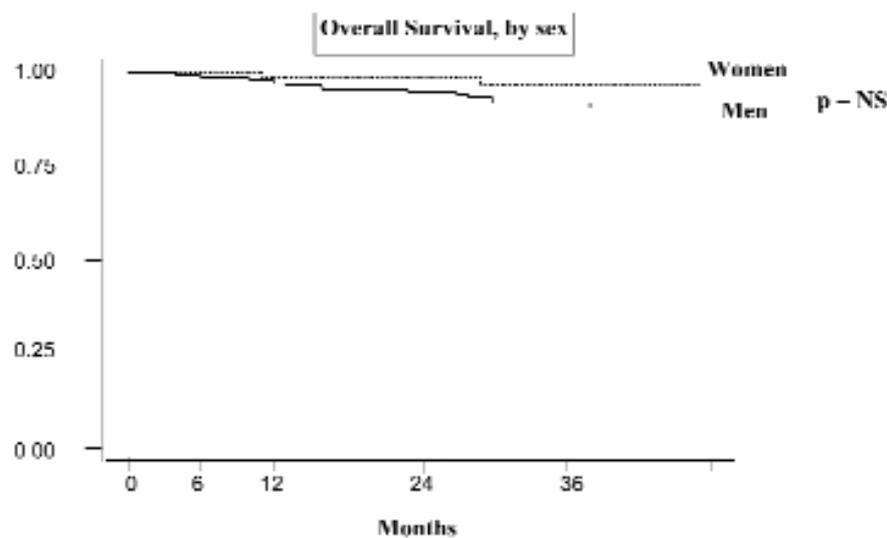


Figure 2. Unadjusted survival curves of women vs men after percutaneous coronary intervention.

teristics in women may be associated with a more frequent need for multiple and multivessel stenting to achieve adequate procedural results but no statistically significant gender-related differences in major hospital events. In our study, glycoprotein IIb/IIIa receptors antagonists were used in a small percentage of cases, their use would have probably further reduced the major acute periprocedural and in-hospital events. The long-term clinical outcome was similar as demonstrated by equivalent incidence of death, non-fatal myocardial infarction (actually lower in absolute terms) or need for surgical or repeat percutaneous revascularization during a 2-year follow-up. The relatively high rate of major adverse cardiac events in both populations further confirms the importance of diabetes mellitus as the major determinant of cardiovascular events regardless of gender.

This study supports the concept of a “gender paradox” even in a diabetic population after PCI. Women with diabetes undergoing PCI present with overall worse clinical and angiographic characteristics and

may still pay a price in initial risk even with current techniques, but fare surprisingly well long-term after coronary stenting. Several reports have already noted the discrepancy between baseline adverse clinical features, with higher periprocedural hazard^{2,4,5} but unexpectedly similar long-term clinical results in women than men after PCI⁶⁻¹¹. A paucity of controversial data exist, however, on gender-specific interactions between diabetes and PCI outcome. Some studies have reported a disproportionately stronger negative impact of diabetes in women than men after PCI. Mehilli et al.³, in a retrospective analysis of 4375 consecutive patients (3349 men, 1025 women), described a 23% relative adjusted risk reduction in restenosis in women compared with men. The difference was evident only in the subgroup without diabetes (26% in women vs 33.3% in men, $p < 0.001$), which turned out to have a stronger negative impact in women. In this study there was no significant difference in the restenosis rate in a diabetic population (36.6% in women vs 36.1% in men, $p = 0.86$), while the 1-year mortality was significantly

higher ($p = 0.009$) in diabetic women compared with men. These findings have not been confirmed by others. West et al.¹⁵ retrospectively analyzed all stented diabetic patients from 16 studies of PCI (418 out of a total of 3090 patients, or 14%). By stepwise multivariate logistic regression analysis, only size of the reference vessel, body mass index and stented length were found to be independent predictors of increased restenosis rates, with similar outcome between sexes even at univariate analysis ($p = 0.26$). In another study of 1450 consecutive patients treated with PCI after non-ST-elevation acute coronary syndrome, Mueller et al.¹⁷ showed that women had a significantly lower incidence of major adverse cardiac events (death or myocardial infarction) during a mean follow-up of 20 months. In their study the presence of diabetes was not independently associated with worse outcome.

Our findings of an “early hazard” after PCI in women are consistent with data from much larger series of patients when crude data, unadjusted for comorbid conditions or angiographic characteristics, are analyzed^{4,9,18}. We did find a slightly higher incidence of periprocedural infarction and overall major in-hospital adverse cardiac events, including need for bypass surgery, but the trends were not statistically significant in the relatively small population that we examined.

The incidence of peripheral vascular complications was, however, significantly higher in female patients, as previously reported by several other studies¹⁹⁻²². Age, female gender and lower body size are known predictors of vascular complications²² and most likely played a role in determining our findings. They remind us of the importance of technical (femoral puncture) and management (heparin and/or glycoprotein inhibitor dosing, sheath removal) issues in the female population.

Several speculative explanations to account for a presumed “protective” effect of the female gender after coronary stenting have been offered. The role of estrogens in attenuating the response of vessel wall to injury may be mediated by receptor-dependent or receptor-independent regulation of endothelial function²³. Estrogens have been demonstrated to upregulate the endothelial nitric oxide synthase activity via receptor-mediated system²⁴ and also to upregulate prostacyclin synthase and diminish thromboxane A₂ and endothelin-1 synthesis, thus they promote vasodilation of diseased coronary arteries and may inhibit the inflammatory response to balloon injury^{25,26}. Additionally, estrogens may prevent restenosis by upregulating the expression of vascular endothelial growth factor and inhibiting endothelial cell apoptosis, as well as smooth muscle cell migration and proliferation²⁷. Receptor-independent pathways also include antioxidant effects. Estrogens may increase the expression of matrix metalloproteinase-9 and, therefore, prevent the accumulation of extracellular matrix²⁸. A persistent “estrogenic effect” even in an older population with similar hormonal lev-

els may stem from a relative imbalance in estrogen receptor sensitivity caused by the additional presence of androgen hormones in male patients²⁹.

Development of atherosclerosis later in life in women has been associated with differences in plaque composition among sexes. Histological studies have demonstrated more hypercellular plaques and less dense connective tissue in women, which could in part explain a different response to percutaneous injury of the vessel wall³⁰.

In conclusion, our study of a consecutive series of diabetic patients undergoing PCI with current stenting techniques reveals that the female gender is associated with higher procedural complexity, need for multiple stenting and peripheral complications, but unexpectedly favorable long-term clinical outcomes when compared to men.

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