

Cardiovascular Disease in Women (III)

Effect of Sex on Revascularization Strategy

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Cardiovascular disease and, in particular, ischemic heart disease are major causes of morbidity and mortality in women. Diagnosis of ischemic heart disease in women is made more difficult by the occurrence of atypical symptoms, a perception that the risk is low, the limited accuracy of non-invasive tests, and underuse of coronary angiography.

Women with ischemic heart disease, with either stable or unstable angina or non-Q wave or ST-elevation myocardial infarction, benefit as much as men from percutaneous or surgical revascularization. However, hemorrhagic complications occur more often in women and periprocedural mortality is slightly higher with both techniques, though the sex difference has tended to decrease in recent years. Moreover, drug-eluting stents, arterial revascularization, and off-pump procedures are equally beneficial to men and women. Nevertheless, strict control of risk factors is essential following any revascularization procedure.

Selecting which of the 2 revascularization procedures is more appropriate depends on the patient's age and comorbid conditions, the number, location and type of coronary lesions, ventricular function, and the patient's preferences, among other factors. Nowadays, a significant number of patients can be revascularized using either technique. Therefore, open discussion of each case and close collaboration between interventional cardiologists and surgeons are essential so that joint decisions about the most appropriate treatment can be made in a consistent manner.

Key words: *Women. Percutaneous revascularization. Surgical revascularization. Acute coronary syndromes.*

Estrategias de revascularización: importancia del sexo

La enfermedad cardiovascular en general y la cardiopatía isquémica en particular constituyen una importante fuente de morbimortalidad en la mujer. La sintomatología más atípica, la baja percepción del riesgo por parte de las mujeres, la menor precisión diagnóstica de las pruebas no invasivas y la menor utilización de la coronariografía dificultan el diagnóstico de la cardiopatía isquémica en la mujer.

La mujer con cardiopatía isquémica, tanto en el contexto de la angina estable e inestable como del infarto sin onda Q o con elevación del segmento ST, se beneficia tanto como el varón de la revascularización percutánea o quirúrgica, aunque la tasa de complicaciones hemorrágicas y la mortalidad periprocedimiento son algo más elevadas en la mujer; sin embargo, se observa una tendencia hacia una reducción en las diferencias en los últimos años. Tanto los *stents* farmacoactivos como la revascularización arterial sin circulación extracorpórea aportan beneficios similares en varones y mujeres. El estricto control de los factores de riesgo es imprescindible tras cualquier procedimiento de revascularización.

La selección del método de revascularización más adecuado en cada paciente dependerá de la edad, la comorbilidad, el tipo, el número y la localización de las lesiones coronarias, la función ventricular y las preferencias del paciente, entre otros factores. Hoy día, un número considerable de pacientes puede ser revascularizado por ambas técnicas. Por ello es imprescindible la discusión conjunta de casos y la estrecha colaboración de cardiólogos intervencionistas y cirujanos, que lleve a la toma conjunta de decisiones terapéuticas que puedan ser convenientemente evaluadas y modificadas.

Palabras clave: *Mujeres. Revascularización percutánea. Revascularización quirúrgica. Síndromes coronarios agudos.*

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INTRODUCTION

Ischemic heart disease is an important source of morbidity and mortality in women. It is the leading cause of mortality in the United States and causes more than 250 000 deaths per year.¹ In 2002, ischemic

heart disease was the second cause of mortality among Spanish women and the direct cause of 17 119 deaths (3 times more than breast cancer), 47 246 hospitalizations and 400 000 hospital stays.² Although mortality related to ischemic heart disease is considerably lower than in men until the eighth decade of life, coronary disease causes more deaths in women than in men from 75 years old onwards.

Ischemic heart disease in women has some characteristics which differ from those of men regarding epidemiology, pathophysiology, clinical characteristics, prognosis, and therapeutic response. The disease appears later and is associated with a large number of coronary risk factors, especially hypertension and diabetes. Whereas ischemic heart disease in men is mainly due to obstructive atherosclerotic lesions in the epicardial coronary arteries, other factors also play an important role in the pathophysiology of ischemia in women, such as alterations in microvascular autoregulation, endothelial dysfunction and increase in epicardial coronary tone.³⁻⁶ The WISE study sponsored by the NHLBI has substantially contributed to the better understanding of ischemic heart disease in women.⁴⁻⁶

The symptomatology of ischemic heart disease in women tends to be less typical⁷ and, for less well-understood reasons, tends to manifest more often as angina and less often as acute myocardial infarction (AMI) or sudden death than in men. Despite female sex being associated with better ventricular function, heart failure is more prevalent in women. Screening tests for ischemia have less diagnostic accuracy^{8,9} in women, which contributes to hindering or delaying diagnosis. On the other hand, the lower prevalence of ischemic heart disease in women has contributed to the false belief that it is an uncommon disease and, thus, does not need to be researched to the same extent as it is in men.¹⁰

Once diagnosed, the prognosis of ischemic heart disease depends, as in men, on the extent and severity of the coronary disease and on the established treatment. The therapeutic response of women, both to pharmacological treatment and revascularization procedures, presents certain peculiarities.

The purpose of this review is to analyze current indications for coronary angiography and myocardial revascularization procedures, their outcome in the context of various clinical situations, and the peculiarities of ischemic heart disease in women.

ANGIOGRAPHIC DIAGNOSIS OF ISCHEMIC HEART DISEASE IN WOMEN

Despite its limitations, coronary angiography is the reference test to diagnose ischemic heart disease and is essential to any revascularization procedure. A paradox is encountered in women where, on the one

hand, it is underused¹¹⁻¹⁹ in some groups of patients and clinical situations where clinical guidelines recommend its use,^{20,21} and on the other, after being used the absence of significant obstructive lesions is reported in a significantly greater percentage of women than men in all age groups.

Various trials and registries have shown that, in similar clinical situations, coronary angiography is carried out less frequently in women than in men. For example, the EuroHeart Survey¹⁶ collected information from 197 centers in European countries that, in 2002, treated 3779 patients with stable angina, 43% of whom were women in a worse clinical situation than men and whose average age differed by only 1 year. Women underwent fewer non-invasive tests (odds ratio [OR] =0.8; 95% confidence interval [CI], 0.69-0.95), coronary angiographies (OR=0.59; 95% CI, 0.48-0.72) and revascularization procedures (OR=0.38; 95% CI, 0.52-0.94), even though they had a worse risk profile as shown by a bad prognosis (OR of death/heart attack at 1 year =2.07; 95% CI, 1.16-3.72). Data from Spain¹⁵ confirm that fewer coronary angiographies are done in women admitted for AMI.

Although the problem of this imbalance in the use of resources has been addressed in numerous forums in recent years and, in fact, it has tended to disappear in certain centers,^{17,18} differences between sexes continue to be detected not only regarding indications for coronary angiography, but even in relation to indications for revascularization¹¹⁻¹⁶ once coronary disease has been diagnosed.

At the other end of the spectrum lies the “excess” of coronary angiographies carried out in women where obstructive disease is not confirmed in the epicardial coronary arteries. However, it is important to recall that under coronary angiography we are only able to study the internal lumen of the coronary arteries (lumenogram), but we cannot detect plaque of considerable size that, when associated with positive vessel remodeling, does not reduce its lumen. Positive vessel remodeling seems to be more intense in women and has been associated with hormonal factors.³ Coronary angiography cannot detect the presence of eroded plaque, a phenomenon that has been described more frequently in women as a cause of acute coronary syndrome, or endothelial dysfunction and functional alterations in macrovascular or microvascular coronary autoregulation, which are an important component in the pathophysiology of myocardial ischemia in women.² In the WISE²² study (Figure 1), 34% had coronary arteries without obstructive lesions and 57% did not have any lesions >50% diameter. However, the prognosis of women with normal coronary arteries who tested positive for ischemia was worse (persistence of symptomatology and appearance of cardiovascular events) than that found in women without evidence of ischemia, which

supports the idea that the “absence of coronary lesions” does not necessarily represent normal coronary perfusion in certain physiological situations.

As only patients with coronary obstructions benefit from revascularization, in women with a low risk of presenting coronary disease (due to age, atypical symptoms or the presence of few risk factors) and with positive or doubtful screening tests for ischemia, non-invasive coronary angiography via multislice computed tomography (CT) makes it possible to correctly identify (sensitivity and specificity greater than 90%) women “without significant coronary lesions” who are not candidate for revascularization.

PERCUTANEOUS REVASCULARIZATION

After coronary angiography, coronary revascularization tends to be done less frequently in women, although clinical guidelines do not differentiate between sexes regarding indications.^{20,21} This fact can be due to older age and comorbidity in women,²³⁻²⁶ the greater risk involved in revascularization procedures,^{27,28} or bias on the part of the physician regarding indications or by patients regarding accepting treatment. At present, one-third of American patients who undergo angioplasty are women. In Spain, the percentage is between 20% and 25%, with a slight increase in recent years.

Elective Revascularization

Angiographic Success and Complications

In the early days of balloon angioplasty, female sex was associated with a lower success rate and higher rate of complications, including acute occlusion, infarction, need for surgery and serious hemorrhages, in addition to greater mortality (Figure 2) which was 2 or 3 times greater than that observed in men.²⁷ However, in the medium- to long-term the differences seemed to decrease or disappear.^{28,29}

With improvements in angioplasty equipment (guidewires, balloons, stents) and the widespread use of stents in the second half of the 1990s, the outcome of angioplasty greatly improved in terms of success and differences in outcomes between the sexes were reduced.³⁰⁻³⁵ At present, angiographic success depends on the type of lesion, not on the patient, and is very high in cases of favorable lesions and lower in the case of less favorable lesions, such as chronic total occlusion (>3 months) where the success rate is around 50%. Regarding the less favorable characteristics of coronary lesions, calcification is more accentuated in men, whereas tortuosity is greater in women, which can hinder access to lesions in the medial or distal segments.

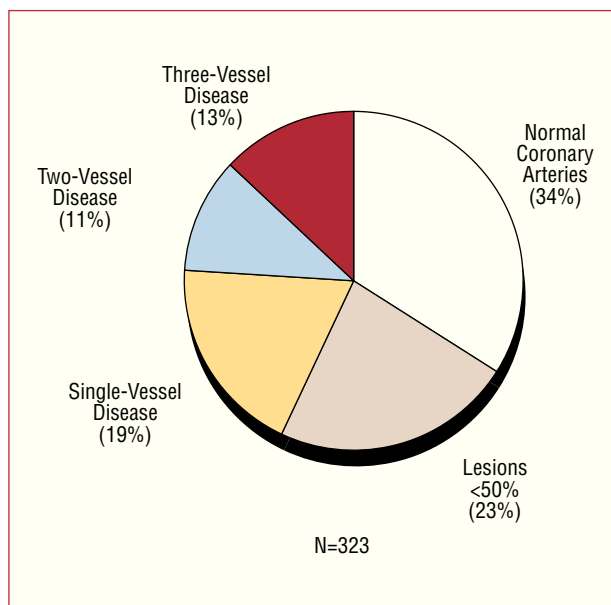


Figure 1. Angiographic findings in women referred for coronary angiography with suspected coronary disease in the WISE study. Adapted from Sharaf et al.²²

Ischemic complications during angioplasty are due to dissections, or transitory or permanent occlusion of the treated vessel or the lateral branches; no differences have been reported between sexes. An increase in myocardial injury markers are also similar and have the same prognostic meaning as in men. Neither have differences been reported in subacute occlusion rates or in those of late occlusion in the case of antiproliferative drug-eluting stents. Procedural mortality is somewhat greater in women, but tends to level out when adjusted to the greater risk profile found in women.

However, vascular complications and hemorrhages³⁵ (large hematomas, retroperitoneal hematoma, pseudoaneurysm, arteriovenous fistula, need for transfusion, and reparative surgery) continue to be more frequent in women. Although the use of weight-adjusted heparin, smaller caliber introducers and their early withdrawal and the radial approach tend to reduce vascular complications, treatment with heparin, combined platelet aggregation inhibitors, and glycoprotein IIb/IIIa inhibitors contribute to increasing them. The greater susceptibility of women to hemorrhaging is not a well-understood phenomenon, although the smaller body surface and the greater amount of fat in the inguinal region, which hinders both puncture and compression, could be involved.

Kidney failure caused by contrast agents is also more frequent among women, partly due to their association with old age, diabetes and hypertension, but also as an independent factor.³⁶

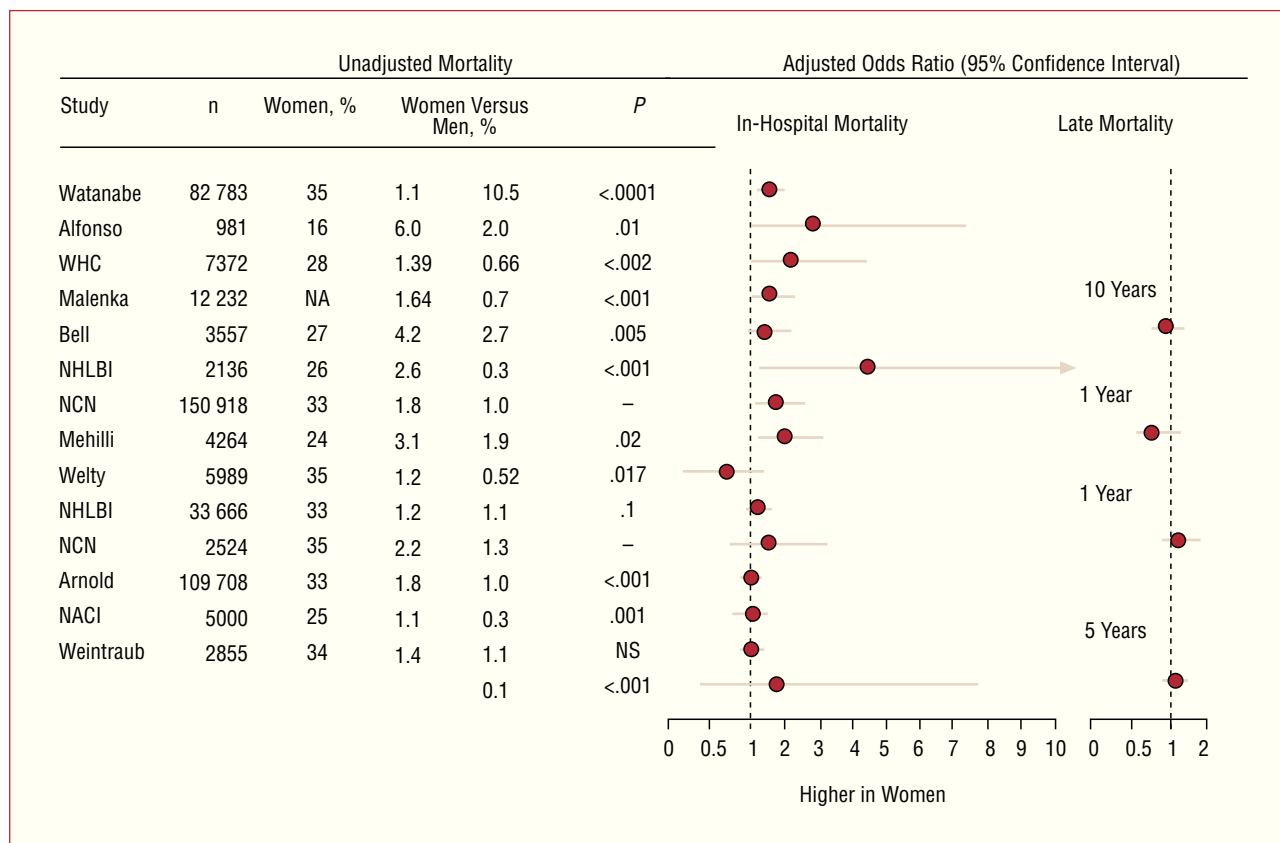


Figure 2. Immediate and late mortality in coronary angioplasty according to the sex of the patient in various series. Taken from Lansky et al.⁹⁵

Initial Clinical Results

After successful angioplasty, persistent angina is more frequent in women than in men,³⁷ a fact that has been attributed to microvascular or endothelial dysfunction. Heart failure is also more frequent in women, even though ventricular function tends to be better, a fact that has been attributed to ventricular hypertrophy, diastolic dysfunction, and rapid atrial arrhythmias, all of which are more common in women.

Medium-Term Results. Restenosis

Regarding restenosis, in most studies and registries using balloons, conventional stents and drug-eluting stents, sex is not a factor contributing to a higher rate of restenosis. Nevertheless, the restenosis rate after conventional stent implantation in absolute figures tends to be greater in women³⁸ due to other characteristics that favor restenosis, such as smaller sized vessels or the greater frequency of diabetes. This finding is also valid for paclitaxel-eluting stents³⁹ and sirolimus-eluting stents.^{40,41} It is important to point out that, in absolute terms, the benefit contributed by drug-eluting stents regarding reduced restenosis rates

and the need for repeat revascularization³⁹⁻⁴¹ is similar in men and women (Figure 3).

Percutaneous Revascularization in Acute Coronary Syndromes

Non-ST-Segment Elevation Acute Coronary Syndrome (NSTEMACS)

Various clinical trials, registries, and cohort studies done in recent years in different countries have described clinical differences between men and women with NSTEMACS.⁴²⁻⁴⁷ In general, women are older, have more comorbidity, a lower incidence of infarction, better ventricular function and a greater frequency (around 25%) of coronary arteries without significant angiographic lesions.

The CURE study,⁴⁷ which included 4836 women and 7726 men with NSTEMACS, demonstrated less use of coronary angiography and a higher number of coronary arteries without lesions in women. Once coronary disease was demonstrated, both the number of revascularizations (Figure 4) and major events was similar in both sexes.

Several randomized⁴⁸⁻⁵² studies have demonstrated that an early invasive strategy (coronary angiography

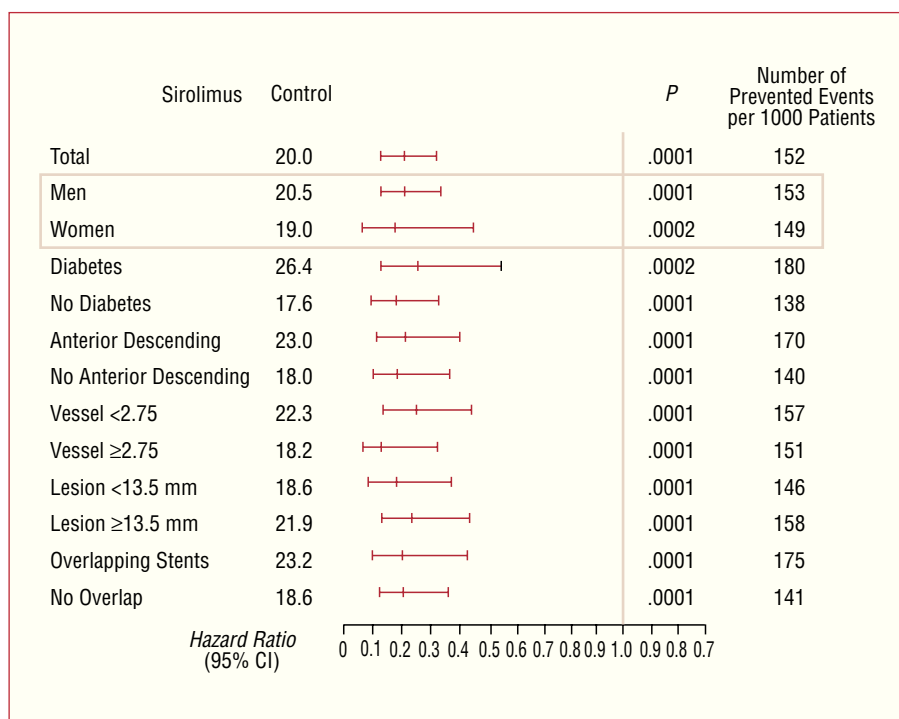


Figure 3. Need to revascularize the treated vessel at 1 year in patients randomized to receive a sirolimus-eluting or conventional stent in the Sirius study. Taken from Holmes et al.⁴¹

and revascularization) is better than a conservative one when treating NSTEMI. However, the benefit is less evident in women and, in fact, there have been contradictory results in this regard.

In the TACTICS-TIMI 18 study^{50,51} (2220 patients, 34% women), the invasive strategy (tirofiban and coronary angiography) demonstrated benefit in the combined endpoint of death, infarction, or rehospitalization at 6 months in men (OR=0.64; 95% CI, 0.47-0.88) as well as in women (OR=0.72; 95% CI, 0.47-1.11), and especially benefited the subgroup of women with high troponin values (OR=0.47; 95% CI, 0.26-0.83).

However, in the FRISC II study⁴⁹ (2457 patients treated with dalteparin vs unfractionated heparin and randomized to invasive or conservative strategy, 30% women) a reduction was found in the incidence of death/infarction per year (10% vs 16%; $P<.001$) in the men assigned to invasive strategy, but not in women (12% vs 10%; $P=NS$). It should be pointed out that, in this study, the number of patients who underwent surgical vascularization was greater than in other studies, and that surgical mortality in women was significantly greater than in men, which influenced the excess mortality in women assigned to the invasive strategy.

In the RITA-3 study⁵² (1810 patients, randomized to invasive or conservative strategy, 38% women), the invasive strategy reduced the endpoint of death/infarction at 1 year in men (10% vs 7%), but not in women (5.1% vs 8.6%; $P=.011$) in whom, in fact, it significantly increased.

The reason for the observed discrepancies could be that the population of women with NSTEMI is more heterogeneous than that of men, with a high proportion of very low risk patients (up to 25% without coronary lesions with little probability of benefiting from an invasive strategy) and, on the other hand, a population of women with greater revascularization-associated morbidity and mortality than men. Thus, the key factor is correct stratification of women with NSTEMI. In low-risk women, ischemia screening tests (exercise stress test, stress echocardiography) or new imaging techniques make it possible to select for coronary angiography those patients with a high probability of needing revascularization. In contrast, high-risk women benefit from an early invasive strategy, like men, and therefore this is recommended in the guidelines.^{20,21,53,54}

It should be pointed out that in all the studies and registries, and regardless of the antiplatelet/antithrombotic regimen used, with or without associated coronary intervention, hemorrhagic complications were always more frequent in women than in men.

Acute Myocardial Infarction With ST-Segment Elevation

Mortality in women diagnosed with AMI admitted to hospital is higher than in men up to the age of 75, after which it is the same. This difference is especially important in the young women group, where mortality due to AMI is double that in men (6.1% vs 2.9%).⁵⁵⁻⁵⁸

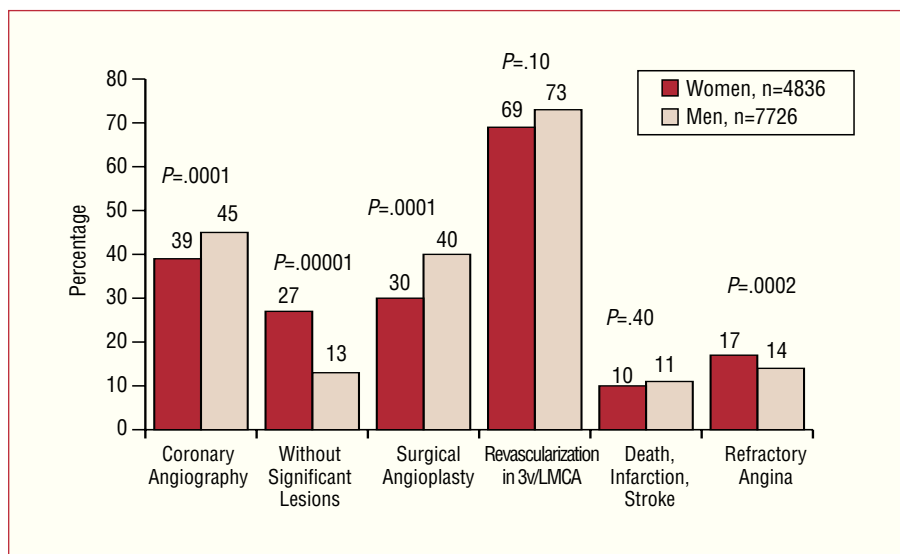


Figure 4. Diagnostic and therapeutic procedures done in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI) in the CURE study. Adapted from Anand et al.⁴⁷ 3v indicates 3-vessel disease; LMCA, left main coronary artery disease.

Thrombolytic agents represent an important advance in the treatment of AMI and have proven to reduce mortality, although at the risk of cerebral hemorrhage which is greater in women than in men.⁵⁹ As an initial revascularization method in AMI, primary angioplasty generally provides similar angiographic results (successful dilatation with TIMI 3 flow) in men and women.⁶⁰

The PAMI study⁶¹ (395 patients, 107 women) compared the results of balloon angioplasty and thrombolysis in ST-segment elevation AMI. Angioplasty reduced the incidence of death and reinfarction in men as well as women. Specifically, mortality in women treated with r-TPA was greater than in those treated with angioplasty (14% vs 4%; $P=.006$); this difference was not found in men (4% vs 2%; $P=.46$, respectively). The benefit of angioplasty in women is above all due to the reduction in cerebral hemorrhagic events, which is a more frequent complication in women treated with fibrinolytic agents than in men (5.3% vs 0.7%; $P=.037$).⁶²

In the GUSTO IIB study,⁵⁹ primary angioplasty reduced mortality (OR=0.68; 95% CI, 0.36-1.32) compared to fibrinolysis, both in men and women, although this reduction did not reach statistical significance. In terms of event reduction, angioplasty prevented more events in women than in men (56 vs 42 per 1000 patients treated, respectively).

The CADILLAC study⁶³ (balloon vs stent, abciximab vs placebo, 2x2 design, 2082 patients; 27% women) demonstrated that stenting reduced the need for new revascularization, both in men and women (Figure 5). Other studies⁶⁴⁻⁶⁷ have confirmed the usefulness of stenting in men and women with AMI.

Outside the world of clinical trials and centers with great experience, it seems that there are differences between sexes in mortality due to AMI treated with

primary angioplasty. In the primary angioplasty registry done in New York state in 1995,⁶⁶ women had a worse profile, were treated later and had greater mortality than men (7.9 vs 2.3%; OR=2.3; 95% CI, 1.2-4.6; $P=.016$); these differences were maintained after adjusting for the greater risk profile in women.

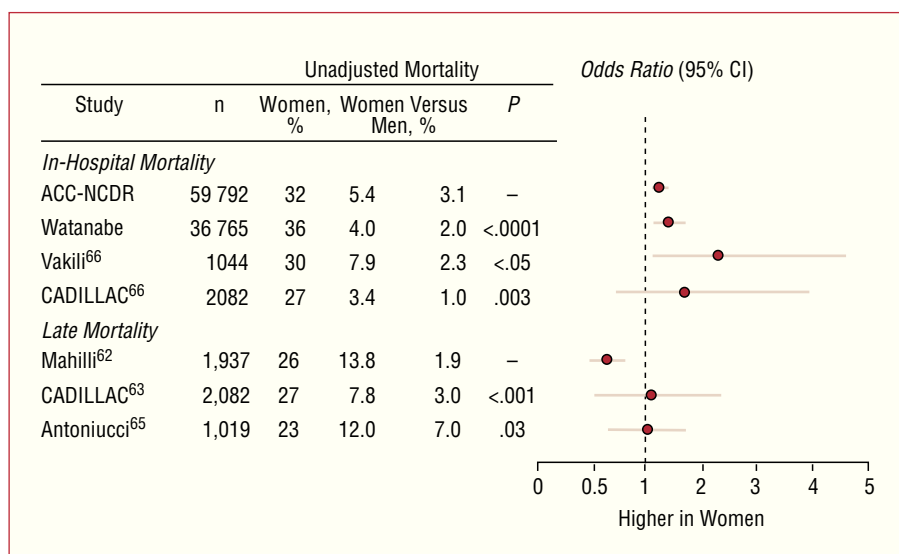
Primary angioplasty, if available, is currently considered the best treatment in ST-segment elevation AMI⁶⁷ for both men and women, although this could require transfer to another hospital^{68,69}; it is considered to be a class Ia indication when performed by an expert team^{20,21} within a 90-min window from the time of presentation.

Otherwise, immediate fibrinolysis is preferable to an excessively delayed angioplasty, both in men and women. In cases of late presentation, which is more frequent in women than in men, primary angioplasty is more effective than fibrinolysis, whose efficacy strongly decreases 3-4 h from symptom onset.

When thrombolysis is contraindicated, angioplasty is indicated (class Ia recommendation, level of evidence: C) independently of delay, always within 12 h from symptom onset with persistent pain and/or ST-segment elevation. Rescue angioplasty after failed fibrinolysis (class IIa recommendation, level of evidence: B) is another indication set out in the guidelines and should be done as quickly as possible in patients of both sexes, especially if accompanied by hemodynamic instability (class Ia indication), which is more frequent in women. Prognostic angioplasty (elective, following thrombolysis within the first 24 h of the infarction, class Ia indication, level of evidence A in European guidelines) or indicated due to ischemia (class Ia indication, level of evidence: B) are equally indicated in both sexes.

Cardiogenic shock appears in 8%-10% of ST-segment elevation AMI, is more frequent in women,⁷⁰

Figure 5. Hospital and late mortality in men and women with acute myocardial infarction and ST-segment elevation treated with primary angioplasty in different studies. Taken from Lansky et al.³⁵ ACC-NCDR indicates American College of Cardiology-National Cardiovascular Data Registry.



and is associated with mortality >50%⁷¹ in both sexes. Although in most patients this is due to severe ventricular dysfunction, in 25% of cases it is due to mechanical complications (papillary muscle dysfunction/rupture and interventricular septal rupture, both more frequent in women), tamponade, or right ventricular infarction. In the SHOCK study (done between 1993 and 1997), patients in cardiogenic shock were randomized to an invasive strategy (early coronary angiography followed by percutaneous or surgical revascularization) or a conservative one, demonstrating that the invasive strategy improved prognosis (1-year survival, 46% vs 33%; OR=0.72; 95% CI, 0.54-0.95). The SHOCK registry (done in parallel to the study, with 1190 patients, 481 women, eligible for but not included in the SHOCK study) described the “real world” of cardiogenic shock. No differences were found between men and women regarding infarction location, coronary angiography (62% in both sexes), the number of diseased vessels, thrombolysis (32% in women, 36% in men; $P=NS$) or angioplasty (35% vs 32%, respectively; $P=NS$). However, intraaortic balloon counterpulsation was used more in men (55% vs 48%; $P<.05$) whereas women received more transfusions (47% vs 35%; $P=.001$). The number of angioplasties (57% vs 50%; $P=NS$) and surgical interventions (12% vs 17%; $P=NS$) was similar in women and men among the patients who underwent coronary angiography. Mortality was similar in women and men in the general series (63% vs 59%), among those revascularized (44% and 38%, respectively), those treated via angioplasty and in those who underwent surgical intervention.

Regarding cardiogenic shock, the guidelines currently recommend coronary angiography and early revascularization regardless of sex (class Ia

recommendation, level of evidence: A). If revascularization is done via a percutaneous approach and the patient has multivessel disease with critical lesions, multivessel angioplasty may be indicated, rather than the strategy normally employed which is to only treat the vessel related to the infarction. Although it has been pointed out, in line with the SHOCK study, that revascularization would not be indicated in patients >75 years old, in favorable cases coronary angioplasty is a reasonable option (class IIa recommendation, level of evidence: B).

Pharmacological Treatment During Coronary Intervention

Antiplatelet Agents

– Acetylsalicylic acid. Except in cases of hypersensitivity or intolerance, the administration of acetylsalicylic acid is indicated in all women, as well as men, with acute coronary syndrome (ACS) or elective angioplasty (160-325 mg/day), and as secondary prevention (75-162 mg/day), indefinitely in every patient with known ischemic heart disease. The administration of acetylsalicylic acid in primary prevention is not indicated in men or women.

– Thienopyridines (ticlopidine, clopidogrel). These are indicated in acute coronary syndrome or after elective angioplasty in combination with acetylsalicylic acid, both in men and women. Due to its better safety profile (fewer hematological side effects), clopidogrel has replaced ticlopidine. The maximum antiaggregation effect is obtained after several days of administration. In the majority of patients, a 300 mg dose achieves an effective antiaggregation effect in 6 h, and 600 mg in 2 h. Although there are other factors, such as weight or

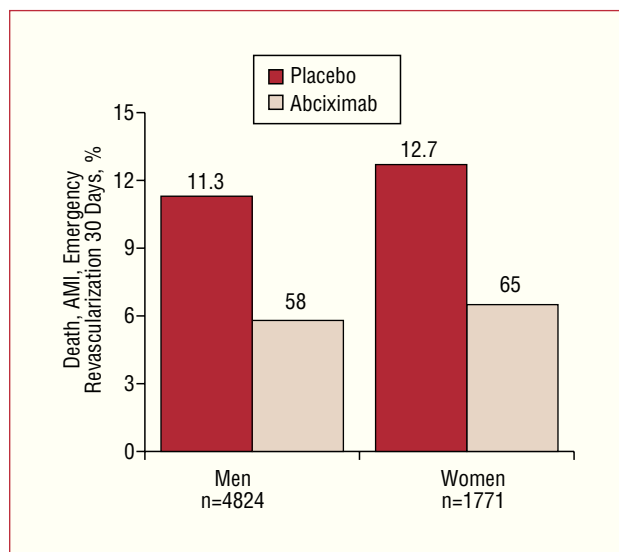


Figure 6. Effect of abciximab in patients undergoing coronary angioplasty. Results of the EPIC, EPILOG, and EPISTENT studies. Adapted from Cho et al.⁷⁸

body surface area which can affect the intensity and speed of the antiaggregation effect obtained, the influence of gender on the effectiveness of thienopyridines is not well understood.

In elective angioplasty,^{72,73} with clopidogrel preloading, the administration of glycoprotein IIb/IIIa inhibitors does not reduce thrombotic complications, which means that their administration seems unadvisable, especially in women, given their greater risk of hemorrhagic complications.

– Glycoprotein IIb/IIIa receptor inhibitors. Abciximab decreases ischemic events, both immediate and in the first year,⁷⁴⁻⁷⁷ and mortality in patients who undergo high-risk elective angioplasty and in those presenting ACS. The patients who can benefit the most are those at higher risk, including patients with diabetes and women. Taking the data from the EPIC, EPILOG, and EPISTENT studies together (6595 patients, 27% women), abciximab reduced the combined endpoint of death, infarction, or emergency revascularization (Figure 6) in women, with a reduction in mortality per year from 4% to 2.5% ($P=.03$).⁷⁸ Minor hemorrhagic complications were more frequent in women treated with abciximab (6.7% vs 4.7%; $P=.02$).

With respect to the other 2 glycoprotein IIb/IIIa inhibitors, tirofiban and eptifibatide are both safe in women but have proved less effective than abciximab when compared directly in the context of coronary intervention. In the case of eptifibatide, a direct comparison has only been done with a single-bolus regimen; comparative data is not available on the currently recommended double-bolus regimen.

The usefulness of the administration of tirofiban or eptifibatide has been demonstrated in the context of

NSTEMACS, if an invasive strategy is considered; otherwise, they have little clinical benefit, especially in low-risk women with normal troponin values,⁷⁹ where the potential benefit in the reduction of ischemic events is low and the probability of hemorrhagic complications is high.

Abciximab has provided clinical benefit in primary angioplasty, both in men and women, which means that its early administration (the earlier the better) is recommended in the guidelines.^{20,21} Clinical benefit is less clear in rescue angioplasty following thrombolysis, and hemorrhagic complications are more frequent, thus its systematic use is not recommended.

Antithrombotic Agents

– Unfractionated heparin. During coronary angioplasty, the heparin dose should be weight-adjusted in both men and women (60-70 U/kg bolus at the beginning). If the procedure is prolonged, then additional doses can be administered to maintain the activated coagulation time (ACT) at 250-300, withdrawing the introducer early when the ACT drops below 150. When glycoprotein IIb/IIIa inhibitors are administered, the dose of heparin should be reduced to 70%, and no more than 4000 U of heparin should be administered to patients with AMI treated with thrombolytic agents.

– Low-molecular-weight heparin. Although its prolonged use in coronary units has undoubted advantages, these advantages are less clear when used during invasive procedures compared to unfractionated heparin, and, in fact, its use is associated with more minor hemorrhagic complications than with unfractionated heparin.⁸⁰ In patients with NSTEMACS treated with low-molecular-weight heparin, angioplasty can be done without additional heparin if the last dose has been administered <6 h before the beginning of the procedure. It is important to control concentrations of antifactor Xa in very heavy patients or those with kidney failure.

– Direct antithrombin agents (hirudin, bivalirudin). These have greater specificity for thrombin and do not cause platelet activation or thrombocytopenia. Bivalirudin has proven to reduce ischemic complications in NSTEMACS as well as hemorrhages (34 vs 20% with unfractionated heparin; $P<.0001$) in women undergoing angioplasty.⁸¹

SURGICAL REVASCULARIZATION

Mortality in coronary surgery has been consistently higher in women⁸²⁻⁸⁶ than in men. In the American College of Cardiology registry (334 013 coronary surgeries done in the 1990s; 28% women), mortality in women was 4.5% versus 2.6% in men ($P<.0001$).

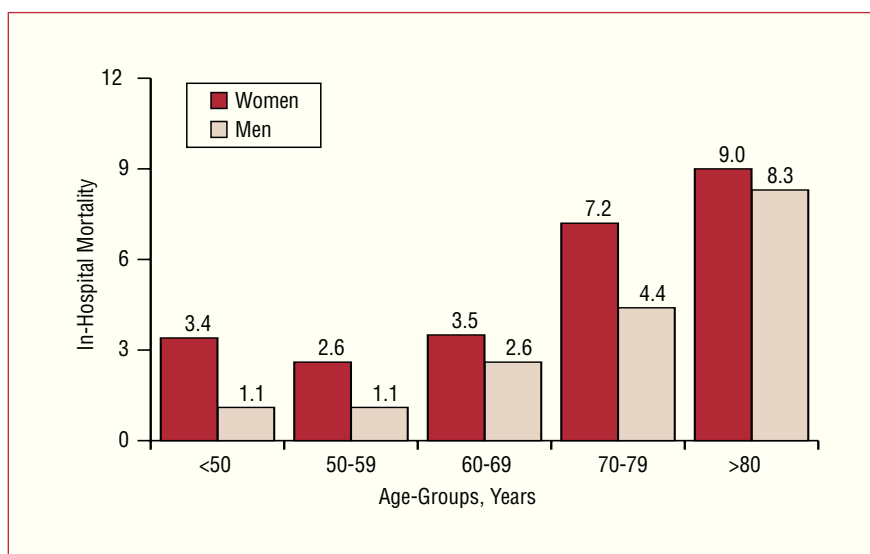


Figure 7. Perioperative mortality in coronary surgery in men and women according to age group. Adapted from Vaccarino et al.⁹².

Nevertheless, women treated with heart surgery constitute a population at greater risk than men due to the coexistence of other factors, such as older age, diabetes, hypertension, less body surface area, smaller sized coronary arteries or emergency intervention, all of which are involved in mortality. In fact, female sex is a factor in the 2 currently used surgical risk estimation systems, the Parsonnet^{87,88} and EuroSCORE systems,⁸⁹ similarly weighted for age (75-80 years in the Parsonnet system) and for an ejection fraction of 30%-40% in both systems.

In recent years, operative mortality in coronary surgery in men and women,^{90,91} corrected for comorbidity, has been converging, although it continues to be higher in women. This difference is maximal in patients <50 years, where mortality in women is triple that of men (3.4% vs 1.1%),⁹² falling with age until it disappears in those older than 80 years (Figure 7). In recent years, the profile of patients of both sexes undergoing coronary surgery has considerably worsened,^{90,91} despite which surgical mortality has not increased in men or in women due to improvements in the surgical technique itself and anesthetics and better postoperative patient care, as reflected in the registries of the American Society of Thoracic Surgeons⁹³ and the Spanish Society of Cardiovascular Surgery.⁹⁴ At present, women represent between 20% and 30%⁹⁵ of patients undergoing coronary surgery, a percentage which has been increasing in recent years. The clinical guideline updates⁹⁶ make the same recommendations for both sexes.

Regarding surgical techniques, complete arterial revascularization, if technically possible, offers the same advantages as in men, although it poses specific problems. The use of the 2 internal mammary arteries,^{97,98} especially in women with diabetes, carries a greater risk of infection due to sternal ischemia, whereas

the radial artery can be too small to be used while ensuring patency. The perioperative administration of calcium antagonists can prevent spasticity both during surgery and the postoperative period.

Coronary surgery without cardiopulmonary bypass seems to benefit women more⁹⁹⁻¹⁰⁵ and bring the mortality associated with such surgery closer to that of men, in addition to allowing this intervention to be done in elderly women who previously would have been rejected due to excessive surgical risk.

During the postoperative period the appropriate management of blood glucose, hematocrit, blood plasma volume, and clinical or subclinical hypothyroidism is particularly important. Blood glucose should be maintained (via continuous insulin IV) at values <150 mg%, since this is associated with less mortality^{106,107} and morbidity (less mediastinitis) in diabetic patients, especially in women.

Optimal management of hematocrit is particularly important in women with small body surface area or previous anemia, especially if cardiopulmonary bypass is employed. During cardiopulmonary bypass hemodilution can result in a hematocrit <20%, whereas a value of >22% is recommended.¹⁰⁸ Hemoconcentration methods, reducing blood volume or transfusion of red blood cells are used to achieve this. In patients not undergoing cardiopulmonary bypass and in the immediate postoperative period, maintaining the hematocrit higher than 30% but lower than 35% is recommended to avoid rheodynamic problems¹⁰⁸ associated with a high hematocrit.

Regarding hypothyroidism, appropriate treatment with thyroid hormone totally corrects the high mortality¹⁰⁹ such patients present without adequate hormonal treatment. Another important aspect is adjusting the anesthetics and sedatives to the smaller body surface area of women.

Postoperative complications,¹⁰⁰⁻¹⁰⁴ such as perioperative infarction or the need for prolonged ventilation, are similar in both sexes. However, there is a greater frequency of heart failure, low cardiac output, need for vasoactive drugs, and kidney failure in women, which probably reflects the need to optimally adjust preloading in relation to the high prevalence of hypertensive heart disease and diastolic dysfunction among them. Other more frequent complications in women include paroxysmal atrial fibrillation and neurological complications,¹⁰⁵ which are best prevented by avoiding cardiopulmonary bypass and to exclusively use arterial grafts in situ, anastomosing the additional grafts to the internal mammary arteries.

The greater frequency of surgical wound infection, especially in diabetic patients implanted with 1 or 2 internal mammary arteries, can be minimized by adequate blood glucose control and skeletonization of the internal mammary artery (separation of the internal mammary artery from its nerve-vascular pedicle), which helps to preserve sternal vascularization and prevent infection.

From the medical-pharmacological standpoint, postoperative control of coronary risk factors is important. Diabetes control has to be optimal, since it has been demonstrated that patients with poorly controlled diabetes have worse clinical evolution.¹⁰⁶ Treatment with statins should start in the immediate postoperative period, and be maintained indefinitely. Treatment with acetylsalicylic acid should be started early regarding platelet antiaggregation. Double antiaggregation therapy with acetylsalicylic acid and thienopyridine has been recommended for some months following surgery, especially in diabetic patients, who currently form one-third of surgically revascularized women. Hormone replacement therapy in menopausal patients is not indicated since it increases thrombotic complications.

The postsurgical evolution of women treated via coronary surgery tends to be more problematic than in men, with slower functional recovery,¹¹⁰ a greater degree of depression reported in psychological questionnaires, greater frequency of persistent angina,¹¹¹ and more hospital readmissions due to heart failure, angina, atrial fibrillation, infections and cerebrovascular disease.¹¹¹⁻¹¹³ However, long-term survival is similar to that of men and is even better in some series.^{114,115}

CHOOSING THE TYPE OF REVASCULARIZATION

One-or-Two-Vessel Disease

Once the need for revascularization has been established according to the clinical data and/or the ischemia screening tests, angioplasty is generally

recommended for all women with 1- or 2-vessel disease and lesions suitable for percutaneous revascularization.^{20,21} In the case of lesions less suitable for angioplasty (chronic occlusion, bifurcation), and if there is severe disease of the anterior descending artery, the probability of failure/complications with this technique regarding the risk/complications involved in surgical treatment should be assessed. If the anterior descending artery is not diseased, medical treatment versus incomplete revascularization via coronary angioplasty of the most favorable lesion should be assessed.

Multivessel Disease

There is little specific information on comparing angioplasty with surgery in women with multivessel disease. In BARI study,¹¹⁶ 1829 patients (27% women) were randomized between 1988 and 1991 to balloon angioplasty or surgery. The number of vessels treated with angioplasty was similar in both sexes, but women received fewer internal mammary artery grafts (72% vs 85%; $P<.05$). Heart failure and hemorrhagic complications were more frequent among women in both treatment groups but there were no differences in mortality between sexes or between treatment groups (12%-13% at 5 years). Neither were there differences between men and women regarding repeat revascularization, which was much more frequent after angioplasty than after surgery in both sexes.

In the ARTS study¹¹⁷ (1205 patients with multivessel disease randomized to conventional stenting or surgery; 23% women), gender did not influence mortality (7%-8% for men and women treated with stenting or surgery) or the need for revascularization at 5 years (30% in angioplasty group; 9% in the surgical group). Only 10% of the patients treated with angioplasty required surgery at 5 years, which confirms the safety of percutaneous treatment in patients of both sexes with a suitable anatomy. It is important to point out that in the 2 studies mentioned and in all randomized angioplasty versus surgery studies, the patients included represented <10% of those eligible with 3-vessel disease.

In the revascularization registry done in northern New England,¹¹⁸ the results of 10 198 surgical interventions and 4295 angioplasties done between 1994 and 2001 were evaluated in patients with multivessel disease. In this series of patients in the "real world," the long-term survival of patients with 3-vessel disease and disorder of the proximal anterior descending artery was better in patients who underwent surgical revascularization than in those undergoing angioplasty (OR=0.60; $P<.001$), both in men and women.

There is no specific information regarding the choice of the type of revascularization in diabetic patients.

Left Main Coronary Artery Disease

Until recently, significant disease in the unprotected left main coronary artery (LMCA) was considered an absolute indication for coronary surgery. Nevertheless, during the 1990s, considerable experience was gained regarding the treatment of patients with protected LMCA disease, in inoperable patients or within the context of AMI. The initial results were generally good in clinically stable patients with favorable anatomy, although a high rate of restenosis was reported and a higher than expected late mortality.

With the appearance of the stent, and later the drug-eluting stent, relatively large series (>100 patients) reported good initial and late results, without specific references to the outcome regarding gender.

Although severe disease of the LMCA is considered a class Ia recommendation in surgical guidelines and as a class IIb indication in angioplasty guidelines, what is certain is that angioplasty of the LMCA is done with increasing frequency in both men and women. Disease of the ostial LMCA without calcification in young women without other coronary lesions is an infrequent anatomical situation although it is particularly favorable for angioplasty. However, many patients have a less favorable anatomy, with disease of the distal LMCA, severe calcification, serious tortuosity, and additional lesions in the anterior descending or circumflex arteries, or present severe ventricular dysfunction. Surgery is the best option in many of these cases.

As in the case of multivessel disease, joint discussion between the cardiac catheterization specialist and surgeons regarding each case, and later assessment of the outcomes of both techniques, help to establish in each center consistent indications that can be evaluated and modified depending on local results or evidence provided by clinical trials (the SYNTAX trial).

Elderly Patients

The number of very elderly women (>85 years) who need revascularization is much higher than men. The morbidity and mortality associated with surgical revascularization is considerable in such women, which means that in most cases percutaneous treatment is preferable, with less morbidity and mortality, although this does not provide complete revascularization.

Patients Having Had Previous Surgery

In the patients who have undergone previous surgery, especially if they have a patent internal mammary artery, the percutaneous approach to native coronary lesions and/or bridges is preferable to reoperation, both in men and women.

CONCLUSIONS

Although ischemic heart disease can be due to microvascular factors and endothelial dysfunction in younger women, atherosclerotic disease of the coronary arteries is the most frequent cause of ischemic heart disease in post-menopausal women and its consequences have an important impact on morbidity and mortality in this population. The low perception of risk on the part of women, the atypical symptoms, and the lower diagnostic precision of non-invasive tests hinder the diagnosis of ischemic heart disease in women. Coronary angiography is indicated in women less frequently than in men in situations where the guidelines recommend their use.

Once diagnosed, both in stable and unstable clinical situations, percutaneous and surgical revascularization procedures are as effective as in men, although the rate of certain complications and mortality associated with the procedures are somewhat higher in women.

Measures that can help to improve the evolution of ischemic heart disease in women include general information campaigns to alert the population to the risk of coronary disease and its prevention, raise physicians' awareness of this problem and report on their frequent atypical presentation with the aim of referring them as early as possible to the specialist. Furthermore, it is necessary to improve women's knowledge of ischemic heart disease, as well as to apply new treatment strategies and evaluate new treatments, to which end it is indispensable that women are adequately represented in the clinical trials.

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