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Management of Acute Coronary Syndromes from a gender perspective

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Abstract

Acute Coronary Syndromes are the most frequent manifestations of coronary heart disease (CHD). Gender differences in treatment intensity, including differences in level of care, have been reported. Also differences in benefit from certain treatments, especially invasive treatment, have been discussed. Finally, difference in outcome between men and women, have been proposed. Results have been inconsistent, partly depending on if and how adjustment for differences in background characteristics has been made.

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Introduction

Myocardial infarction mortality has, for a number of reasons, decreased markedly during recent decades. (1) In spite of improvements, the incidence of acute MI has remained high and cardiovascular disease is still the leading cause of death, afflicting almost 50 % of both men and women. Coronary heart disease accounts for most of the cardiovascular events, and MI is the single most important contributor to mortality and morbidity.

Historically, fewer women than men have been included in studies on coronary heart disease (CHD). Whether this is caused by lower incidence in women or actual exclusion of women from the trials have been debated. (2, 3) The consequence is that the evidence base for several treatments is less firm for women than for men.

Gender differences in treatment

Many early studies, (4-11) but not all, (12) indicated that women were treated less intensively in the acute phase of ACS. For example, women have less often received reperfusion therapy, early antithrombotic therapy and antiplatelet therapy at discharge. Moreover, men have more often been referred for coronary angiography. (4, 5, 7-9) In some of the studies, after adjustment for age, comorbidity and severity of the disease, most of the differences disappeared. (9, 10, 13) There is also conflicting evidence on gender differences in evidence-based treatment at discharge.(4, 6, 8, 9, 11, 13-16) During the last two decades increased attention has been paid to gender differences in treatment of ACS. However, there are major differences in baseline characteristics between a female and a male population with ACS that may affect the attending physician's choice of treatment, appropriateness of a certain treatment and maybe even the patient's preferences for a certain treatment.

Patophysiology

Pathogenesis of ACS involves two different processes. A slow atherosclerotic process, with low degree of reversibility, that lasts for decades, and a fast, dynamic and potentially reversible process characterized by plaque rupture or erosion, with subsequent thrombus formation. A plaque that has become large enough to compromise blood flow is the anatomical foundation for stable angina. An ACS, on the

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other hand, is usually characterised by a sudden erosion of the endothelial wall or rupture of a plaque. (17) Plaque rupture or erosion leads to presentation of thrombogenic factors to the blood elements, with immediate activation of platelets and activation of the coagulation cascade, which is a pivotal part of the pathophysiological process of ACS. (18)

Endothelial erosion is more common in younger ACS patients and women. (17, 19) which may explain the more frequent angiographic lack of significant stenosis in women than men. (20-22) These observations indicate that there may be different pathophysiological mechanisms, afflicting men and women somewhat differently.

Risk Factors

The INTERHEART study, a case-control study from 52 countries all over the world, investigated the association of nine potentially modifiable risk factors for a first MI. (23, 24) The six factors positively associated with increased risk for a first MI were hyperlipidemia (ApoB/ApoA1 ratio), smoking, hypertension, diabetes, abdominal obesity and psychosocial stress. The three factors negatively associated with MI (i.e. protected from MI) were physical activity, low risk diet (daily vegetables and fruits) and moderate alcohol consumption. The study confirmed that CHD determinants were the same in women and men, and these nine factors accounted for 90% of the population attributable risk in men and 94% in women. However, there were small differences between the genders in the strength of a certain risk factor. Hypertension, diabetes, physical inactivity and lack of alcohol intake were more strongly associated with MI in women than men. The study also indicated that the higher risk for MI in younger men (<60 years) compared to women of the same age was mainly due to difference in risk factor burden. Smoking is a strong risk factor for both genders but several studies have shown that smoking is an even more powerful risk factor in women. (25-27)

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Medical treatment

Antiplatelet treatment

Acetylsalicylic acid

Randomised trials of aspirin compared with placebo, showed already in the 1980s a consistent benefit for patients with UAP/NSTEMI by reducing the risk for death or non-fatal MI by approximately 50%. (28-30) Moreover, in the ISIS-2 study 35-day mortality was 23% lower with aspirin compared to placebo, without significant difference between women and men.(31, 32) Indirect comparison of maintenance doses has shown similar effect in a broad range (75-1500 mg) but a dose-dependant increase in bleeding. (33) A very recent meta-analysis revealed similar effect in men and women in secondary prevention. (34)

Adenosine Diphosphate-receptor antagonists

The ADP-receptor antagonists ticlopidine and clopidogrel are drugs that seem at least as effective as aspirin in the treatment of ACS. (35, 36) The adverse effects of ticlopidine have however limited its use, especially after introduction of clopidogrel as an alternative. Clopidogrel has proved effective in combination with aspirin after NSTE ACS in the CURE study, with another 20% risk reduction of the composite endpoint cardiovascular death, MI or stroke [9.3% vs. 11.4%, RR = 0.80, 95% CI (0.72-0.90)]. (37) In a recent meta-analysis of all blinded randomised clinical trials comparing clopidogrel and placebo the relative efficacy and safety of clopidogrel reducing CVD events in women and men was analysed. This analysis showed that there were no significant gender differences in treatment effect, reducing CVD events by 14%. Although a greater number of women experienced bleeding complications there was no statistically significant difference between the genders. (38)

In the TRITON trial, prasugrel was compared to clopidogrel in ACS patients (74% NSTE ACS), on top of aspirin. The combined end point death from cardiovascular causes, nonfatal MI or nonfatal stroke was reduced with prasugrel [9.9% vs. 12.1%, HR = 0.81, 95% CI (0.73-0.90)]. However the rate of major bleedings was significantly higher in patients receiving prasugrel (2.4% vs. 1.8%, p = 0.03). (39) Gender

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differences paralleled those in the CURE trial, with less pronounced and statistically not significant, although directionally the same, risk reduction in women.

In the recently published PLATO-trial the reversible ADP-receptor antagonist ticagrelor was also proved superior to clopidogrel in ACS-patients (38 % STEMI), with lower rate of the primary end point cardiovascular death / MI or stroke [9.8% vs. 11.7%, HR 0.84, 95% CI (0.77-0.92)] (40) Subgroup analysis revealed similar, and statistically significant, benefit in both men and women.

Non-responders to antiplatelet treatment

Substantial inter-individual variation in effect of both aspirin and clopidogrel has been observed (41, 42) and these so called "non-responders" or "low-responders" appear to be at increased risk for new ischemic events. (43, 44) Optimal individual management of antiplatelet therapy may therefore in the near future involve monitoring of platelet activity and individual tailoring of treatment (i.e. choice of drug or dose adjustment) based on individual responsiveness.

There are reports on differences in the proportion of men and women that could be defined as non-responders, why monitoring of responsiveness may be even more important in women. (45)

Glycoprotein (GP) IIb/IIIa antagonists

A meta-analysis of the six large randomised GP IIb/IIIa antagonist trials in patients with UAP/NSTEMI, not routinely scheduled to undergo coronary angiography, showed a modest benefit by reducing the combined endpoint death /MI by 30 days [11.8% vs. 10.8%, OR = 0.91, 95% CI (0.84-0.98)]. Effect was mainly restricted to patients with high risk features such as elevated troponin or ST-depression. Patients undergoing PCI or CABG had greater risk reduction compared to those not revascularized. (46) In the same meta-analysis, a subgroup analysis revealed significant interaction with gender. While men had a significant benefit in reduction of death/MI by 30 days, harm was indicated in women (OR = 0.81 vs. 1.15, p for interaction < 0.0001).

The observed difference may well be due to difference in risk profile between women and men and not gender per se, as indicated in an analysis from the ISAR-REACT 2 trial. (47)

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Anticoagulation

Low-Molecular-Weight Heparin (LMWH)

Trials of LMWH added to treatment with aspirin have generally shown favourable results for the combination in the acute phase, but extended treatment after hospital discharge has been less convincing. (48)

For example in the FRISC trial treatment with dalteparin vs. placebo resulted in a marked risk reduction for the primary end-point death/new MI during the first 6 days [1.8% vs. 4.8%, RR = 0.37, 95% CI (0.20-0.68)], but after extended 40 days of treatment the difference, although directionally consistent with outcome at 6 days, was no longer statistically significant. The observed early benefit appeared to be even more pronounced in women than men. (49) The FRISC II trial randomised patients with NSTE ACS to 90 days of dalteparin treatment vs. placebo. Again early benefit, with a relative risk reduction of death/MI with 47% was not statistically significant at longer follow-up. (50)

The ExTRACT-TIMI 25 study compared enoxaparin to UFH as an adjunctive to fibrinolysis. The net clinical benefit (death/MI/major bleeding) was significantly reduced in both men and women with enoxaparin. (51)

Direct thrombin inhibitors

Hirudin has been extensively studied but with mixed results, including excess bleeding. (52, 53) The synthetic hirudin analogue bivalirudin was compared to UFH/enoxaparin in ACS-patients (65% NSTE ACS) in the ACUITY trial. Bivalirudin alone was non-inferior to bivalirudin+GPIIB/IIIa or UFH/LMWH+GPIIb/IIIa in the composite ischemic endpoint death/MI/unplanned revascularisation at 30 days, but with lower rate of bleeding. Subgroup analysis revealed that effect on the ischemic endpoint was restricted to patients receiving thienopyridines. Bleeding rates were lower with bivalirudin in all subgroups. (54) Although several subgroup analyses were performed, data on gender differences was not presented.

In the published 1 year follow-up non-inferiority with bivalirudin alone persisted. Subgroup analysis according to gender showed no difference in effect. (55)

Lack of difference in effect between the genders was confirmed in a separate analysis on patients that had PCI performed. (56)

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Similarly, in the context of STEMI and PCI, the HORIZONS-AMI compared bivalirudin to heparin+GPIIb/IIIa. Patients assigned to bivalirudin had significantly reduced rate of net adverse clinical events (9.2% vs. 12.1%, p=0.005) due to a lower rate of major bleeding (4.9% vs. 8.3%, p=<0.001).(57) No analysis according to gender was presented.

Factor Xa inhibitors

In the OASIS 5 trial, more than 20 000 patients with NSTE ACS were randomised to fondaparinux or enoxaparin for a maximum of 8 days. The composite primary efficacy outcome death, MI or refractory ischemia at 9 days was 5.7% with fondaparinux vs. 5.8% with enoxaparin, which satisfied the prespecified non-inferiority criteria. Rates of major bleeding were lower with fondaparinux (2.2% vs. 4.1%), hence the composite efficacy and safety endpoint was in favour of fondaparinux. At 6 months the composite death, MI and stroke was significantly lower with fondaparinux [2.5% vs. 11.3%, HR = 0.89, 95% CI (0.82-0.97)]. At all time-points bleeding rate was lower with fondaparinux. (58)

Parallell with OASIS 5 trial the OASIS 6 trial was conducted, randomising 12 092 STEMI patients to fondaparinux or usual care (i.e. UFH or placebo). The results showed that in this patientgroup, especially those not undergoing primary PCI fondaparinux significantly reduced cardiac events without increasing bleeding and strokes. Subgroup analyses regarding the primary outcome revealed no gender interaction in any of the trials.(59)

Fibrinolytic treatment

Even if the preferred STEMI treatment of today is primary PCI there is still room for fibrinolytic treatment in certain cases. Early studies indicated similar benefit with fibrinolytic therapy in men and women. (32, 60) 10 year follow-up of the GISSI trial comparing streptokinase with placebo showed sustained benefit with fibrinolyisis, without significant interaction according to gender. (61) The GUSTO-I trial showed increased benefit with tPA compared with Streptokinase. (62) No analysis according to gender was performed. Several studies have shown that women with STEMI present at the hospital after a significantly longer delay since symptom onset compared to their

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male counterparts. This could be one reason why women with STEMI have been treated with fibrinolytic therapy more seldom than men as time from symptom to treatment is crucial using this type of reperfusion therapy. Fibrinolytic therapy for treatment of STEMI has been associated with a higher risk of stroke and bleeding in women compared to men.

Bleeding complications

Bleeding complications are the most frequent non-ischemic complications in ACS patients. For example, the CURE trial reported significantly higher rate of major bleeding with the aspirin/clopidogrel combination compared to aspirin alone (3.7% vs. 2.7%, p = 0.001). (37) Data from real life management in the GRACE register showed rates of major bleeding between 2.7 % (in UAP), 4.7 % (in NSTEMI) and 4 % in STEMI. (63) Independent predictors of major bleeding included female sex, age, renal dysfunction, history of bleeding and use of GP IIb/IIIa inhibitors. In a multivariate analysis the adjusted OR for bleeding was 1.71 (95% CI, 1.35-2.17) in women compared to men. (63) In the CRUSADE register about 14% of the patients were given red blood cell transfusion (and significantly more of these patients were treated with an early invasive strategy) indicating higher bleeding rates in real life clinical circumstances. (64)

Recent trials have highlighted a strong impact on prognosis with bleeding complications in ACS. (63, 65, 66) In two large scale meta-analyses increase in bleeding was associated with a stepwise increase in mortality. Not only mortality, but also ischemic events increased with major bleeding. (67, 68)

Female sex has been an independent predictor of bleeding in several ACS trials with different anticoagulation strategies. (65, 69, 70)

There are several factors that may explain worse outcome associated with major bleeding. Among them, potential confounders such as older age, comorbidity and renal failure, but also more causative factors such as hemodynamic instability and the possibility that bleeding triggers pro-thrombotic and pro-inflammatory processes. Furthermore, discontinuation of antiplatelet and antithrombotic therapy as a consequence of bleeding has been put forward as a major reason for increased risk of ischemic events. (68) Women appear to be at higher risk for excess doses of antithrombotic medication and as a consequence, higher bleeding rate. (69, 70) Also,

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impaired renal function is more common among female patients, and associated with higher bleeding rates. (70)

Anti ischemic drugs

Beta-blockers

Evidence for beta-blockers in the context of ACS is based on a limited amount of randomised trial data, and most of the studies were performed more than two decades ago. Data from the ISIS-1 trial indicated only a modest benefit with early atenolol treatment in acute MI, with a significantly lower vascular mortality (3.9% vs. 4.6%) during day 0-7. (71) However, a post-hoc analysis of the GUSTO-1 trial did not support routine early use of iv. atenolol. (72)

Morover, based on data from the COMMIT trial (i.v.followed by p.o. metoprolol vs. placebo) routine early use of betablocker in AMI has again been questioned. Metoprolol did not significantly reduce death or the combined endpoint death/reinfarction or cardiac arrest. Similar lack of benefit with early betablocker treatment was observed in both men and women. (73)

A large meta-analysis of 82 earlier trials, including over 50 000 patients did not find evidence for acute treatment with betablockers in the context of an acute MI. Long-term treatment after the acute phase, on the other hand, is clearly indicated based on several trials. (74)

Recommendations are also based on extrapolation from trials in stable angina and unselected MI. (75) In a meta-analysis treatment with beta-blockers vs. placebo, in patients with UAP, was associated with 13% risk reduction in progression to STEMI. (76)

In patients with ACS undergoing PCI pooled results from recent trials indicated effect on mortality at 30 days (0.6% vs. 2.0%, $p < 0.001$) and 6 months (1.7% vs. 3.7%, $p < 0.001$) with beta-blocker therapy. (77)

Although there is a paucity of gender specific data, there were no obvious differences in effect between the genders in one trial. (78)

Beta-blockers are recommended for secondary prevention in the absence of contraindications, without difference between the genders.

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Nitrates

In an early and small randomised trial a reduction in infarct size and left ventricular dysfunction associated with nitroglycerin-infusion was indicated. In the sub-group with anterior MI even reduction in mortality was noted. (79)

More recent and large scale trials showed no benefit with nitroglycerin treatment. (80, 81)

Nitrates are recommended and used primarily for symptom relief, without any known difference in effect between men and women.

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Lipid lowering treatment

Statin therapy improves long-term outcome (82) and is recommended to be initiated early in all patients with ACS. (83-86) Men were in majority in most statin trials, and still gender-specific data are scarce, with somewhat contradictory results. There are studies reflecting secondary prevention, (87) primary prevention in high risk individuals (86) and primary prevention in individuals with low cholesterol but elevated CRP (88) with no apparent difference in effect between the genders. However, with a lower event rate in women, benefit was more uncertain. Moreover, the PROSPER trial (including 2 804 men and 3 000 women with a history of, or risk factors for, vascular disease) found a significant beneficial effect only in men. (89)

ACE-inhibitor / A2-receptor blockers

Several studies have shown that ACE-inhibitors are beneficial in reducing remodelling and improving survival in patients with reduced left ventricular systolic function after MI. (90-92) In patients who are intolerant to ACE-inhibitors angiotensin-2 receptor blockers are indicated. (93, 94) In more recent years a number of trials have suggested an anti-atherogenic effect of ACE-inhibitors, irrespective of LV-function in patients with established atherosclerotic disease or high risk for atherosclerotic disease. (95-97) Treatment is indicated in all ACS patients with left ventricular dysfunction, diabetes or hypertension. (90-92)

A meta-analysis (based on 10 267 men and 2 396 women) indicated similar effect in men and women. (98)

Revascularisation

Revascularisation is performed in the setting of ACS to relieve symptoms and to prevent progression to extended myocardial damage. In STEMI patients the treatment of choice is fast reperfusion therapy, preferably performed as primary PCI.

Regarding NSTEACS the issue has not been so easy to solve. Since the 90s there has been an intense debate whether an invasive approach, with routine coronary angiography, (followed by revascularisation if feasible), is superior to a more conservative approach in these patients. In patients with ongoing ischemic symptoms or hemodynamic or rhythm instability there is today a consensus that urgent catheterisation is the preferred treatment strategy. But, for the majority of patients with NSTE ACS, without need for urgent revascularisation, when cooled off, with pharmacological stabilisation. , the preferred strategiy is still under debate even if most (99-103) but not all (104-106) of the studies have been in favour of a routine invasive strategy. Evidence are conflicting, especially concerning the gender aspects.

Three earlier randomised trials comparing a routine invasive with a selective invasive strategy in NSTE ACS have reported outcomes separately for women and men.
In the FRISC II trial and RITA 3 (20), in contrast to a clear favorable outcome with a routine invasive strategy in men there was no benefit in women. In contrast, the TACTICS-TIMI 18 (22) trial indicated similar benefit in men and women with a routine invasive strategy, but mainly restricted to those with elevated markers. Finally, the OASIS 5 Women substudy, performed as a substudy to the OASIS 5 trial, included women only. There was no difference between the routine invasive and the selective invasive strategies in the primary outcome measure death/MI/stroke or the secondary outcome death/MI during one year. However, higher rate of death was indicated with a routine invasive strategy. (107)

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A meta-analysis presented together with data from the OASIS 5 WSS suggested a clear benefit with a routine invasive strategy compared to a selective invasive strategy in men for death/MI that could not be seen in women. Another meta-analysis published in JAMA 2008 included 8 trials (3 075 women and 7 075 men) (108) and showed no significant difference in outcome with a routine invasive vs. a more selective invasive strategy in the endpoint death/MI, either for men or women.

The reasons for this possible gender difference in effect of early revascularisation could be several.

One reason could be that women have less obstructive coronaries. The relative paucity of obstructive stenoses may obviously dilute the treatment benefit with an invasive strategy.

Another reason could be the observed gender difference in proportion of patients with elevated markers since benefit with an invasive strategy in, especially in women, appeared to be restricted to patients with elevated markers.

A third reason could be that there is a higher risk associated with an invasive strategy for women, especially regarding CABG. The higher event rate in women compared to men, treated with a routine invasive strategy, in the FRISC II trial seemed largely due to an increased rate of death and recurrent MI in women that had CABG surgery performed. Whether worse outcome in women with CABG is explained by difference in coronary artery size, comorbidity or yet other factors, is still not clear.

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Conclusions

We have in this article tried to shed some light on the gender differences and similarities regarding treatment of patients with acute coronary syndromes. It is a fact that women have during the years been included in less numbers than men in clinical trials, whatever is the reason. For the future it is of utmost importance to integrate experimental studies with clinical research in order to be able to individualise the management of the patient disregarding gender and age. To get there it is necessary to have enough numbers of patients from both genders included in trials, to be able to draw proper conclusions. Until now

most results regarding women and ACS have been based on sub study analyses without enough statistical power, which by the way is also valid for the men. Women have an increased bleeding tendency which has been shown in trials on fibrinolysis and invasive treatment. Either this is a dosing question or that women have a different metabolism than men is not clear.

It is very much important with more research in this area in order not to harm women with our treatment because of a paucity of knowledge. It is also as important not to withdraw proper treatment from women when they can benefit from it.

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