Coronary revascularisation in women

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Coronary heart disease is the leading cause of death in men and women worldwide. It is still considered a disease of men and there has been little recognition of its importance in women. Gender differences exist in acute and chronic ischaemia in terms of clinical manifestations, investigations and treatment. There are clear gender differences in coronary revascularisation with a higher mortality seen in women. At the time a woman presents with coronary artery disease she is older and has more co-morbid factors. Furthermore, women have smaller coronary arteries making them more difficult to revascularise. In recent years there has been a general trend towards improved outcomes in women undergoing both surgical and percutaneous coronary intervention. The increasing use of drug eluting stents and adjunctive medical treatment as well as the use of off-pump bypass surgery needs further evaluation in terms of gender differences. This article reviews the current literature on coronary revascularisation in women.

Coronary heart disease (CHD) remains the leading cause of death in men and women worldwide, with cardiovascular deaths exceeding the number of deaths from all cancers combined. One in six women in the United Kingdom and Europe, and one in three women in the United States, die of CHD. At the time of presentation women tend to be 10 years older than men, and at the time of their first myocardial infarction (MI) they are usually 20 years older.^{1,2} This is largely because of the protective effects of oestrogen until after the menopause. Coronary heart disease, however, is not only a disease of older women; more than 20 000 women in the United States under the age of 65 years have an MI each year.¹ Yet CHD is still considered a disease of men and there has been little recognition of its importance in women.

Although risk factors for developing CHD are common to both men and women, certain risk factors impart a greater risk for women than men. Furthermore smoking rates in women are declining less than for men and the prevalence of obesity is increasing in the female population. Women with diabetes have 2.6 times the risk of dying from CHD than women without diabetes compared to a 1.8-fold risk among men with diabetes.¹ Similarly hypertension is associated with a two- to threefold increased risk of coronary events in women.¹ In terms of lipids, low concentrations of high density lipoproteins are a better predictor of coronary risk in women than high concentrations of low density lipoproteins.¹

Clear sex differences in patients undergoing coronary revascularisation with a notably higher mortality seen in women continues to exist. The reasons are thought to be that at the time a woman presents with chest pain, she has more co-morbid factors such as diabetes mellitus, hypertension, hypercholesterolaemia, peripheral vascular disease and heart failure. Furthermore, women's coronary vessels tend to be smaller than those of men making them more difficult to

revascularise both percutaneously and surgically. In addition, women tend to have more urgent procedures because of their late presentation.

Women have hitherto been under-represented in clinical trials of CHD treatment. It is important that this be changed in future studies so that the gender differences in managing CHD may be addressed. This article reviews the literature so far on coronary revascularisation in women.

PERCUTANEOUS CORONARY INTERVENTION

From the 1980s and early 1990s, most registries comparing gender-related differences following plain balloon angioplasty have demonstrated a higher in-hospital mortality, a lower procedural success rate and higher complication rate (death, dissection, abrupt vessel closure, vasospasm and ventricular fibrillation) in women.³ More recent studies, however, have shown a general improvement in outcome in women undergoing percutaneous coronary intervention (PCI). When comparing data from the 1993–94 National Heart, Lung, and Blood Institute (NHLBI) percutaneous transluminal coronary angioplasty registry with that from the 1985–1986 registry,⁴ women in the more recent registry were older (64.3 years *v* 61.0 years, *p* < 0.001), had more diabetes (34.3% *v* 19.9%, *p* < 0.001), congestive cardiac failure (13.7% *v* 8.6%, *p* < 0.05) and co-morbid disease (19.5% *v* 9.3%, *p* < 0.001). Despite this, they had greater angiographic success rate (90.0% *v* 85.1%, *p* < 0.05), comparable in-hospital mortality (1.5% *v* 2.6%, *p* = NS), and lower combined end point of death, MI and emergency coronary artery bypass graft (CABG) surgery (4.4% *v* 9.7%, *p* < 0.01).⁴ Data from the NHLBI Dynamic PCI registry, reported in 2002, also showed a general improvement in the overall success rate in women undergoing PCI, despite women having more co-morbid factors at the time of PCI.⁵ This could be explained by an improvement in operator experience, technique and equipment. Women, however, remain predisposed to vascular access complications and bleeding problems.⁶ At one year, mortality (6.5% in women *v* 4.3% in men, *p* = 0.02) and combined end point of death, MI and CABG were higher in women than men (18.3% *v* 14.4%, *p* = 0.03), respectively.⁵ Gender itself was not a significant predictor of death or death

Abbreviations: ACS, acute coronary syndromes; AMI, acute myocardial infarction; BARI, bypass angioplasty revascularization investigation; CABG, coronary artery bypass graft; CADILLAC, controlled abciximab and device investigation to lower late angioplasty complications; CHD, coronary heart disease; EPIC, evaluation of 7E3 for the prevention of ischemic complications; EPILOG, evaluation in percutaneous transluminal coronary angioplasty to improve long-term outcome with abciximab Gp IIb/IIIa blockade; EPISTENT, evaluation of platelet IIb/IIIa inhibitor for stenting; FRISC II, Fragmin and fast revascularization during instability in coronary artery disease; GUSTO, global use of streptokinase and t-PA for occluded coronary arteries; MACE, major adverse cardiac events; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; PAMI, primary angioplasty in myocardial infarction; PCI, percutaneous coronary intervention; REPLACE 2, randomization evaluation in PCI linking Angiomax to reduced clinical events; RITA-3, randomized intervention trial of unstable angina-3; TACTICS TIMI 18, thrombolysis in myocardial infarction 18

plus MI at one year after controlling for risk factors. Women, however, tended to have more symptoms of angina compared to men.⁷

In the Northern New England cardiovascular disease study group, gender differences in outcome following PCI were studied in 33 666 patients from 1994 to 1999.⁸ In this study, there was a greater use of stents (> 75% in 1999). Although women had more co-morbid factors, there was a reduction over time in procedure related MI (by 29.7%, $p_{\text{trend}} = 0.378$) and need for emergency CABG surgery (in 1999 0.06%, $p_{\text{trend}} \leq 0.001$) with no significant differences in mortality between genders (mean 1.21% in women, 1.06% in men, $p = 0.096$). In 2001 Peterson *et al* studied data from the National Cardiovascular Network database from 1994 to 1998 in almost 110 000 patients.⁹ Thirty three per cent were women and stents were used in 37% of them. Although the procedural success was approximately 90% in both genders, women continued to have a higher mortality after stent implantation compared to men (1.8% *v* 1.0%, $p < 0.001$). Women were also twice as likely to have a stroke (0.4% *v* 0.2%, $p < 0.001$), vascular complications (5.4% *v* 2.7%, $p < 0.001$) or an MI (odds ratio 1.28, 95% confidence interval 1.1 to 1.5). However, after adjustment for baseline risk factors, especially body surface area, there were no gender differences in mortality risks.⁹ In women undergoing saphenous vein PCI between 1994 and 1998, Ahmed *et al* reported a higher in-hospital and 30 day mortality compared to men (3.2% *v* 1.6%, $p = 0.07$, and 4.4% *v* 1.9%, $p = 0.02$) despite similar procedural success in both genders.¹⁰ However, mortality did not differ after one year (13% in women *v* 11% in men, $p = \text{NS}$).

Various studies have reported either similar or lower target vessel revascularisation in women compared to men.^{3 11 12} In a meta-analysis of 31 studies, gender did not appear to have an influence on the rate of restenosis.¹¹ In contrast, a more recent study in 4374 consecutive patients (1025 women and 3349 men) demonstrated that women had significantly lower restenosis compared to men.¹² Clinical restenosis was present in 14.8% of women compared to 17.5% of men ($p = 0.048$).¹² The incidence of angiographic restenosis was also significantly lower in women compared to men (28.9% *v* 33.9%, $p = 0.01$).¹² This appears to be a surprising finding considering the fact that women have smaller coronary arteries and a higher incidence of diabetes mellitus. A possible explanation could be the fact that the protective effect of oestrogen may attenuate the response of the vessel wall to balloon injury. Furthermore, oestrogen may prevent restenosis by accelerating endothelial cell growth resulting in the increased production of nitric oxide.¹² Although gender differences in restenosis rates in females remains undefined, there is a lower rate of follow-up revascularisation in women. This may either reflect a referral bias among women who are less likely to be admitted for subsequent revascularisation or a true reduction in the need for repeat revascularisation. Furthermore, the studies mentioned above were conducted before the era of drug eluting stents. A recent study investigating the use of paclitaxel-eluting stents showed that the benefits of Taxus stents in reducing clinical and angiographic restenosis were applicable to both genders.¹³ In this study, women had a higher unadjusted one year rate of target lesion revascularisation compared to men (7.6% *v* 3.2%, $p = 0.03$). Female gender was not an independent predictor of target lesion or target vessel revascularisation after Taxus stent implantation. Furthermore, the Taxus stent resulted in an almost identical 70% reduction in angiographic restenosis in both sexes. In women, randomisation to the Taxus stent was the only independent predictor of a reduction in restenosis.¹³ Similarly a report using the sirolimus eluting stent (SIRIUS three year follow up) was

presented at the American College of Cardiology in March 2005. This showed a 60–80% benefit across all lesion and patient subsets using the sirolimus eluting stent.

Despite a general trend in recent years in improved outcome in women following PCI, the use of additional interventional devices, such as rotablation, directional coronary atherectomy as well as laser therapy appear to be associated with a higher complication rate in women compared to men.^{14–16} Atherectomy requires the use of larger arterial sheaths and guiding catheters. This increases the risk of both peripheral vascular and coronary artery complications. Studies from the 1990s have shown that women, because of their smaller vessel calibre, had almost 3–4 times more frequent peripheral vascular complications compared to men. A success rate of 89% in women compared to 95% in men has been reported for directional atherectomy.² Furthermore the risk of procedure-related MI has been shown to be 5% in women compared to 4% in men.² The percutaneous Excimer laser coronary angioplasty registry has also demonstrated a higher incidence of perforations in females especially in those with diabetes.^{14–16}

With the advancement of interventional techniques, smaller sheath sizes as well as weight adjusted heparin are now current practice. Whether this change in practice has made any significant difference to the increased vascular complications seen in women remains unclear. More studies, however, are needed to investigate the adjustment of sheath size to body surface area as well as the use of various weight adjusted anticoagulation regimens in order to reduce this complication. The transradial technique has been shown to cause less peripheral vascular complications in experienced hands compared to the femoral approach. However, the benefit of the former technique compared to the latter in women remains undefined. A study of 500 transradial cases showed that success with this technique in males (93.6%) significantly exceeded that in females (90.1%, $p < 0.05$).¹⁷

The benefits of adjunctive medical treatment in women appear to be beneficial, although their use may be complicated by a higher prevalence of bleeding complications. The pooled analysis from the EPIC (evaluation of 7E3 for the prevention of ischemic complications), EPILOG (evaluation in percutaneous transluminal coronary angioplasty to improve long-term outcome with abciximab Gp IIb/IIIa blockade) and EPISTENT (evaluation of platelet IIb/IIIa inhibitor for stenting) trials have shown that abciximab reduced the 30 day major adverse cardiac events (MACE) in women from 12.5% to 6.5% ($p < 0.0001$).¹⁸ Women had a higher rate of major and minor bleeding complications with abciximab compared to men, however. In women, major bleeding was similar with and without abciximab (3.0% *v* 2.9%, $p = 0.96$) respectively with a small significant increased risk of minor bleeding (6.7% *v* 4.7% $p = 0.01$) with abciximab versus placebo respectively.¹⁸ The gender sub-analysis of the CADILLAC (controlled abciximab and device investigation to lower late angioplasty complications) investigated 2082 patients (27% women) with acute MI treated with primary angioplasty with or without the use of abciximab.¹⁹ At one year the unadjusted MACE rate was higher in women compared to men (23.9% *v* 15.3%, $p < 0.001$), respectively. Female gender was an independent predictor of MACE and bleeding complications. However, the presence of co-morbid factors and body surface area but not gender predicted one year death. Furthermore the addition of abciximab to primary stenting reduced the 30 day target vessel revascularisation without increasing bleeding risk in women.¹⁹

Although heparin has been conventionally used during PCI, the role of the direct thrombin inhibitor, bivalirudin, in women has not been fully elucidated. The REPLACE 2

(randomization evaluation in PCI linking Angiomax to reduced clinical events) demonstrated that bivalirudin with provisional glycoprotein IIb/IIIa inhibition was not inferior to heparin plus planned glycoprotein IIb/IIIa blockade in the prevention of acute ischaemic end points.²⁰ The use of bivalirudin was also associated with significantly less bleeding at 30 days after PCI (2.4% *v* 4.1%, *p* < 0.001). In all patient subgroups, there was a non-significant trend towards lower one year mortality with bivalirudin which was of greatest magnitude in the high-risk patients such as women.²⁰

ACUTE CORONARY SYNDROMES

It is well known that women tend to present more often with atypical symptoms such as nausea, vomiting, fatigue, dyspnoea and abnormal pain location than men.²¹ Furthermore, women present more often with non-ST elevation MI (25%) than men (16%).^{2 22–24} Women with acute coronary syndromes (ACS) tend to be older and are more likely to have diabetes and hypertension.¹ An elevated troponin concentration, however, equally predicted the risk for men and women for mortality.²⁵ The FRISC II (Fragmin and fast revascularization during instability in coronary artery disease) study, compared an early invasive treatment with revascularisation within seven days to a conservative strategy.²⁶ This study showed that men had a better outcome with early invasive treatment than with late ischaemia driven revascularisation. In contrast, older women who had less severe disease, less left ventricular failure and had less troponin rise did not benefit from an early invasive strategy.²⁶ At 12 months, there was no difference in death and MI rate for women in the invasive versus non-invasive groups (12.4% *v* 10.5%, *p* = NS), respectively. This is in contrast to the favourable effect seen in the invasive group in men (9.6% *v* 15.8%, *p* < 0.001). When comparing both genders, however, there was a significant difference (*p* = 0.008) with a worse outcome seen in women undergoing early invasive treatment. The notably higher mortality in patients undergoing CABG in this study may have accounted for the worse outcome seen in women in the revascularisation group.²⁶ Furthermore, the delay in the timing of the intervention (seven days) may also have contributed to the worse outcome seen in women.

Similar findings were demonstrated in RITA-3 (randomized intervention trial of unstable angina-3),²⁷ where early invasive treatment had no benefit for women and was in fact associated with a worse outcome. At one year, death or MI occurred in 5.1% versus 8.6% of women and 10.1% versus 7.0% of men in the conservative and invasive groups, respectively. In contrast in TACTICS TIMI 18 trial (thrombolysis in myocardial infarction 18) trial, an early invasive strategy (within 48 hours of presentation) was equally beneficial in both men and women with an improved benefit in women at high risk (dynamic ST segment changes, elevated troponin concentration), (odds ratio 0.47, 95% confidence interval 0.26 to 0.83).²⁸

From the above trials, the best strategy in terms of invasive versus non-invasive treatment in the setting of ACS in women remains controversial with the suggestion that only women at high risk benefit from an early invasive treatment.²⁹ The above trials, however, were conducted before the era of drug eluting stents. With the current practice which includes an increasing use of drug eluting stents and glycoprotein IIb/IIIa inhibitors as well as a shorter delay in the timing of coronary intervention, more studies are needed to further evaluate gender differences in the use of early invasive treatment in the setting of ACS.

ACUTE MYOCARDIAL INFARCTION

Women with acute myocardial infarction (AMI) tend to present with more atypical symptoms than men. This, together with their late presentation to hospital, may well result in delays in receiving effective reperfusion therapy including thrombolysis, angiography and angioplasty. Furthermore, at the time of presentation, women tend to be 20 years older and have more co-morbid factors than their male counterparts. Women younger than 50 years have been shown to have almost twice the in-hospital mortality compared to men.³⁰ Most studies have also reported a higher rate of complications in women with AMI, such as cardiogenic shock, congestive cardiac failure, reinfarction, bleeding and stroke.^{31 32} Most strokes have been shown to occur in women who have received thrombolysis. In the GUSTO study (global use of streptokinase and t-PA for occluded coronary arteries),³³ women had a twofold risk of stroke compared to men. In the PAMI trial (primary angioplasty in myocardial infarction),³⁴ 5.3% of women who received thrombolysis had cerebral bleeding compared to 0.7% of men.

The PAMI-1 trial was one of the first multicentre trials to compare primary angioplasty with thrombolysis and which specifically analysed gender differences.³⁴ In women, the in-hospital mortality was 3.3 times higher compared to men mainly because of a higher mortality rate in women 65 years or older who were treated with thrombolysis.^{34 35} In contrast, there were no gender differences in outcome in the primary angioplasty group in all ages. Furthermore, the mortality rate was 22% in women aged 65 years who received thrombolysis compared to 6% treated with primary angioplasty.^{34 35} From this study, it appeared that primary angioplasty was more effective than thrombolysis in women because of the associated reduced risk of haemorrhagic stroke. In a further study on primary angioplasty for AMI, acute procedural success rates were similar for both men and women (97% *v* 92%).³⁶ Women, however, had a higher mortality rate at 30 days and at seven months than men. This difference appeared to be due to women being older, having more cardiogenic shock and having smaller coronary vessels.³⁶ After control for baseline characteristics, however, gender was not an independent predictor of survival.³⁶ A recent review of 23 randomised studies of primary angioplasty versus thrombolysis for AMI demonstrated the effectiveness of primary angioplasty over the latter treatment. This review, however, failed to analyse gender specific data.³⁷

CORONARY ARTERY BYPASS GRAFT SURGERY

In the majority of studies, women undergoing CABG surgery have greater operative mortality compared to men, with the relative risk for women ranging from 1.4 to 4.4.^{38–41} Women undergoing surgical revascularisation also tend to have more co-morbid factors, such as diabetes and hypertension, than their male counterpart.^{38 41} Women also have a smaller body surface area, smaller coronary arteries, are older, have a higher prevalence of urgent or emergency surgery, and in some studies have been shown to receive less internal mammary grafts.² The majority of studies on CABG surgery in women have demonstrated that gender was not an independent risk factor for operative mortality following statistical adjustment for body surface area, age, coronary artery size and risk factors. In terms of intra- and perioperative complications, several studies have demonstrated a higher incidence of stroke, postoperative haemorrhage,^{38 41} prolonged mechanical ventilation³⁹ and heart failure.^{38 41 42}

Despite the operative mortality for women being higher than men, there appears to be no difference in long term survival between men and women.⁴³ Women, however,

remain more symptomatic compared to men,⁴³ they have a greater rate of graft occlusion,⁴³ and at follow-up require more revascularisation which could be explained by the fact that women receive less internal mammary artery conduits compared to men. Postoperatively, women have a worse functional status and mental health compared to men.⁴⁴

More recent studies have shown that in-hospital mortality in women undergoing CABG surgery is decreasing.⁴⁵ Nevertheless, women remain at higher risk compared to their male counterparts.⁴⁵ Vaccarino *et al*⁴⁶ showed that women younger than 50 years of age who undergo CABG surgery were three times more likely to die than men (3.4% *v* 1.1%) and women 50–59 years of age were 2.4 times more likely to die than men (2.6% *v* 1.1%).⁴⁶ Ninety seven per cent of the excess mortality in women was due to diabetes or urgent or emergency presentation.⁴⁶

The BARI trial (bypass angioplasty revascularization investigation) studied 1829 patients with multivessel disease who were randomised to either CABG surgery or PCI.⁴² Only 27% of the patients were women. After CABG, in contrast to previous studies, the in-hospital mortality was similar for men and women (1.3% *v* 1.4%), respectively, whereas congestive cardiac failure was more common among women (9.8% *v* 1.8%, *p* < 0.001). In women, the in-hospital mortality was the same irrespective of treatment strategy. At five year follow-up, the unadjusted survival was similar for women and men (87% for women *v* 88% for men). After adjustment for baseline risk characteristics the investigators concluded that female gender was a predictor of a higher survival at five years (odds ratio 0.60, 95% confidence interval 0.43 to 0.84; *p* = 0.003). This, however, should not be taken to imply that women do not have an increased procedural risk but rather that gender per se does not impart this increased risk. It is the adverse baseline risk profile which is responsible for the higher risk in women. In addition, women who had CABG surgery had an excess of Q wave MI, heart failure and pulmonary oedema compared to those randomised to PCI.⁴²

Although the use of off-pump CABG, in terms of graft patency, remains controversial,^{47–48} the potential benefit of this form of surgery has been recently investigated in women. A study in 16 871 consecutive women undergoing off-pump and on-pump CABG surgery has shown that women undergoing off-pump surgery had reduced mortality, respiratory complications and length of hospital stay.⁴⁹ A more recent study investigated a total of 7376 women undergoing CABG surgery.⁵⁰ Compared to a propensity-matched sample of women who underwent conventional CABG, women who underwent off-pump CABG surgery had a 32.6% lower mortality rate, a 35.1% lower complication rate due to bleeding, a 118.6% lower rate of neurological complications, and a 49.3% lower rate of respiratory complications.⁵⁰

CONCLUSIONS

Although the mortality for women undergoing percutaneous or surgical revascularisation appears to be improving, it still remains higher than those for their male counterparts. The role of improved procedural techniques such as off-pump and minimally invasive coronary surgery, as well as the wider use of drug eluting stents and the increasing use of adjunctive medical treatment such glycoprotein IIb/IIIa inhibitors, needs further evaluation. Women continue to be under-represented in research studies with the majority of reports including no more than 30% females. Women are, therefore, being treated on evidence extrapolated from studies mainly based on men. This under-representation of women in studies could largely be explained by a number of factors including the exclusion of women with child bearing age or who are likely to become pregnant at the time of follow-up. In addition age limitations

set by most studies would exclude a large number of women who tend to present with CHD in their later years. Furthermore, a number of interventional trials tend to exclude patients with small coronary vessels, the majority of whom are likely to be females. As gender differences continue to exist in cardiovascular disease, it is imperative that it be considered in both the design and the analysis of research studies and trials. Both single gender studies and the adequate representation of women in trials are needed in order to provide reliable evidence for the management of cardiovascular disease in women.

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