The Emergency Department Assessment of Women with Acute Coronary Syndrome

The Women's Health Council

The Irish Association for Emergency Medicine

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Introduction:

Heart disease is the most common cause of death for women in Ireland [1].

The Women's Health Council (WHC) has identified cardiovascular health as a key priority for women's health in Ireland. The WHC initiated collaboration with the Irish Association for Emergency Medicine to develop a resource to support the clinical management of suspected Acute Coronary Syndrome (ACS) in women who present to Irish Emergency Departments (EDs). This document "*The Emergency Department Assessment of Women with Acute Coronary Syndrome*" aims to increase awareness among Emergency Medicine health care professionals of issues relating to women and heart disease. It highlights the spectrum of women's presenting symptoms and outlines current best practice guidelines for the management of women presenting with ACS.

Background:

Circulatory diseases include ischaemic heart disease (IHD) and cerebrovascular disease. Many terms are used interchangeably in the international literature when referring to cardiovascular disease and this can influence the interpretation of data presented. For clarity, IHD includes a spectrum of clinical presentations including silent ischaemia, angina both stable and unstable, myocardial infarction, heart failure and sudden death. The term Acute Coronary Syndrome (ACS) comprises unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) [2]. Practitioners of emergency medicine play an essential role in both the management of ACS and the recognition of IHD in its more subtle manifestations.

More women and men in Ireland die from circulatory diseases than from any other cause [3]. Women in Ireland have a higher than average death rate from IHD. In 2006 the standardised death rate from IHD for women in Ireland was 74.9 per 100,000 compared to an EU average of 66.6 [4]. The World Health Organisation predicts that cardiovascular disease will remain the leading cause of mortality up to 2030 [5].

The burden of long-term morbidity associated with IHD is significant, in terms of its effect on patients' lives and the associated healthcare demands and costs.

There is a false perception that IHD is a predominantly "male" disease [6-8]. Women are more likely to die as a result of IHD than they are from breast cancer, though women may believe that cancer is the greater health problem [9]. In Ireland in 2005 2,229 women died as a result of IHD accounting for 43% of the deaths from IHD. 387 women died from breast cancer in the same year [2, 10].

Figure 1: Causes of Death: Central Statistics Office: Report on Vital Statistics 2005
Adapted with permission from the CSO.
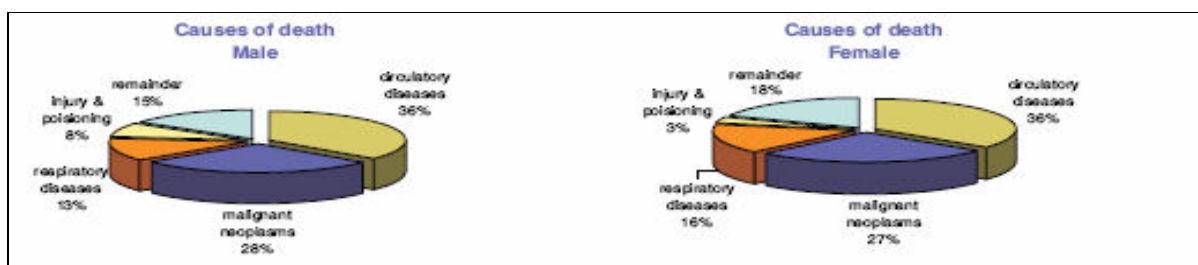
It is internationally recognised that the management of women with heart disease is suboptimal [7,11-13]. This has been related to a number of gender specific factors (Table 1). Women, particularly those younger than 50 years have higher mortality rates following AMI [14]. Women tend to have worse outcomes than men from ACS even after adjustment for age and extent of disease [15]. They also have worse outcomes from cardiac interventions [15].

Table 1: Gender specific differences in women presenting with ACS

Gender specific differences in women presenting with ACS:	
Incidence	• Women are ten times more likely to develop coronary heart disease than breast cancer throughout their lives [15]. • At age 40 the predicted lifetime risk of coronary heart disease is 31.7% for women and 48.6% for men [16].
Age/menopause	• Women have a lower risk of coronary events during their premenopausal years and on average appear to develop IHD ten years later than men [17]. • Younger women have a higher risk of early death after myocardial infarction than men of similar age [14]. • The assessment of women may be more difficult because they present at an older age and are more likely to have co-morbidities [13] such as diabetes [18].
Perception	• Women may not recognise IHD as the greatest threat to their health [11]. • Women may not attribute their symptoms to a cardiac cause and therefore delay presentation for treatment [7].
Presentation	• Women are more likely than men to present with symptoms labelled as "atypical" [19,20] and are less likely to report chest pain [20].
Assessment & Management	• Inequalities in the assessment and management of women with ischaemic heart disease have been identified [7,11, 12, 21, 22]. • There is under-utilisation of drug therapies in women. Drugs that are under-prescribed include aspirin, betablockers [22], ACE-inhibitors [13], statins and fibrinolytics [23]. • Women have been shown to undergo percutaneous coronary intervention (PCI) less often than their male counterparts [13, 22] and are also less likely to be offered angiography after non-invasive testing for angina [24].
Ethnicity	• The risk of coronary events is higher among black women in the US than white women. However black women have been shown to receive appropriate therapy less often [25].
Clinical research	• Clinical research inequalities have been identified, with under-representation of women in study populations and deficient sub group analysis by gender [8].

Pathophysiology of Ischaemic Heart Disease in Women:

Some of the observed gender related differences in presentation and outcome of IHD may be due to subtle differences in the pathophysiology of the disease in women. Clinical data and experimental studies suggest that women may have different plaque morphologies to men, that their coronary anatomy is smaller and that there may even be gender differences in microvasculature and endothelial function [26-28].

In an autopsy series on the hearts of women who suffered sudden cardiac death, Burke et al found that certain risk factors exerted greater relative effects on the mechanism of sudden cardiac death at different ages [29]. In women aged 50 or younger, smoking and the development of plaque erosion were implicated most frequently as factors causing death from coronary artery thrombosis. In women older than 50 years of age, hypercholesterolaemia and plaque rupture were more frequent. Plaque rupture refers to an acute thrombus "continuous with an underlying-lipid rich core" [30] whereas plaque erosion consists of an acute thrombus in direct contact with intimal plaque without rupture of a lipid pool [29, 30]. Younger women also tended to have less narrowing of the coronary arteries at the time of death. This has implications for the interpretation of angiography findings and functional investigation in women.

Evidence from the Women's Ischaemia Syndrome Evaluation (WISE) Study, which was sponsored by the National Heart, Lung and Blood Institute suggests that "traditional disease management approaches that focus on detection of a critical stenosis often fail to identify those women critically at risk" [31]. The WISE investigators hypothesise that vascular dysfunction with and without obstructive coronary disease has a greater role to play in the genesis of cardiac ischaemia in women than in men and that this may be due to sex hormone differences. They advise that greater study and understanding of gender specific pathophysiology is needed to direct appropriate investigative and management strategies for women.

The role of oestrogen:

Oestrogen has been postulated to have a protective effect in the premenopausal years as evidenced by the dramatic increase in the prevalence of obstructive coronary disease in the post menopausal years. However the evidence does not support the routine prescription of hormone replacement to prevent cardiovascular disease in post menopausal women [32-35]. Manson et al in a large randomised controlled trial of oestrogen plus progestin vs placebo, found that hormonal treatment did not confer cardiac protection on healthy post menopausal women and in the first year of treatment actually increased risk of cardiac events [32]. These findings echo those of Hulley et al [33] who found similar results in an evaluation of hormonal therapy for secondary prevention of cardiac events. Hence, the American Heart Association (AHA) does not recommend the use of hormone therapy for cardiovascular disease prevention [35].

The initial assessment of women who present with symptoms of ACS to the Emergency Department:

Symptoms:

Chest pain is the most common presenting symptom of ACS in both women and men [20,36, 37].

There is significant debate in the medical literature regarding the symptoms experienced by women with ACS. Symptoms have been classed in the past as "typical" or "atypical" based largely on the experience of white middle-aged men [8]. Studies of ACS symptoms are limited by the retrospective nature of most studies, lack of standardisation of data collection, inconsistency of data collection and heterogenous study populations [20, 36].
The WISE investigators propose that the term "atypical" is defunct in the description of ACS symptoms in women given the range of symptoms that can occur [36].

Women and men experience a range of other ACS symptoms both in the presence and absence of chest pain. These include fatigue, shoulder or neck pain, dyspnoea, palpitations, nausea, abdominal discomfort, vomiting, syncope or cardiac arrest [20, 37, 38]. Women have been shown in several studies to report more back, jaw and neck pain and nausea than men [37, 39]. Unusual fatigue has been identified frequently as a prodromal symptom for ACS in women [7, 40]. Canto et al conducted a large review of the literature pertaining to symptom presentation of ACS [20]. They found that in a summary of 9 large cohort studies 37.5% of women and 27.4% of men presented without chest pain or discomfort.

Minimising the risk of misdiagnosis of acute myocardial infarction (AMI) is a challenge. Studies have shown rates of misdiagnosis between1.9%-4% [41-43]. Women under the age of 55 are more likely to be misdiagnosed [43].

In general, patients with symptoms of ACS without chest pain are more likely to be older, diabetic and female [19]. ACS presentations without chest pain adversely affect clinical outcomes as outlined in Table 2.

Table 2: Adverse risks associated with ACS presentations without chest pain [18].

Patients with ACS in the absence of chest pain

- Are less likely to be diagnosed with ACS on admission.

- Are older and have more co-morbidity than those who present with chest pain.

- Are more likely to receive suboptimal treatment.

- Experience greater morbidity and a higher mortality across the spectrum of ACS.

It is essential that from the time of first contact with Emergency Healthcare Providers, when ambulance personnel first meet a patient or a patient self-presents to an ED, ACS is considered and recognised, even in those patients without classical chest pain, and that appropriate, timely treatment is instituted. Women should not experience treatment delays for ACS due to a failure to recognise the significance of their symptoms or a flawed expectation of the male stereotype of ACS.

Risk factor assessment:

Emergency Healthcare Providers need to be aware of the risk factors for IHD, so that they identify those patients who are more likely to have ACS. The recognised risk factors for IHD are smoking, hypertension, hyperlipidaemia, diabetes, family history of premature CVD, being overweight, lack of exercise and poor diet. Lower socio-economic group increases coronary heart disease risk in both women and men [44].

ACS is multifactorial in origin. Total risk evaluation is essential in order to appreciate how certain combinations of risk factors may be associated with increased risk [24]. Some IHD risk factors have a different effect on women compared to men. In women cardiovascular risk is delayed for 10 years compared to men [17].

Table 3: Risk factor effects in women:

Emergency healthcare workers should be aware that:	
Smoking	• Smoking even 1 to 4 cigarettes per day can double the risk of fatal and nonfatal myocardial infarction in women [45]. • 21% of all deaths from coronary artery disease are associated with smoking [11].
Diabetes	• Heart disease is a leading cause of death among people with type 2 diabetes [46]. • Sedentary lifestyle is the commonest risk factor for IHD in women and commonly coexists with obesity and type 2 diabetes [11].
Hypertension	• As they get older, particularly over the age of 45, more women than men develop hypertension [24].

Emergency Management:

Emergency Medicine deals with the resuscitation and initial clinical management of patients with life-threatening emergencies and medical, surgical and psychological conditions requiring urgent care, across the entire spectrum of undifferentiated presentations. In the ED, patients are triaged, or prioritised, for rapid clinical assessment to identify and treat potentially life-threatening problems.

The triage nurse has a crucial role to play in the early recognition of women with potential ACS. In a small qualitative study, Arslanian-Engoren found differences related to gender and age in the triage decisions made for women and men presenting with symptoms suggestive of ACS [47]. O'Donnell et al identified greater delays from triage to first medical contact for women presenting with AMI [21].
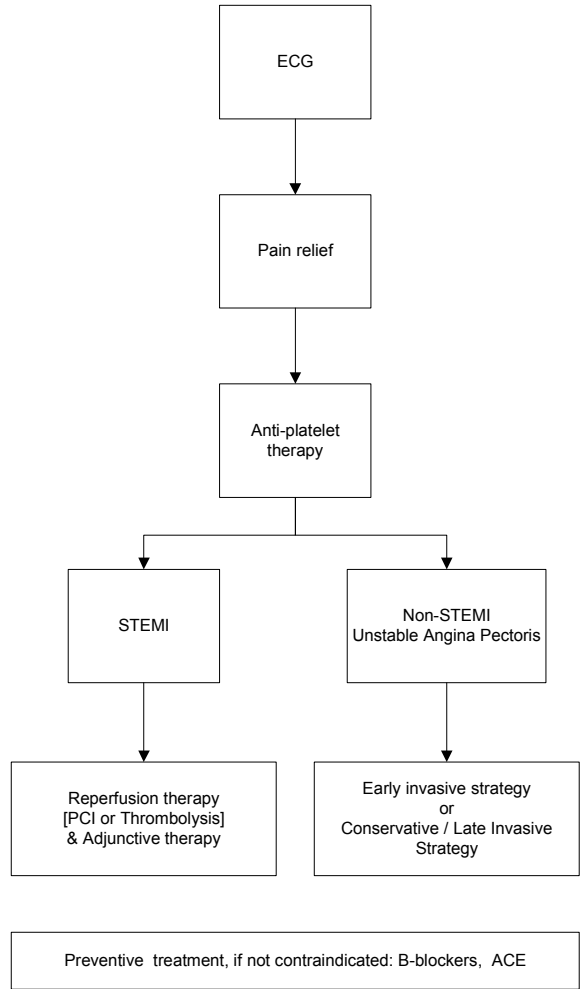
A clinical history to identify possible symptoms of ACS and an immediate ECG are key steps in the triage of patients with possible ACS. Further investigations may be undertaken at a later stage to identify the cause of the patient's symptoms.

Assessment of the patient with possible ACS may start at first contact with pre-hospital personnel when an ambulance is called or may be commenced by the patient's General Practitioner. Some ambulance services transmit ECG recordings directly to hospitals to expedite ACS patient care and EDs will be pre-notified by the ambulance service when patients with suspected AMI or physiological instability are en-route to the ED. Pre-hospital treatment may involve the administration of aspirin, glyceryl trinitrate (GTN) and pain relief, or fibrinolysis in areas where there are long travel times to hospital. Minimising delay to coronary revascularisation through angioplasty or fibrinolysis is a crucial treatment goal. A well co-ordinated team approach minimises delays and initial assessment steps are often performed in parallel in the ED, with rapid ECG recording being undertaken while an ED Doctor or Nurse obtains a brief initial history.

International guidelines for the initial management of ACS:

All Pre-Hospital Services and all EDs should have standard protocols for the assessment and management of patients with suspected ACS based on best practice guidelines. Hospital protocols will also be influenced by the local availability and organisation of specialised care resources, such as Interventional Cardiology. International guidelines for the assessment of ACS include those produced by the European Resuscitation Council [48], the European Society of Cardiology [2,49], the American Heart Association and the American College of Cardiology [50,51]. Detailed discussion of these guidelines is beyond the scope of this document, but the basic management steps are outlined in figure 2.

Figure 2: Outline of management of suspected ACS in the ED:

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                        │     ECG     │
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                        ┌─────────────┐
                        │ Pain relief │
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                        │ Anti-platelet│
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        │             │              │ Unstable Angina Pectoris│
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   ┌──────────────────────┐       ┌──────────────────────────┐
   │ Reperfusion therapy  │       │  Early invasive strategy │
   │ [PCI or Thrombolysis]│       │           or             │
   │  & Adjunctive therapy│       │ Conservative / Late Invasive│
   │                      │       │         Strategy         │
   └──────────────────────┘       └──────────────────────────┘

   ┌──────────────────────────────────────────────────────────┐
   │ Preventive treatment, if not contraindicated: B-blockers, ACE │
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Adapted from ERC Guidelines for Resuscitation 2005

Specialist Cardiology Care:

Close collaboration between Emergency Medicine and specialist cardiology services is vital in optimising care for patients presenting with ACS. A joint approach to the design and implementation of clinical care pathways should support the provision of consistent and equitable treatment for all patients presenting with ACS.

Further assessment in the ED:

In this section gender specific differences in the Emergency Medicine management of suspected ACS are highlighted.

Electrocardiograph (ECG):

- An ECG should be performed as standard in all patients in whom ACS is suspected. If the ECG is non-diagnostic, the early detection of ST-segment changes is facilitated by repeating the ECG at 15 to 30 minute intervals, at least initially, in patients with persistent symptoms and particularly if one has a high clinical suspicion of ACS [50, 52].

Pain relief:

- Morphine is recommended for patients with nitrate resistant ischaemic pain.
- Glyceryl trinitrate may be administered to those with ischaemic chest pain provided there are no contraindications [48].

Anti-platelet therapy:

- **Aspirin**
  There is a large body of evidence demonstrating benefits for the use of aspirin in ACS, after revascularisation and for secondary prevention of ischaemic heart disease in both men and women [53]. Aspirin should be given as soon as possible after even potential ACS has been recognised [48, 52]. The initial recommended doses are in the range of 160mg-320mg [48]. Several studies have shown that women are less likely to receive anti-platelet therapy during the treatment phase and at hospital discharge [26,54]. In an Irish context, O' Donnell et al found a significantly longer "door to aspirin" time for women with ACS compared to men [21].

- **Clopidogrel**
  Prompt initiation of clopidogrel as a loading dose is recommended pre-PCI for NSTEMI/STEMI and as an alternative to aspirin in aspirin allergic patients [52, 55].

Anticoagulant therapy:

- Anticoagulant therapy is indicated for those deemed to be at intermediate/high risk of ACS. Options include unfractionated heparin and low molecular weight heparin (LMWH). The ExTRACT-TIMI 25 study, an international multi-centre randomised control trial, found that treatment with Enoxaparin in women receiving fibrinolytic therapy for STEMI to be a superior alternative to unfractionated heparin, reducing the primary end point of death or non-fatal recurrent MI [26]. Newer agents being recommended include Bivalirudin and Fundaparinux especially for women, older patients and those with impaired renal function [52].

Biomarkers:

- Biomarkers, particularly Troponin T and Troponin I, play a central role in establishing or ruling out NSTEMI. This is as important in women as in men. Local protocols may direct the use of these and other markers such as CKMB. The ERC guidelines [48] use Troponin to differentiate between patients with Unstable Angina Pectoris (Troponin negative) and NSTEMI (Troponin positive) among patients with high risk indicators. High risk indicators include dynamic ECG changes, ST depression, haemodynamic or rhythm instability and diabetes mellitus.
  The assessment of patients with suspected cardiac failure may include the use of B-type natriuretic peptide (BNP) and NT-proBNP, markers of activation of the cardiac neurohumeral system [56]. These markers have been shown to carry prognostic significance in ACS [51, 56].
  Inflammatory markers such as CRP have shown promise in more long term risk assessment for coronary events in women [31,56] but further study is needed to determine the therapeutic implications of these tests.

Reperfusion therapy:

- **Percutaneous Coronary Intervention (PCI)**
  Many studies have shown differences in rates of PCI between men and women. The large prospective observational study based on the AMIS Plus Registry found that female gender was an independent factor for undergoing PCI less often [13]. This has been borne out in other studies [57, 58]. Recent evidence from GRACE (Global Registry of Acute Coronary Events)[59] and GWTG-CAD (Get with the Guidelines-Coronary Artery Disease)[22] also demonstrated that women were less likely to receive PCI. Historically, worse outcomes have been reported for women following PCI [60] but there has been a general trend towards improved outcomes in women following PCI over the years [61]. The best strategy in terms of invasive versus non-invasive treatment of ACS in women remains controversial. Developments such as the use of drug eluting stents, GPIIb/IIIa inhibitors and shorter delay to coronary intervention should prompt new studies to further evaluate potential gender differences in access to and the efficacy of these treatments.

- **Fibrinolysis**
  Optimum results from fibrinolysis for STEMI are obtained with a door to needle time of 30 minutes or less [51]. Greatest efficacy is achieved within 3 hours of symptom onset [48]. Several studies have shown that fibrinolysis is used less often in suitable women [62,63] and that women often wait longer than men for treatment [22,26,64,65]. Investigators in the ASSENT II Trial found that despite evidence for survival benefit with aggressive treatment for re-infarction, women were treated with repeat fibrinolysis significantly less often than men [65].

- Women are at greater risk than men for stroke as a complication of fibrinolysis. In the GUSTO-1 trial, a large RCT comparing 4 different fibrinolytic regimes, women had twice as many strokes as men (2.1%vs 1.2%)[64].

- The GUSTO-1 investigators concluded that women who received fibrinolytic therapy for treatment of AMI were at greater risk for both fatal and non-fatal complications than men in their study population [64].

Invasive strategy for NSTEMI / UAP:

- Women are less likely to receive angiography than men after non-invasive testing for stable angina [66] and in the setting of NSTEMI/UAP [57]. Women have a lower prevalence of obstructive CAD by angiography as compared to men and are less likely to have three vessel disease [59]. Gender and racial bias has been shown to exist in relation to referral for angiography, with women and blacks least likely to be referred [67].

Assessment of low/intermediate risk patients:

Among patients presenting with symptoms suggestive of ACS, a proportion will have AMI and NSTEMI ruled-out via protocolised assessment. Best practice guidelines indicate that this patient group benefits from more comprehensive cardiac risk assessment including provocative testing, such as Exercise Stress Testing or CT coronary angiography. Chest Pain Assessment Units (CPAU) [68] have been established as part of Emergency Medicine services to facilitate this comprehensive risk assessment for the "low" risk group in a cost effective way [69-71]. There are significant gender related differences in the provocative tests used in CPAU protocols and cardiology services for the assessment of relatively low risk patients.

- Exercise Stress Testing (EST):
  There is evidence to suggest less accuracy for EST as a predictor for occlusive coronary artery disease in females. One such study suggests that the specificity and positive predictive value of EST before angiography is significantly lower in women than in men [72]. This is particularly so in low risk patients. Conversely single vessel disease, which is more common in women than in men, may not be identified by routine EST [24, 73]. Menopausal status may influence EST diagnostic accuracy. It is also postulated that women are often incapable of performing > 5 METs (metabolic equivalents) of treadmill exercise leading to inadequate heart rate responses. These women may need retesting

with pharmacologic stress imaging. Gender differences in the application of EST and the interpretation of test results need to be appreciated [31].

- Advanced testing:
  Exercise or pharmacologic stress cardiac imaging should be considered in women with diabetes, abnormal resting ECG or maximum exercise capacity < 5 METs [31, 73]. These modalities include single photon emission computed tomography (SPECT), Echocardiography and MR assessment. Local expertise and the availability of these more advanced modalities will determine the use of these investigations [68].

- Measurement of coronary artery calcium (CAC) as an indicator of burden of atherosclerosis is possible with coronary CT. However more sex specific research is needed to define the prognostic value of CAC levels in women [73].

Pharmacotherapy for Secondary Prevention of ACS:

Many observational studies on different patient populations have found gender-based discrepancies in the use of pharmacological agents post-ACS and for secondary prevention. Bennett et al [74], in an Irish study in 2002, found that men were more likely than women to receive all secondary preventative therapies except statins, despite evidence of the benefits of betablockers, aspirin, ACE inhibitors and statins. Women are also disadvantaged because these therapies are more likely to be prescribed to younger patients [74] and women are more likely to develop IHD at a later age. Echoing this research, recent evidence from Liverpool [75] and the Cleveland Clinic [76] found that women with established cardiovascular disease are treated less aggressively than men with standard secondary preventive treatments.

- Aspirin:

  Aspirin is recommended for primary prevention in high-risk patients and selected intermediate risk patients [35]. Interestingly, a meta-analysis of aspirin use for primary prevention in a mainly low risk population showed a significant benefit for prevention of stroke in women but not for prevention of AMI. In contrast, aspirin significantly reduced the risk of AMI in men but had a non-significant effect on risk of stroke [77, 78].

- Beta-blockers/statins/ACE inhibitors:

  It is recommended that oral beta-blocker therapy be introduced within the first 24 hours of care for the patient with ACS [50] and more promptly in patients with STEMI who do not have contraindications [52]. Despite proven benefits, women have been shown to receive beta-blockers less frequently and later than men [22, 23, 26, 74]. Similar disparities are found in prescription of statins [23] and ACE inhibitors [74].

Coronary Artery Bypass Surgery:

There are gender differences in morbidity and in operative mortality rates from Coronary Artery Bypass Graft Surgery (CABG) [61]. There is no difference in long term mortality following CABG. However women remain more symptomatic and have a greater rate of graft occlusion [61].

Health Promotion:

The development of IHD relates strongly to lifestyle and to modifiable physiological and biochemical factors. Health promotion and risk factor modification have been shown to reduce IHD mortality and morbidity [79]. There are ample opportunities in the ED for raising awareness among women about risk of cardiovascular disease. Women need to see themselves as possible victims of heart disease and adopt cardiac protective lifestyles. Lifestyle changes incorporating smoking cessation, healthy diet, weight management and optimal levels of physical activity should be encouraged [35]. Effective interventions in populations of lower social class may help reduce inequity from the burden of heart disease. Patients with cardiovascular risk factors,

irrespective of gender, should be referred to specialist services or to their GP for risk factor assessment and modification. The Quality in Practice Committee of the Irish College of General Practitioners, with the support of the Women's Health Council, has produced guidelines for the Primary Care assessment and management of cardiovascular disease in women [80]. These guidelines include cardiovascular risk assessment, clinical presentations, clinical investigation, risk modification, guidelines for blood pressure and lipid management along with addresses for patient information. The Irish Heart Foundation has also published "A Woman's Heart", a magazine designed to educate women about heart disease.

Resources have also been developed in Canada and USA for health care professionals managing heart disease in women. This information can be accessed at
- http://www.genderandhealth.ca
- www.hearttruth.gov
- www.emergencycareforyou.org/

Summary:

Reducing mortality rates and the burden of long-term morbidity from cardiovascular disease is a key priority for women's health in Ireland. The WHC and the IAEM have collaborated to produce this document with the aim of improving clinical outcomes for women who present to Emergency Departments with ACS. The false perception that IHD is a predominantly "male" disease needs to be dispelled. Gender differences in symptom patterns and the effects of risk factors should be recognised. The equitable application of best practice guidelines for the initial management of ACS should ensure that all patients with ACS receive high quality care in the ED and achieve optimal clinical outcomes.

Emergency Department strategies to improve outcomes for women with ACS:

- Increase awareness of the spectrum of ACS symptoms in women

- Appreciate the effect of gender when interpreting the results of clinical investigations

- Apply best practice guidelines equitably for the management of women and men with ACS

- Maximise opportunities in ED for health promotion and risk factor modification

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