Abstract

Aim

To evaluate and summarize the current evidence base in relation to the gender specific presentation and assessment of coronary heart disease.

Background

Coronary heart disease (CHD) is one of the leading causes of death in both men and women worldwide. There remains a common misconception that CHD is predominantly a ‘man’s disease’ and that CHD doesn’t affect women until they are much older. Much of the evidence base is underpinned by male based population studies.

Design

A systematic review of current qualitative and quantitative primary research literature was used to establish if coronary heart disease patients would benefit from a gender specific approach.

Data Sources

Cochrane library (1898–2014), PubMed (1996–2014), MEDLINE (1946–2014), AMED (1985–2014), Embase (1974–2014), Cinahl (1937–2014), British Nursing Index (1994 – 2014), PsycINFO (1800- 2014).

Results

Selected studies reviewed in English and critiqued in accordance with the critical review framework utilized by the National Institute for Health and Care Excellence

Conclusion

There are clear differences between the genders in relation to coronary heart disease. It is imperative that nursing practice therefore acknowledges this through the greater application of gender specific care.

Keywords

Coronary heart disease, gender bias, gender specific care, health behaviour, cardiac nursing practice

Key point sentences

- Gender specific care for coronary heart disease is currently not recognized by both clinicians and patients.
- Without this recognition, women in particular, could potentially be receiving sub-standard care.
- Underpinning evidence base is founded upon male bias research studies.

- A gender discrepancy exists in the presentation of coronary heart disease.
- Health behaviour of women is different and therefore health promotion and clinical practice must reflect this.
- Clinical guidelines should reflect the need for gender specific care.

- To encourage targeted specific health promotion in relation to gender specific care.

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally (World Health Organisation 2010). Although improvements have been seen in the prevention and treatment of CVD over the last decade, with a 40% reduction in mortality rates in the

under 75's, CVD remains one of the major causes of death and disability in the UK (Department of Health Cardiovascular Disease Team 2013). Premature death (before the age of 75) from CVD accounted for 28% of deaths in men and 19% of deaths in women in 2010 (Townsend *et al.* 2012). Coronary heart disease (CHD) is the largest subset of CVD and the main cause of mortality in older people of both genders almost everywhere in the world (World Health Organisation 2009). It is also the single most common cause of premature death in the UK (Townsend *et al.* 2012)

Historically, medicine has used men as the standard frame of reference for all diseases shared by both genders (Xhyheri & Bugiardini 2010), with conclusions then extrapolated to females (Legato, *et al.* 2006, Matura 2010). This over exaggeration of the male template has been compounded by the under representation of women in clinical trials (Melloni *et al*. 2010). As with many diseases men and women experience CHD differently. Women are significantly less likely than men to present with chest pain, but more likely than men to present with fatigue, neck pain, syncope, right arm pain, dizziness and jaw pain (Coventry, Finn & Bremner 2011). The World Health Organisation (2009) acknowledged that CHD in women is unrecognised and undiagnosed, in part because, they present with differing symptoms to men, which ultimately leads to under-diagnosis.

Current treatments for CHD are equally effective between the genders (NICE 2013), yet a timely and accurate diagnosis could significantly reduce mortality within women (Mieres *et al.*2005). Shirato & Swan (2010) suggest that delays in clinical assessment of women is mainly due to cardiac symptoms differing from the classic, defined and well established presentation seen in men. This is an important

consideration, as these studies form the basis upon which current guidelines are based. However, attempts to ‘mainstream’ gender into healthcare have turned out to be over-simplified reports of gender differences, without taking account of the complex life conditions of men and women (Kuhlmann & Annandale 2012). This is typified by the National Institute for Health and Clinical Excellence (NICE) clinical guideline number 95 – Chest pain of recent onset, which states: “Do not assess symptoms of an ACS differently in men and women” (NICE 2010).

The Framingham Heart Study (Haynes & Feinleib 1980) was a pivotal investigation into coronary heart disease and showed that gender has a significant effect. This landmark study highlighted that women develop heart disease about ten years later than men and that women’s CHD risks were lower. It also provided insights into the now well-established risk factors that are fundamental to the prevention of CHD, such as: the effects of tobacco use, unhealthy diet, physical inactivity, obesity, raised blood cholesterol, raised blood pressure and diabetes mellitus (Mendis 2010).

What the Framingham Heart study did not demonstrate, is why these differences exist between the genders (Wizemann & Pardue 2001). Several reasons for these differences have been posed by other studies; Sheifer *et al.* (2000) reported an intrinsic sex effect on coronary dimensions, with women possibly having smaller coronary artery size reflecting natural somatic variation. It has been argued by Williams, Fraser and West (2004) that the potential differences between the genders is attributable to age of presentation rather than gender differences directly. Fransoo *et al.* (2010) agreed with this potential difference, as their study confirmed that age was the main predictor, rather than gender. In contrast, Bösner *et al*. (2011)

concluded that the observed gender differences could not be explained by differences in age and underlying risk factors.

Diabetes is a known coronary heart disease risk factor and is thought to accelerate atherosclerosis through multiple mechanisms, especially in women (Worrall-Carter *et al*. 2011). This acceleratory effect could lead to exacerbation of other known CHD risk factors, such as hyperlipidaemia and hypertension which results in increased risk profile (Juutilainen *et al.* 2004). In the RIACE study (Penno *et al.* 2013) a significant proportion of the female diabetic patients studied did not achieve the recommended targets for CHD prevention. Thus, it is plausible that the observed gender differences could be at least partly explained by poorer diabetes control in women, however, there is little primary research data to support this.

The belief that women suffer with CHD in the same way as men, is deeply ingrained in society (Shirato & Swan 2010). This belief inadvertently prevents effective recognition of cardiac signs and symptoms in women, leading to women not knowing when to seek medical advice or treatment for coronary heart disease (O'Keefe-McCarthy 2008). This has been frequently experienced within the author's own clinical practice, providing the impetus underpinning this review

Aim

To evaluate and summarize the current evidence base for gender specific care in relation to coronary heart disease

Design

A systematic review of current qualitative and quantitative primary research literature was used to establish if coronary heart disease patients would benefit from gender specific care.

Search methods

The following electronic databases were searched in January 2014 with the full list of keywords and Boolean combinations listed in Table 1:

- Cumulative Index to Nursing and Allied Health Literature, via EBSCO host
- Medical Literature Analysis and Retrieval System Online, via EBSCO host
- The Allied and Complementary Medicine Database, via EBSCO host
- PsycINFO, via EBSCO host
- Embase, via OVID
- British Nursing Index,
- Wiley Online Library and
- The Cochrane Library.

A web based search utilising Google Scholar and review of the national and international organisations publications and cardiology professional organisations websites, such as: the British Heart Foundation, European Society of Cardiology, American Heart Association and the National Institute for Health and Care

Excellence, were also reviewed.

Inclusion Criteria

- must substantially focus on gender similarities or differences in relation to coronary heart disease
- should be primary research (including meta-analysis)
- must be written and published in English
- published within the period January 2010 to February 2014, providing current credibility.

Exclusion Criteria

- Primarily comprise of non-cardiac issues relating to gender e.g. depression.
- Have a patient population 18 years old or younger.
- Are not relevant to current clinical practice.
- Are non-primary research / literature review.

Search Outcome

This strategy and the inclusion/exclusion criteria identified a large number of articles listed in figure 1; these were then hand searched for relevancy. A manual search

was conducted by the first author of the bibliographies and references from excluded systematic reviews. If the article, on initial reading of the title and abstract, did not substantially address the theme of the review, then it was removed from the list of articles. This list of articles was then thoroughly assessed to determine their individual eligibility, by reviewing the full text of the article. This electronic and manual searching resulted in 150 articles that appeared relevant for reviewing. This was then refined to 35 articles. The list was reviewed and agreed by the second author and this formed the basis of the literature review.

Quality appraisal

To assess study quality, the critical review framework design, utilised by the National Institute for Health and Care Excellence, (NICE 2004) was used to review strengths and limitations. There is no NICE approved check list for cross sectional studies, therefore the checklist designed by Mann. (2003) was additionally utilised. The results of the search strategy are outlined in table 2.

In reviewing the 35 selected articles, the following themes were identified and provide the basis for this narrative systematic review;

- Clinical presentation between the genders

- Diabetes Mellitus as a confounding factor

- Differing health behavious between the genders

- Delay in seeking medical assistance

Similarities and differences in the clinical presentation of acute and chronic CHD between the genders

Typical symptoms of acute CHD presentation are defined as: central crushing chest pain, pain radiating to the arm, jaw, back, neck or shoulder and collapse (Farquharson, Johnston & Bugge 2012). Khan *et al.* (2013) reported that chest pain was the most common symptom in men and women presenting with Acute Coronary Syndrome (in studies totalling 2054 patients), and despite women reporting a greater number of symptoms, there was no difference in their clinical presentation (Lansky *et al.* 2012, Golden, Chang & Hollander 2013, Pickett *et al.* 2013). There is however disagreement within the reviewed literature in relation to the clinical presentation of CHD between the genders.

Chest Pain

O'Donnell *et al.* (2012), Khan *et al.* (2013), Pickett *et al.* (2013), Tamura *et al.* (2013) all reported that there were no differences in gender presentation with regards to chest pain. However Hess *et al.* (2010), Matura (2010), Napoli & Choo (2012) reported that men presented with chest pain more frequently than women. These studies, however, only included patients reporting chest pain and patients with atypical symptoms were either not included (Hess *et al.* 2010) or only limited symptoms were included (Matura 2010, Napoli & Choo 2012).

The study by Ghezeljeh *et al.*(2010) was a cross sectional, multi-centre study undertaken in Iran, consisting of a stratified sample of 500 participants and it

concluded that there were gender differences in symptom characteristics. Women were more likely than men to report pain in the left arm and hand (p=0.006), left scapula (p<0.001), jaw (p=0.006) and neck (p<0.001); whereas, men were more likely to complain of pain in the left lower chest (p=0.007). Women were significantly older, 62.1 years compared to 59 years in men (p<0.001) and more likely to be diagnosed with diabetes mellitus (p=0.03). However an identified weakness with this study was, it focused solely upon pain as a symptom of angina utilising a characteristics questionnaire and did not allow the patients to fully describe their experience of angina. The Chest Pain of Recent Onset Guidelines (NICE 2010) state that practitioners should not assess symptoms of ACS differently in different ethnic groups, making the Ghezeljeh study results applicable to western populations.

Another study by Hess *et al.* (2010) asserts that women presented less frequently with typical chest pain and had a lower rate of significant CHD. The sample women were statistically older than men (p=0.006), but the diagnosis of diabetes mellitus was equivocal between the genders (p=0.99). This study excluded patients with non-chest pain symptoms such as shortness of breath, nausea, back pain, palpitations or generalised fatigue.

In a single-centre prospective cohort study by Tamura *et al.* (2013) of 124 Japanese patients with chest pain, women were typically older than men, 74.3 years compared to 69.8 years (p=0.01). This study was undertaken in a relatively small population and although the relative incidence of chest pain was not ‘statistically significant’ between men and women, the occurrence of non-chest pain symptoms was more common in women (31% vs 14%, p=0.02), particularly right shoulder/upper arm pain

and neck/throat pain. This dichotomy of symptoms was also reported by Ghezeljeh *et al.* (2010) who concluded that there were gender specific variations in the description, intensity and location of the angina symptoms. They offered a different interpretation of the findings, hypothesising that women were better than men at communicating and verbalising their symptoms.

A study by Kreatsoulas *et al*. (2010) reported differing intensity of angina symptoms between the genders. Women with class IV angina were more likely than men to have severe CHD ($p < 0.01$); in comparison, men with severe CHD were more likely to have class 0 to II angina ($p < 0.01$). This was a large registry study from South Canada with 23,757 consecutive patients referred for coronary angiography (38.4% women and 61.6% men) over a four year period and can be extrapolated to the general population. Women were significantly older than men (65.2 years vs 62.3 years, $p<0.01$), and more likely to be hypertensive ($p<0.01$), but there was no significance in diabetes diagnosis ($p=0.15$). There are several limitations to this study. Patients with previously confirmed CHD were excluded and no follow up data was collected. The decision to refer patients for angiography was based upon physician decision rather than protocol driven; meaning referral bias may have been present. Matura (2010) did note that women had a higher absolute and percentage value of CHD mortality compared with men (85%:79%) and a preponderance in history of previous CHD diagnosis.

Atypical symptoms

Women have been shown to have a higher prevalence of atypical symptoms

compared to men (Ghezeljeh *et al*. 2010, O'Donnell *et al.* 2012, Newman, *et al.* 2013, Tamura *et al.* 2013). In contrast, the studies by O'Donnell *et al.* (2012) and Khan *et al.* (2013) were the only studies in the review articles to include patient populations with both typical and an unrestricted number of atypical symptoms reported in clinical practice. The large multi-centre Genesis Praxy study (Khan *et al.* 2013) demonstrated that women were more likely to present without chest pain than men (19.0% vs 13.7%, p=0.03). Those presenting without chest pain reported at least one non-chest pain symptom with women having more overall symptoms than men. This led to the conclusion that non chest pain symptoms, particularly in women, should be given credence in the assessment of possible acute coronary syndrome.

An observational cohort study of 206 patients by Golden, Chang and Hollander (2013) demonstrated that women were less likely to be told that their symptoms could be a result of heart disease and where more likely to be given the diagnoses of reflux disease (p = 0.03), or 'unknown aetiology'. This was despite the fact that an ACS diagnosis was considered in all the patients included and the similarity of the presenting symptoms between the genders.

Age

Canto *et al.* (2012) conducted an observational study of 1,143,513 patients from the National Registry of Myocardial Infarction and concluded that gender differences diminished with increasing age in patients presenting without chest pain. They also reported differences in plaque composition related to age and pathology. Younger women presented with plaque erosions, but relatively little coronary narrowing, and

older women with plaque ruptures and relatively severe coronary narrowing. This study also showed that younger women had greater hospital mortality despite the lack of obstructive coronary disease demonstrated in previous studies (Burke, *et al.* 1998). Despite women being older at time of referral, in females with normal coronary arteries, the angina symptoms could be due to vasospasm or non-obstructive disease (Kreatsoulas *et al.* 2010).

Carotid intima-media thickness increases with advancing coronary artery disease and is widely established as a marker of coronary atherosclerosis (Lansky 2012). A prospective multi-centre study of 788 healthy subjects showed that healthy women between 30 and 50 years of age had thinner intima-media thickness in all carotid segments compared to men of the same age ($p<0.0001$), but the differences between the genders disappeared as the women reached their sixties ($p=0.29$), and also possibly with the onset of menopause (Kozàkovà *et al.*2013). This might explain the findings of the study conducted by Mega, *et al.*. (2010) who showed that women were less likely than men to have obstructive CHD, but more likely to report angina and to have ischaemia on electrocardiogram. Conversely, the prospective multi-centre Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study highlighted that women had fewer non-culprit lesions ($p=0.005$), but there was no difference in culprit lumen diameter between the genders (men, 2.79mm: women, 2.72mm, $p=0.06$), emphasising that males have more extensive atherosclerotic burden (Lansky *et al.* 2012). This study indicated that female atherosclerotic lesions as severe as those in men, manifested seven to eight years later, possibly accounting for the different presentation in ages seen by Kreatsoulas *et al.* (2010).

Diabetes Mellitus as a confounding factor

Khan *et al.* (2013) showed significant difference ($p<0.001$) in the clinical diagnosis of diabetes mellitus between the genders, although there was no significance ($p=0.13$) in relation to the absence or presence of chest pain. Mega *et al.* (2010) reported higher rates of diabetes mellitus among women ($p<0.001$), their study showed higher rates of ischaemic symptoms and less coronary narrowing in women relating to micro-vascular disease. What is not apparent however, is the cause of the micro-vascular disease and whether the increased diagnosis of diabetes mellitus is a significant finding.

Differing health behaviours between the genders

Several studies (Galdas *et al.* 2010, Mochari-Greenberger, *et al* 2010, Villablanca *et al.* 2010, Herning *et al.* 2011, Bangalore *et al.* 2012) have suggested that patients lack knowledge of the various symptoms of CHD, especially females and that opportunities for effective interventions are missed by clinicians and patients alike (Leifheit-Limson *et al.* 2013). Kavanagh *et al.* (2010) suggested that education shapes an individual's health through its influence on people's capacity to assess and interpret health information.

A qualitative study by Herning *et al.* (2011) explored 14 women's experiences and behaviour surrounding their myocardial infarction. They reported that the women had false expectations about the location and intensity of chest pain. They expected heart attacks to be more dramatic and sudden; they did not see themselves as being

at risk as they were female and believed themselves to have healthy lifestyles, despite evidence to the contrary. They further delayed seeking medical attention by denying the severity or by being ambivalent to the situation, not wanting to inconvenience other people. Another qualitative study utilising in-depth semi-structured interviews of 20 individuals, by Galdas *et al*. (2010) explored health-seeking behaviours by gender. The female patients in their study reported employing delaying techniques, a reticence around accessing treatment and an overall sense of ambiguity about the severity of their condition The authors concluded that gender specific health promotion was needed and that culturally-dominant gender ideals were misguided.

The detrimental effect of gender roles was also recorded in the questionnaire-based prospective cohort from the Alberta Provincial Project for Outcome Assessment (Norris *et al.* 2010), where gender discrepancies were seen with health-related quality of life outcomes. The authors surveyed their cohort of 2403 patients one year after their preliminary angiography; females presented with more anxiety ($p<0.001$) and increased angina symptoms ($p<0.001$) when compared with the men. Their analysis showed that improvement in angina symptoms and physical limitations had a direct correlation with an improvement in quality of life perceptions. This study was limited by way of concomitant medications not being recorded. This means the reported differences could be due to under-prescribing.

Delay in seeking medical assistance

Delaying behaviour of women has been widely reported (Herning *et al.* 2011, Galdas

et al. 2010, Bangalore *et al.* 2012, Farquharson, Johnston & Bugge 2012). Farquharson, Johnston and Bugge (2012) in their retrospective questionnaire based study clarified delay behaviour into two categories: 'appraisal delay', being the time taken to decide symptoms are of concern, and 'illness delay', recognising the symptoms and calling for medical assistance. They found that 'illness delay' was the same for both genders, with a median illness delay of 75 minutes, but 'appraisal delay' was longer in women (>2 hours) 57% vs 43% in men ($p=0.047$). The authors suggested that this difference between the genders was because females experience particular difficulties in evaluating multiple or ambiguous symptoms. This study was limited by a low participation rate. As a retrospective trial it could be subject to bias through the participants' experiences and patients may have revised their answers due to their experiences post event. In contrast to these results the study by Newman *et al.* (2013) reported that women under 65 were significantly more likely ($p<0.01$) than men to call for medical assistance. However, this sub-study has been selected from participants in a single-centre study, analysing the prognostic risk conferred by depressive symptoms and clinical depressive disorders at the time of ACS. The calls for medical assistance were self-reported during an in-hospital interview; only 100 out of the 500 participants were verified, with 24 participants being excluded as data was not available on their call.

Discussion

The literature reports that women present later on average than men with their

symptoms and with more advanced disease (Kreatsoulas *et al.*2010, Matura 2010, Mega *et al.* 2010, Aguilar *et al.* 2012, Sheppard *et al.* 2012, Shehab *et al.* 2013), particularly in those aged over 65 years. In studies where age was not identified as a factor these gender differences were still reported (Napoli & Choo 2012).

Women are less likely than men to seek medical help and, therefore, may not get appropriate care until it is too late (World Health Organisation 2009). This may result in the increase in morbidity and poorer quality of life seen in women following a cardiac event (Mosca *et al.*2011).

There is a lack of awareness in both clinicians and patients of the differences in CHD presentation between men and women. Women delay seeking medical assistance for cardiac symptoms and when women do present the diagnostic tests utilised may not diagnose the true cause of their symptoms. This is compounded by the stoicism displayed by women in relation to their CHD symptoms and the belief that they should conform to the gender ideals assigned by society. Delaying behaviour until their attempts to self-treat have been exhausted (Galdas *et al.* 2010) results in poorer quality of life scores compared to men and increased morbidity.

Clearly women are at an increased risk of CHD, this is not currently acknowledged by the existing risk scores utilised in practice, the Framingham risk score underestimates this risk within women as it relies on endpoints of MI and coronary death, with >90% of women classed as low risk and very few assigned high risk status before the age of 70 (Wenger, 2011; Stock & Redberg 2012). The quick reference guide for chest pain of recent onset (NICE 2010) sets out the pathways

that clinicians should follow and gives percentages of people estimated to have coronary heart disease according to typical symptoms, age, gender and risk factors. The consequence is that women with subclinical atherosclerosis are categorised as low risk and the increased mortality risk for younger women with symptoms is not recognised. There is a case for younger women with CHD to be considered high risk and treated aggressively. Additionally this information is adapted from data acquired from 1983 to 1985, so how relevant is 30 year old data to the current population? A good example of this is in female patients with suspected CHD; if the estimated likelihood of CHD is between 61-90%, the guideline suggests offering invasive coronary angiography as the first-line diagnostic investigation. The only women that would qualify (for what is considered the gold standard of care) are high-risk women with typical anginal symptoms, and the criteria for high-risk is any one of the following: diabetes, smoking or cholesterol above 6.47mmol/L. According to these NICE guidelines, women with non-anginal chest pain or atypical angina, regardless of risk category, should not be offered coronary angiography. Whereas, coronary angiography should be offered to over 55 year old high-risk men with non-anginal chest pain, high-risk men with atypical angina regardless of age, and over 60 year old low-risk men with atypical angina. This disparity in treatment means that women do not get equal treatment with men until they present with AMI where the criteria is based upon blood test results and ECG changes. Until guidelines reflect the need for more gender specific care, recognition and implementation by the majority of the health care profession will not happen.

Implications for nursing practice

Findings from this literature review have implications for nursing practice, especially within clinical assessment, health education and health promotion. It has been shown that women present older than men, are significantly less likely to present with typical CHD symptoms and more likely to experience generalised chest discomfort/pain, fatigue, syncope, nausea/vomiting, back pain, palpitations, shortness of breath or sense of dread. Clinicians and nurses must be aware of these differences and the need for a thorough and all-encompassing assessment to identify those at risk of CHD. This has implications therefore for the training and practice of nurses working in Emergency Departments and Primary Care who are most likely to have the initial contact with patients with CHD. Assessment should be based upon the individual's risk factors and gender issues should be considered when diagnostic test are ordered. There is evidence of clear differences between the genders in the presentation of CHD, with the aetiology of CHD in women appearing more complex with obstructive disease and micro-vascular disease playing differing roles. As a consequence the imaging of these vessels needs to detect sub-clinical levels of atherosclerosis and emerging technologies need to be utilised for these at-risk women (Vavas *et al.* 2012). The increased risk of CHD predominately occurs at an older age in women, although younger women's risk of increased mortality from CHD should be acknowledged and addressed. This is not currently being translated into nursing practice, either through clinical assessment or the risk scores utilised by nurses.

According to The World Heart Federation (2014), if patient's have diabetes, their risk of cardiovascular disease is increased for a number of reasons: hypertension, dyslipidaemia and obesity. These are all risk factors in their own right for

cardiovascular disease and occur more frequently in people with diabetes. Educating women on their risk factors and assisting them to achieve the recommended NICE targets through increased education and increased prescribing, means that the gender differences seen within the RIACE study (Penno *et al.* 2013) could be minimised in clinical practice. Nurses are in a prime position to challenge these beliefs as they are involved in the assessment, diagnosis, treatment and rehabilitation of these patients and their families.

There is a need for improved health education around women's risk of CHD. It has been shown that national and international health campaigns can make a large difference and are needed to increase the level of knowledge in the population, as some women continue to have a poor understanding of the symptoms of CHD. The underlying theme of the heath campaigns should be educating the population of the range of symptoms that can be experienced, especially by women.

Implications for research

Women remain under-represented in clinical trials, as shown in this literature review, with a participation rate of 30% (excluding the sole women trials). Tsang *et al.* (2011) suggests this low representation is due to 'age recruitment bias' and strategies to recruit older populations will translate into improved representation. More studies are needed that positively include women to ensure diverse representation and increase understanding of how CHD impacts females.

Women's awareness of the symptoms and presentation of cardiac disease warrants further investigation. This should be done with future prospective study designs and explore progression of symptoms over a sustained period of time, to give a true representation of the gender similarities and differences for CHD. Further research is needed to confirm or refute the possible hypothesis, that a delay in the treatment of women due to a lack of symptom recognition in the emergency department/pre-hospital could explain the disparities between genders. Comparative research into educational interventional strategies is also important as it is necessary to understand which approach is most effective in changing the views of society and make people more aware of the risk to members of their families.

Conclusion

Evidence from this literature review indicates there are clear gender specific differences in the presentation of CHD. However there does not appear to be a consensus in relation to the experience of chest pain between the genders. The studies reviewed, show that using chest pain as the key descriptor for CHD disadvantages women for several different reasons. Primarily, women appear to experience CHD differently from men, implying that there may be a possibility of clinicians and patients confusing the warning signs and symptoms of ischaemic cardiac pain.

The presentation of CHD in women may include vague signs and symptoms, for

example: shortness of breath, fatigue, and back pain (O'Donnell *et al.* 2012). This suggests that chest pain should not necessarily be the primary symptom considered when assessing patients or, more specifically, women for ACS. Secondly, CHD may be overlooked entirely and inaccurate diagnoses given to patients, which could potentially delay further investigations and treatment (Napoli & Choo 2012, Golden, Chang & Hollander 2013). Ghezeljeh *et al.* (2010) suggested women were better at communicating their symptoms, yet this variety of potential symptoms for CHD (up to 87 different symptoms (O'Donnell *et al.* 2012))has not been grasped as significant by clinicians generally, or women are under-playing the severity of the symptoms, or are not aware that the symptoms are significant.

Coronary heart disease is a major cause of death and disability in women, yet the recognition of coronary heart disease symptoms by patients and health professionals is limited by teaching based upon classic literature and male-based populations (Collins 2012). Overall there is a plausible case for gender-specific care, but there is a definite necessity for a better awareness of the differences in CHD presentation between the genders in both health professionals and patients alike.

References

Aguilar SA, Patel M, Castillo E, Patel E, Fisher R, Ochs G, Pringle J, Mahmud E & Dunford, JV (2012) Gender Differences in Scene Time, Transport Time, and Total Scene to Hospital Arrival Time Determined by the Use of a Pre-hospital Electrocardiogram in Patients with Complaint of Chest Pain. *Journal of Emergency Medicine,* 43, 291-297.

Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Chavey WE, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL & Riegel B (2007) ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology,* 50, e1-e157.

Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, & Jacobs AK (2004) ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation,* 110, e82-292.

Bangalore S, Fonarow GC, Peterson ED, Hellkamp AS, Hernandez AF, Laskey W, Peacock WF, Cannon CP, Schwamm LH &Bhatt DL (2012) Age and gender differences in quality of care and outcomes for patients with ST-segment elevation myocardial infarction. *The American Journal of Medicine,* 125, 1000-1009.

Bösner S, Haasenritter J, Hani MA, Keller H, Sönnichsen AC, Karatolios K, Schaefer JR, Baum E & Donner-Banzhoff N (2011) Gender bias revisited: new insights on the

differential management of chest pain. *BMC Family Practice,* 6, 45.

Burke AP, Farb A, Malcom GT, Liang Y, Smialek J & Virmani R (1998) Clinical Investigation and Reports Effect of Risk Factors on the Mechanism of Acute Thrombosis and Sudden Coronary Death in Women. *Circulation,* 97, 2110-2116.

Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G & Zheng ZJ (2012) Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Journal of the American Medical Association,* 307, 813-822.

Coventry LL, Finn J & Bremner AP (2011) Sex differences in symptom presentation in acute myocardial infarction: a systematic review and meta-analysis. *Heart & Lung,* 40, 477-491.

Department of Health Cardiovascular Disease Team, (2013) *Cardiovascular Disease Outcomes Strategy: Improving outcomes for people with or at risk of cardiovascular disease,* [online] London: Crown Copyright. Available at: <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/156450/9387-2900853-CVD-Outcomes_web1.pdf>[Accessed: 21st April 2014]

Farquharson B, Johnston M & Bugge C (2012) Appraisal and illness delay with symptoms of ACS: A questionnaire study of illness representations. *British Journal of Cardiac Nursing,* 7, 493-499.

Fransoo RR, Martens PJ, Prior HJ, Burland E, Château D & Katz A (2010) Age Difference Explains Gender Difference in Cardiac Intervention Rates After Acute Myocardial Infarction. *Healthcare Policy,* 6, 88-103.

Galdas PM, Johnson JL, Percy ME & Ratner PA (2010) Help seeking for cardiac symptoms: beyond the masculine-feminine binary. *Social Science & Medicine,* 71, 18-24.

Ghezeljeh TN, Momtahen M, Tessm, MK, Nikravesh MY, Ekman I & Emami A (2010) Gender specific variations in the description, intensity and location of Angina Pectoris: a Cross-sectional study 1. *International Journal of Nursing Studies,* 47, 965-974.

Golden KE, Chang AM &Hollander JE (2013) Sex Preferences in Cardiovascular Testing: The Contribution of the Patient-Physician Discussion. *Academic Emergency Medicine,* 20, 680-688.

Gu Y, Warren J, Walker N & Kennelly J (2013) Gender differences in cardiovascular disease risk management for Pacific Islanders in primary care. *Quality in Primary Care,* 21, 275-285.

Haynes SG & Feinleib M (1980) Women, work and coronary heart disease: prospective findings from the Framingham Heart Study. *American Journal of Public Health,* 70, 133-141.

Herning M, Hansen PR, Bygbjerg B. & Lindhardt T (2011) Women's experiences and behaviour at onset of symptoms of ST segment elevation acute myocardial infarction. *European Journal of Cardiovascular Nursing,* 10, 241-247.

Hess EP, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Roger VL, Wells GA & Stiell IG (2010) Sex differences in clinical presentation, management and outcome in emergency department patients with chest pain. *Canadian Journal of Emergency Medicine,* 12, 405-413.

Johnson KM & Dowe DA (2010) The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for coronary atherosclerosis. *American Journal of Roentgenology*, 194, 1235-1243.

Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K & Laaks, M (2004) Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care,* 27, 2898-2904.

Kavanagh A, Bentley RJ, Turrell G, Shaw J, Dunstan D & Subramanian SV (2010) Socioeconomic position, gender, health behaviours and biomarkers of cardiovascular disease and diabetes. *Social Science & Medicine,* 71, 1150-1160.

Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ. Pelletier R, Tsadok MA, Dasgupta K, Norris CM &Pilote L (2013) Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Internal Medicine,* 173, 1863-1871.

Korhonen P, Vesalainen R, Aarnio P, Kautiainen H, Järvenp S & Kantola I (2012) Assessment of cardiovascular risk in primary health care. *Scandinavian Journal of Primary Health Care,* 30, 101-106.

Kozàkovà M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Dekker JM, Balkau B & Nilsson PM (2013) Gender-specific differences in carotid intima-media thickness and its progression over three years: A multicenter European study. *Nutrition, Metabolism & Cardiovascular Diseases,* 23, 151-158.

Kreatsoulas C, Natarajan MK, Khatun R, Velianou JL & Anand SS (2010) Identifying women with severe angiographic coronary disease. *Journal of Internal Medicine,* 268, 66-74.

Kuhlmann E & Annandale E. eds. (2012) *The Palgrave Handbook of Gender and Healthcare.*2nd ed. Basingstoke: Palgrave Macmillan.

Ky B, Kirwan BA, De Brouwer S, Lubsen J, Poole-Wilson P, Otterstad JE, Kimmel S.E & St John Sutton M (2010) Gender differences in cardiac remodeling and clinical outcomes in chronic stable angina pectoris (from the ACTION Trial). *American Journal of Cardiology,* 105, 943-947.

Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, De Bruyne B, Farhat N, Niess G, Jankovic I, Lazar D, Xu K, Fahy M, Serruys PW & Stone GW (2012) Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC Cardiovascular Imaging,* 5, S62-S72.

Legato MJ, Gelzer A, Goland R, Ebner SA, Rajan S, Villagra V & Kosowski M (2006) Gender-specific care of the patient with diabetes: Review and recommendations. *Gender Medicine,* 3, 131-158.

Leifheit-Limson E, Spertus JA, Reid K J, Jones SB, Vaccarino V, Krumholz HM & Lichtman JH (2013) Prevalence of Traditional Cardiac Risk Factors and Secondary Prevention Among Patients Hospitalized for Acute Myocardial Infarction (AMI): Variation by Age, Sex, and Race. *Journal of Women's Health,* 22, 659-666.

Leuzzi C, Sangiorgi G & Modena M (2010) Gender-specific aspects in the clinical presentation of cardiovascular disease. *Fundamental & Clinical Pharmacology*, 24, 711-717.

Mann CJ (2003) Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal,*20, 54-60.

Matura LA (2010) Gender and circadian effects of myocardial infarctions. *Clinical Nursing Research,* 19, 55-70.

Mega J, Hochman J, Scirica B, Murphy S, Sloan S, McCabe C, Merlini P & Morrow D (2010) Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease: Observations From Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36). *Circulation*, 121, 1809-1817.

Meisel ZF, Armstrong K, Mechem CC, Shofer FS, Peacock N, Facenda K & Pollack CV (2010) Influence of sex on the out-of-hospital management of chest pain. *Academic Emergency Medicine,* 17, 80-87.

Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, Dolor RJ, Douglas PS, Mar, DB & Newby LK (2010) Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circulation: Cardiovascular Quality and Outcomes,* 3, 135-142.

Mendis S (2010) The Contribution of the Framingham Heart Study to the Prevention of Cardiovascular Disease: A Global Perspective. *Progress in cardiovascular diseases,* 53, 10-14.

Mieres JH, Shaw L.J, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS & Wenger NK (2005) AHA Scientific Statement Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease Consensus Statement From the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation,* 111, 682-696.

Mieres JH, Heller GV, Hendel RC, Gulati M, Boden WE, Katten D & Shaw LJ (2011) Signs and Symptoms of Suspected Myocardial Ischemia in Women: Results from the What is the Optimal Method for Ischemia Evaluation in WomeN? Trial. *Journal of Women's Health,* 20, 1261-1268.

Mochari-Greenberger H, Mills T, Simpson SL & Mosca L (2010) Knowledge, preventive action, and barriers to cardiovascular disease prevention by race and ethnicity in women: an American Heart Association national survey. *Journal of Women's Health,* 19, 1243-1249.

Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V & Wenger NK (2011) Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update A Guideline from the American Heart Association. *Journal of the American College of Cardiology*, 57, 1404-1423.

Napoli A & Choo EK (2012) Gender and stress test use in an ED chest pain unit. *American Journal of Emergency Medicine,* 30, 890-895.

National Institute for Clinical Excellence, 2004 (updated 2005). *Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers*. [pdf] London: National Institute for Clinical Excellence. Available at: <http://www.nice.org.uk/niceMedia/pdf/GDM_Allchapters_0305.pdf> [Accessed 21 April 2014].

National Institute for Clinical Excellence, 2008 (reissued 2010). *NICE clinical guideline 67 Lipid modification: cardiovascular risk assessment and the modification*

of blood lipids for the primary and secondary prevention of cardiovascular disease. [pdf] London: National Institute for Clinical Excellence. Available at: <www.nice.org.uk/CG067> [Accessed 20 April 2014].

National Institute for Health and Clinical Excellence, 2010. *NICE clinical guideline 95 Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.* [pdf] London: National Clinical Guideline Centre for Acute and Chronic Conditions. Available at: <http://www.nice.org.uk/nicemedia/live/12947/47918/47918.pdf > [Accessed 8 February 2014].

National Institute for Health and Care Excellence, (2013). *NICE clinical guideline 167 Myocardial infarction with ST segment elevation The acute management of myocardial infarction with ST-segment elevation.* [pdf] Manchester: National Institute for Health and Care Excellence 2013. Available at: <http://publications.nice.org.uk/myocardial-infarction-with-st-segment-elevation-cg167> [Accessed 08 February 2014].

Newman JD, Davidson KW, Ye S, Shaffer JA, Shimbo D & Muntner P (2013) Gender differences in calls to 9-1-1 during an acute coronary syndrome. *American Journal of Cardiology,* 111, 58-62.

Norris CM, Murray JW, Triplett LS & Hegadoren KM (2010) Gender roles in persistent sex differences in health-related quality-of-life outcomes of patients with coronary artery disease. *Gender Medicine,* 7, 330–339

O'Donnell S, McKee G, O'Brien F, Mooney M & Moser DK (2012) Gendered symptom presentation in acute coronary syndrome: A cross-sectional analysis. *International Journal of Nursing Studies,* 49, 1325-1332.

O'Keefe-McCarthy S (2008) Women's experiences of cardiac pain: a review of the literature. *Canadian Journal of Cardiovascular Nursing,* 18, 18-25.

Penno G, Solini A, Bonora E, Fondelli C, Ors, E, Zerbini G, Trevisan R, Vedovato M, Gruden G, Laviola L, Nicolucci A & Pugliese G (2013) Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. *Journal of Internal Medicine*, 274, 176–191.

Pickett CA, Hulten EA, Goyal M, Surry L & Villines C (2013) Accuracy of traditional age, gender and symptom based pre-test estimation of angiographically significant coronary artery disease in patients referred for coronary computed tomographic angiography. *American Journal of Cardiology,* 112, 208-211.

Shehab A, Yasin J, Hashi, M, Jawad Al-Dabbagh B, Mahmeed WA, Bustani N, Agrawal A, Yusufali A, Wasse A & Alnaeemi A (2013) Gender Differences in Acute Coronary Syndrome in Arab Emirati Women—Implications for Clinical Management. *Angiology,* 64, 9-14.

Sheifer SE, Canos MR, Weinfurt KP, Arora UK, Mendelsohn FO, Gersh BJ & Weissman NJ (2000) Sex differences in coronary artery size assessed by

intravascular ultrasound. *American Heart Journal,* 139, 649-653.

Sheppard JP, Singh S, Fletcher K, McManus RJ & Mant J (2012) Impact of age and sex on primary preventive treatment for cardiovascular disease in the West Midlands, UK: Cross-sectional study 1. *British Medical Journal,* 345, 17.

Shirato S & Swan BA (2010) Women and cardiovascular disease: an evidentiary review. *Medsurg Nursing,* 19, 282-286, 306.

Stock EO & Redber R (2012) Cardiovascular disease in women. *Current Problems in Cardiology,* 37, 450-526.

Tabenkin H, Eaton CB, Roberts MB, Parker DR, McMurray JH & Borkan J (2010) Differences in cardiovascular disease risk factor management in primary care by sex of physician and patient. *Annals of Family Medicine,* 8, 25-32.

Tamura A, Naono S, Torigoe K, Hino M, Maeda S, Shinozaki K, Zaizen H &Kadota J (2013) Gender differences in symptoms during 60-second balloon occlusion of the coronary artery. *American Journal of Cardiology,* 111, 1751-1754.

Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R & Rayner M (2012) *Coronary Heart Disease Statistics 2012 Edition.* London: British Heart Foundation.

Tsang W, Alter DA, Wijeysundera HC, Zhang T & Ko DT (2012) The Impact of Cardiovascular Disease Prevalence on Women's Enrollment in Landmark

Randomized Cardiovascular Trials: A Systematic Review. *Journal of General Internal Medicine,* 27, 93-98.

Vavas E, Hong SN, Rosen SE & Mieres JH (2012). Noninvasive Diagnostic Techniques for Coronary Disease in Women. *Clinical Cardiology*, 35, 149–155.

Villablanca AC, Beckett LA, Li Y, Leatherwood S, Gill SK, Giardina EV, Barron C, Foody JM, Haynes S & D'Onofrio G (2010) Outcomes of Comprehensive Heart Care Programs in High-Risk Women. *Journal of Women's Health,* 19, 1313-1325.

Wenger NK (2011) Coronary Heart Disease in Men and Women: Does 1 Size Fit All? No! *Clinical Cardiology*, 34, 663–667.

Williams R, Fraser A & West R (2004) Gender differences in management after acute myocardial infarction: not 'sexism' but a reflection of age at presentation. *Journal of Public Health*, 26, 259-263.

Wizemann TM & Pardue M-L. eds. (2001) *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: The National Academies Press.

World Health Organization (2009) *Women and Health: Today's Evidence Tomorrow's Agenda*. Geneva: WHO

World Health Organization (2010) *Global status report on noncommunicable diseases 2010.* [pdf] Geneva: WHO. Available at: <http://www.who.int> [Accessed 16 October 2013].

World Heart Federation (2014) *Diabetes Factsheet,* [online] Geneva: WHF. Available at: <http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/diabetes/> [Accessed 05 May 2014].

Worrall-Carter L, Ski C, Scruth E, Campbell M & Page K (2011) Systematic review of cardiovascular disease in women: Assessing the risk. *Nursing & Health Sciences,*13, 529-535.

Xhyheri B & Bugiardini R (2010) Diagnosis and treatment of heart disease: are women different from men? *Progress in Cardiovascular Diseases,* 53, 227-236.

Zègre-Hemsey J, Sommargren CE & Drew BJ (2011) Initial ECG acquisition within 10 minutes of arrival at the emergency department in persons with chest pain: time and gender differences.*: Journal of Emergency Nursing,* 37, 109-112.

Table 1 – Search strategy

Cardiovascular Diseases OR Cardiovascular Risk Factors OR Cardiovascular Care OR Diagnosis, Cardiovascular OR Cardiovascular Agents OR Myocardial Ischemia OR Coronary Disease OR Coronary Arteriosclerosis OR Cardiovascular System Physiology OR Cardiovascular System OR Myocardial Diseases OR Acute Disease OR Cardiovascular Nursing OR Heart Diseases OR Myocardial Ischemia OR Coronary Disease OR Cardiac Patients OR Angina, Stable OR Angina, Unstable OR Angina Pectoris OR Chest Pain OR Cardiac Patients OR Acute Coronary Syndrome OR Acute Chest Syndrome **AND**
Health Behaviour OR Health Services Needs and Demand OR Behavioural Symptoms OR Gender Specific Care OR Gender Bias OR Sex Factors OR Sex Role OR gender **AND**
Female

Figure 1 – Flow chart of the review process

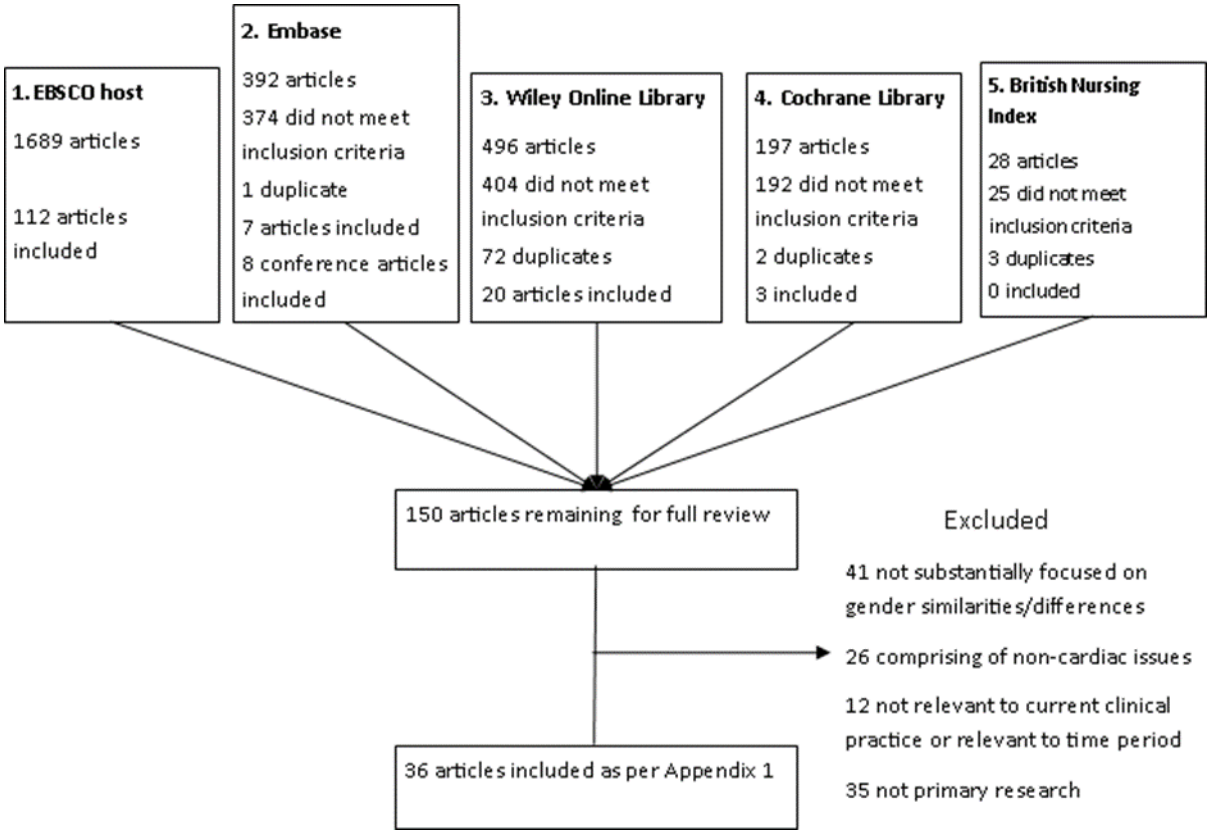

Table 2. Characteristics of included studies

Number	Authors	Study Period	Study Design	Sample size	Female, %	Study Location/Setting	Patient Population	Comments
1	Aguilar, et al. (2012)	2003-2008	Retrospective cohort study	21,742	46	United States. 1 local hospital	Pre-hospital use of ECG in patients with complaints of chest pain	Several limitations to the trial, older females Level = 2-

2	Bangalore, et al. (2012)	2002-2008	Prospective cohort study	31,544	35	United States, 369 centers	Participating in AHA *Get With the Guidelines* CAD registry	Level = 2++
3	Canto, et al. (2012)	1994-2006	Cross-sectional study [1]	1,143,513	42	United States. Multi-centers	Diagnosis of acute STEMI,<12 h after onset of symptoms, and received reperfusion therapy	National registry, over 2.5 million patients Level = 2++

4	Farquharson, Johnston and Bugge. (2012)	2006	Cross-sectional study [1]	182	52	United Kingdom,	Contacted NHS 24 service with chest pain symptoms	Level = 2+
5	Galdas, et al. (2010)	2007-2008	Cross-sectional study [1]	20	45	Canada, 1 center	Diagnosis chest pain of cardiac origin or ACS. Completion of survey questionnaire in acute care facility expressed	Level = 2+

							interest in participating in interview	
6	Ghezeljeh, et al. (2010)	2007-2008	Cross-sectional study [1]	500	50	Tehran, Iran. Multiple sites	Chest Pain < 7 days, confirmed CHD	Varied locations of pain Level = 2+
7	Golden, Chang and Hollander	2011-2012	Cross-sectional study [1]	206	57	Philadelphia, United States. 1 hospital	Acute chest pain presentation to Emergency	Level = 2+

	(2013)						department	
8	Gu, et al. (2013)	2007-2012	Cross-sectional study [1]	10,863	54	New Zealand, 14 general practices	Data collection of residents in the geographical location	Level = 2+
9	Haidinger, et al. (2012)	No details	Cross-sectional study [1]	909	63	Vienna, multiple locations	Anonymous Survey	Level = 2-
10	Herning, et	2009	Phenomenological	14	100	Denmark, 1 center	Open interviews with in-patients	Level =3

	al. (2011)		case study				diagnosed with STEMI	
11	Hess, et al. (2010)	2007-2008	Prospective cohort study	970	40	Ottawa, Canada. 1 local hospital	Acute Chest Pain presentation to Emergency department	Level = 2-
12	Khan, et al. (2013)	2009-2012	Prospective cohort study	1015	30	GENESIS PRAXY, Canada, United States, Switzerland. 26	Hospitalised with ACS	Level = 2++

						hospitals		
13	Korhonen, et al. (2012)	2005-2007	Cross-sectional study [1]	904	53	South Western Finland, 1 center	Survey of residents in the geographical location	Date of surveys not included in article pulled from primary paper Level = 2+
14	Kozàkovà, et al.	2002-2005	Prospective cohort study	788	53	14 European countries. 19	Healthy subjects aged 30-60, low	Level = 2+

	(2013)					centers	risk	
15	Kreatsoulas, et al. (2010)	2000-2006	Prospective cohort study	23,771	38	Central/ South Ontario, Canada. Multi centres	Angiography Registry	Level = 2++
16	Ky, et al. (2010)	1996-1998	Retrospective cohort study	7016	21	19 Countries, Multi-centers	ACTION trial patients with evaluable Echocardiography	Secondary analysis of ACTION Trial patients, clear explanations

								of how patients derived. Study period not in article Level = 2++
17	Lansky, et al. (2012)	2004-2009	Prospective cohort study	697	24	PROSPECT, United States and Europe. 37 hospitals	ACS	Level = 2+

18	Leifheit-Limson, et al. (2013)	2003-2004	Prospective cohort study	2369	33	United States, 19 centers	Diagnosis of AMI presenting to enrolling centre	Sub analysis of PREMIER Study Level = 2+
19	Matura (2010)	2004	Retrospective cohort study	273	40	United States. 1 local hospital	Diagnosed with MI	Chart review, patients presenting with symptoms, but not diagnosed

								with MI, were excluded Level = 2+
20	Mega, et al. (2010)	2003-2007	Prospective cohort study	6560	35	17 countries, 442 centers	Ischemic symptoms at rest, high risk	Secondary analysis of MERLIN-TIMI 36 Trial Level = 2++

21	Meisel, et al. (2010)	2006-2007	Retrospective cohort study	683	50	Single city, 3 hospitals	Complaint of chest pain	Level = 2+
22	Mieres, et al. (2011)	2006-2007	Individual randomised controlled trial	824	100	North American, Multi-centers	Chest pain or angina equivalent symptoms. Increased risk CAD	Level = 1+
23	Mochari-Greenberger, et al.	2005	Cross-sectional study [1]	1008	100	United States	National representative sample given standardised	Level = 2+

	(2010)						questionnaire	
24	Moore, Kimble and Minick (2010)	No details	Hermeneutics case study	7	100	United States, 1 center	Previous history of CHD	Level = 2-
25	Napoli and Choo (2012)	2010	Cross-sectional study [1]	811	52	Rhode Island United States. 1 local hospital	Acute Chest Pain presentation to ED	Secondary analysis Level = 2+
26	Newman, et	2009-	Prospective	476	34	New York, United	Hospitalised with ACS, participants	Level = 2-

	al. (2013)	2010	cohort study			States. 1 hospital	of PULSE study	
27	Norris, et al. (2010)	2006-2008	Prospective cohort study	2403	19	Canada, Multi-centers	Participated in APPROACH registry, undergoing first catheterization	Level = 2+
28	O'Donnell, et al.	2007-2009	Cross-sectional study [1]	1947	28	Dublin, Ireland. 5 hospitals	Hospitalised with ACS	Level = 2++

	(2012)							
29	Pickett, et al. (2013)	2006-2010	Cross-sectional study [1]	1027	41	Maryland, United States. 1 hospital	No previous CAD referred for CCTA	Level = 2+
30	Shehab, et al. (2013)	2007	Prospective cohort study	1697	12	6 Arab countries, 65 hospitals	ACS diagnosis confirmed	Sub-set of Gulf RACE study patients Level = 2+

31	Sheppard, et al. (2012)	2008-2009	Cross-sectional study [1]	36,679	35	United Kingdom, 19 general practice	Primary prevention in patients	Level = 2+
32	Tabenkin, et al. (2010)	2004	Cross-sectional study [1]	4,195	60	New England, 30 centers	Respondent to physician invitation for survey questionnaire	Level = 2+
33	Tamura, et al.	2011-2012	Prospective cohort study	190	42	Beppu, Japan. 1 local hospital	Non-acute Elective PCI	Level = 2+

	(2013)							
34	Villablanca, et al. (2010)	2005-2008	Before and after study [1]	1310	100	United States, 6 centers	High risk women participating in women's health program	Level = 3
35	Zègre-Hemsey, Sommargren and Drew, (2011)	2003-2008	Prospective cohort study	425	47	California, 2 local hospital	Complaint of chest pain, with pre-hospital ECG	Secondary analysis of randomised clinical trial Level = 2-