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CLINICAL REVIEW
Controversies in cardiovascular medicine

Gender in cardiovascular medicine: chest pain and coronary artery disease

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Ischaemic heart disease (IHD) remains the leading cause of morbidity and mortality among women and men yet women are more often underdiagnosed, have a delay in diagnosis, and/or receive suboptimal treatment. An implicit gender-bias with regard to lack of recognition of sex-related differences in presentation of IHD may, in part, explain these differences in women compared with men. Indeed, existing knowledge demonstrates that angina does not commonly relate to obstructive coronary artery disease (CAD). Emerging knowledge supports an inclusive approach to chest pain symptoms in women, as well as a more thoughtful consideration of percutaneous coronary intervention for angina in stable obstructive CAD, to avoid chasing our tails. Emerging knowledge regarding the cardiac autonomic nervous system and visceral pain pathways in patients with and without obstructive CAD offers explanatory mechanisms for angina. Interdisciplinary investigation approaches that involve cardiologists, biobehavioural specialists, and anaesthesia/pain specialists to improve angina treatment should be pursued.

Keywords Angina • Central autonomic nervous system • Microvascular

Ischaemic heart disease (IHD) remains the leading cause of morbidity and mortality among women and men.[1,2] Women, however, are relatively more underdiagnosed or have a delay in diagnosis,[3,4] receive suboptimal treatment,[5,6] and are underrepresented proportionately to prevalence in clinical trials.[7] Women are more likely to have prehospital delay in presentation after symptom onset (by ~30 min compared to men as reported by a recent study),[3,8] as well as underdiagnosis of myocardial infarction (MI) and lower priority for emergency ambulance services, while less likely to be presented to a percutaneous coronary intervention (PCI)-capable facility and receive reperfusion therapy.[9–11] In 846 ST-elevation myocardial infarction (STEMI) patients with a failed prehospital diagnosis, predictors of interhospital transfer to PCI-capable centre were female gender (odds ratio: 1.58), diabetes (1.98), and prior MI (2.86).[9] Women do tend to be older with more comorbidities such as diabetes, which may contribute to delays in aggressive treatment (i.e. door-to-balloon time delay of ~16 min compared to men), and lower statin use (21.1% vs. 23%).[4,5] We may be narrowing the gender gap, as in a recent cohort of 2612 patients with acute coronary syndrome, there was no sex difference in short-term mortality.[12] However, a large contemporary US STEMI registry demonstrates a delayed contact-to-reperfusion time in women compared to men, which was independently related to higher female mortality rates.[13] What contributes to differences that result in outcome disparities for women?

A lack of recognition of sex differences in presentation of IHD may in part explain outcome disparities in women compared to men. One study reported that women with acute MI treated by male emergency physicians had a higher mortality compared to those treated by females.[14] This difference was not observed in male physicians who had at least two female physician colleagues or had treated more women, suggesting the mortality difference could be improved by training. Furthermore, we have demonstrated that a network focused on improving emergency service recognition of STEMI resulted in improved female/equivalent gender in-hospital and long-

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term (5-year) age-adjusted mortality, suggesting that STEMI treatment disparities and mortality in women can be improved using protocols.[15] Again, these results indicate that we can improve IHD outcomes for women by physician training and uniform deployment of evidence-based guideline protocols.

Why do these implicit IHD gender-biases exist? Historically, coronary heart disease (CHD) and coronary artery disease (CAD) were terms used to describe obstructive coronary stenosis, although over the past two decades it has become clear that IHD is a more appropriate term because not all patients with angina and ischaemia have obstructive epicardial stenoses. In particular, women are more likely to present with evidence of *i*schaemia, identified by objective evidence such as abnormal stress or biomarker testing, and *no obstructive coronary arteries* (INOCA) compared to men, although they paradoxically have more chest pain.[16] Furthermore, this appears to have led to misperceptions regarding chest pain and the term angina. Early large angiographic studies[17] determined that women with typical angina had less obstructive CAD compared to men, and contemporary study demonstrates that angina characterization is not diagnostic in women (*Figure 1*).[18] While angina refers to symptoms and not the disease process itself and although angina may not be related to obstructive CAD also in men, the historical identification of IHD as either CHD or CAD has contributed to women being diagnosed with non-specific chest pain, and discharged from subspecialty care and treatment.[19]

How much do women and men differ with regard to chest pain symptoms relative to obstructive CAD? Prior analyses of gender-based differences of acute coronary syndrome have demonstrated varied results, but the majority of studies describe chest pain as the most frequent symptom in both genders.[20,21] Angina is also the most frequently reported symptom in stable IHD in both men and women, but women more often present with atypical angina. While typical angina is characterized by retrosternal pain that is provoked by exertion and relieved by rest or nitroglycerine, atypical angina represents a more diverse symptom presentation with pain or discomfort not only in the chest but also in the arms, jaw, neck, and interscapular area.[22] These symptoms do not necessarily occur at exertion, but can arise after exertion or be triggered by mental stress or even occur at rest. Symptoms may last intermittently over several hours, and atypical presentations include more vague symptoms such as fatigue, anxiety, dyspnoea, dyspepsia, and nausea.[23,24]

Why do relations between chest pain and obstructive CAD differ between women and men? It is now well established that myocardial ischaemia and infarction have a more diverse underlying pathophysiology in women compared to men which includes coronary microvascular dysfunction (CMD), coronary vasospasm, plaque erosions/microemboli, and spontaneous coronary artery dissection. The Women's ischaemia Syndrome Evaluation (WISE) study demonstrated that over 50% of women with signs and symptoms suggestive of IHD lack epicardial coronary stenosis, and other studies worldwide have replicated this finding.[25,26] Those with persistent angina experience higher rates of depression and anxiety with concurrent reduced functional capacity and impaired quality of life.[27,28]Hospitalizations and the use of recurrent diagnostic modalities to evaluate persistent and recurring angina is associated with significant healthcare costs.[29]

A number of findings from studies of PCI for treatment of stable angina in women and men with obstructive CAD[30,31] further elaborate on this disconnect between angina and obstructive CAD. For example, in the ORBITA (*O*bjective *R*andomized *B*linded *I*nvestigation with optimal medical *T*herapy or *A*ngioplasty in stable angina) trial,[30] relief of epicardial stenosis with PCI in patients with obstructive CAD did not out-perform optimal medical therapy for relief of angina in obstructive CAD. In the FAME 2 (*F*ractional Flow Reserve vs. *A*ngiography for *M*ultivessel *E*valuation) trial of open label randomization to fractional flow reserve (FFR)-guided PCI vs. medical therapy group, a large proportion of patients had an improvement in angina after being told that they had no significant obstructive lesion based on fractional flow reserve assessment.[31,32] While these newer data suggest that relations between chest pain and obstructive CAD may be more nuanced that previously thought, inspection of other existing knowledge can assist with formulating investigation to address knowledge gaps in chest pain pathophysiology to improve IHD outcomes for women.

Existing Knowledge

Angina does not correlate with myocardial ischaemia

Lessons learned from silent ischaemia investigations in the ambulatory monitoring era inform us that 66% of 'angina' does not have evidence of myocardial ischaemia, while 85% of ambulatory ischaemia is symptomatically 'silent'.[33] Specifically, prior studies of ambulatory monitoring in women and men with angina and established obstructive CAD or a history of MI demonstrate that the majority of angina episodes do not have ST depressions on Holter monitoring.[34–40] While transient ischaemia that lasts only seconds may be understandably asymptomatic, prolonged ST depressions is most often silent.[41] Chest pain reports in the absence of ischaemia could not be attributed to 'borderline' ST-segment changes.[33] Furthermore, the severity of ischaemia on stress testing does not correlate with angina severity.[40,42] An important methodological limitation of the ambulatory studies is electrocardiographic detection of ischaemia, which has limited sensitivity and specificity. A recent small study which demonstrated correlation between immediate PCI-mediated improved coronary flow and angina in 21 subjects was unblinded, used an unvalidated angina measurement, as well as intra-arterial unfractionated heparin and intracoronary nitroglycerine before physiological measurement, and did not account for the well-established exercise training effect, limiting any conclusions.[43]

Myocardial ischaemia, including silent ischaemia, predicts an adverse cardiac prognosis,[44] and silent ischaemia is considered a treatment target. There is a relationship between silent ischaemic burden and CAD status; e.g. those with multivessel obstructive CAD have more documented silent ischaemic episodes than single vessel CAD.[45] Haemodynamic changes with elevations in heart rate and blood pressure preceding ST depression are documented, suggesting increased myocardial demand plays a role in silent ischaemia.[46] A relevant knowledge gap is that there is no clear explanation of why silent and symptomatic ischaemia occurs in the same patient. Various mechanisms have been considered as an explanation for silent ischaemia, including (i) varying degrees of subclinical atherosclerosis in segmental myocardial territories which lead to a functional mismatch during hyperaemia (maximal vasodilator stress) or during mental stress (vasoconstrictive response), leading to perfusion defects; (ii)

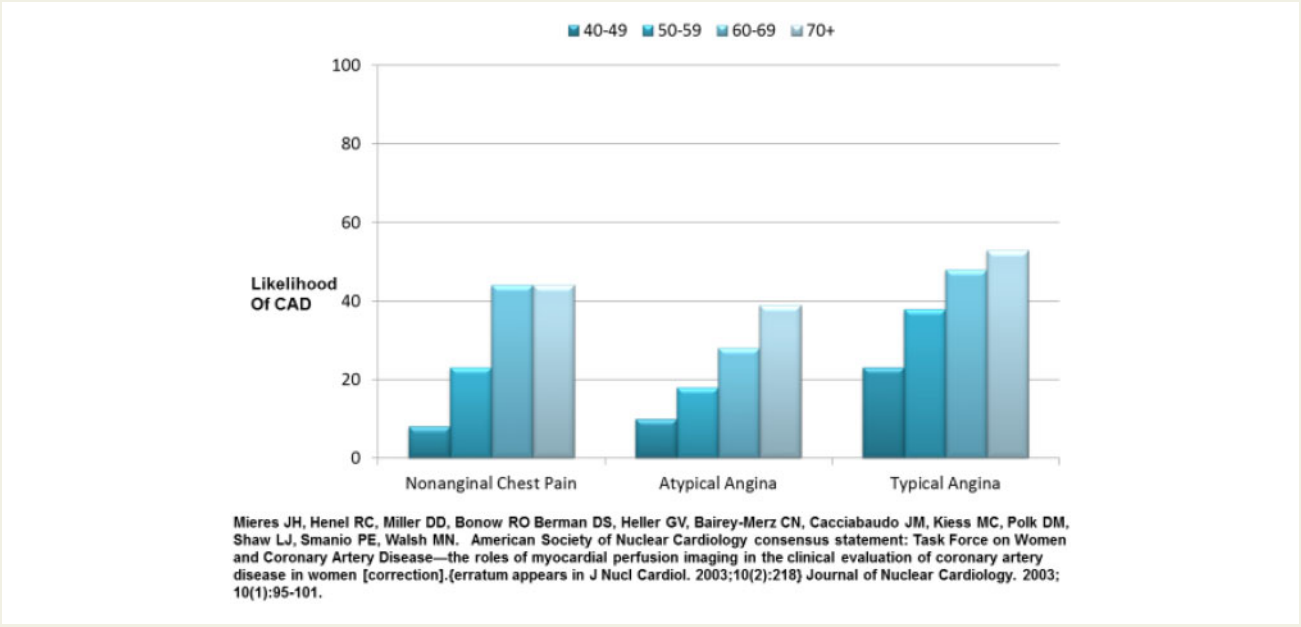


Figure 1 Angina classification and obstructive coronary artery disease in women. Most symptomatic women over 50 years are at intermediate risk (20–50%) (reprinted with permission).

CMD or smooth muscle dysfunction; (iii) lack of stimulation of subepicardial pain fibres because ischaemic episodes are subendocardial; (iv) circadian variation in vasoconstriction; (v) high pain threshold or blunted pain perception; and (vi) increased adrenergic activity. Studies show that self-reported angina symptom severity may or may not be correlated with ischaemia burden.[47,48]

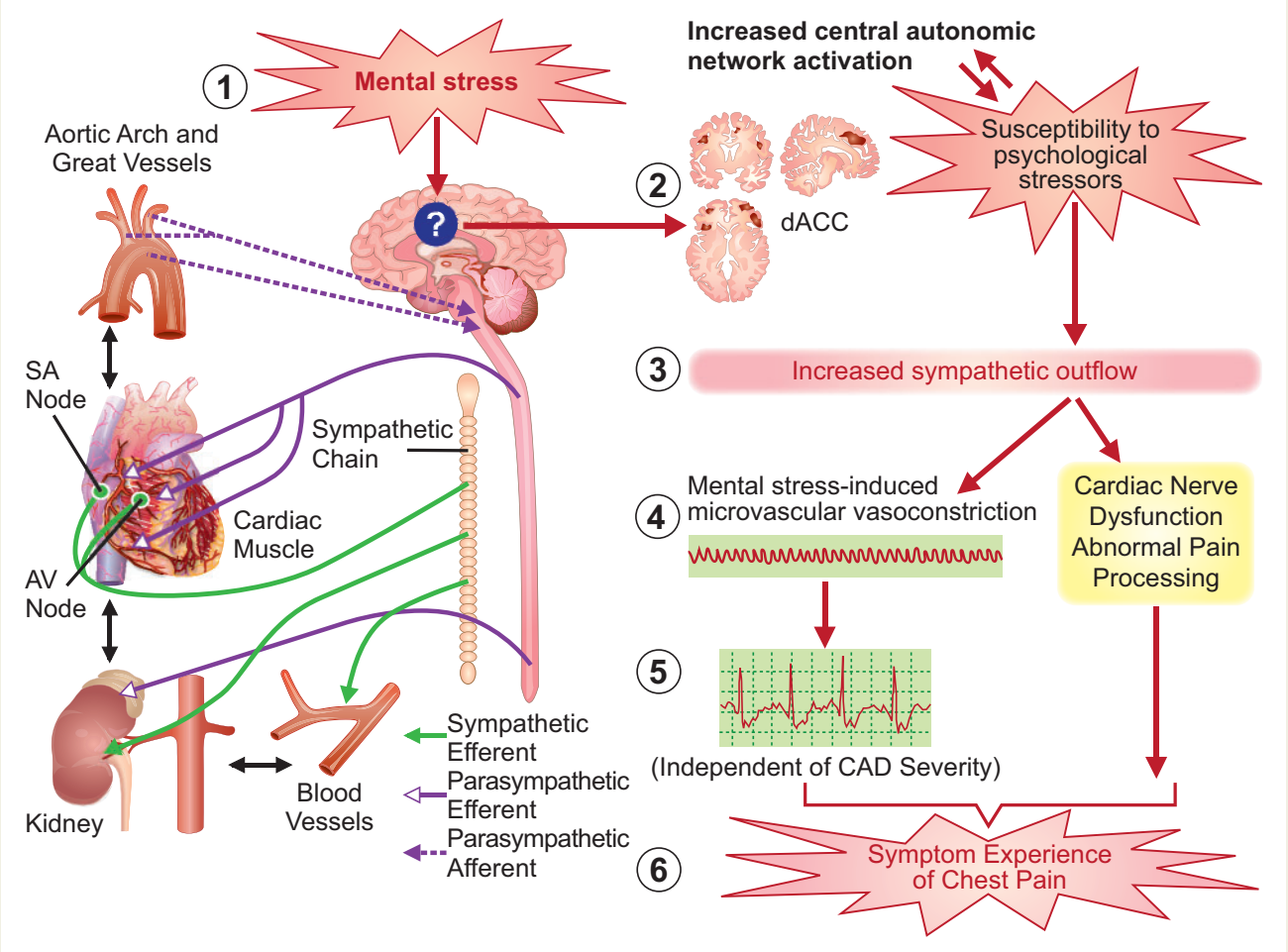
Angina does not correlate with obstructive coronary artery disease

Decades of research has shown that angina can occur in those with or without significant obstructive CAD, and angina also persists in many patients post-PCI. Data from multiple large studies indicate that approximately one-fifth to one-third of patients undergoing PCI have persistent or recurrent angina at follow-up.[49,50] Invasive coronary reactivity testing can demonstrate coronary vasomotor abnormalities in patients with persistent angina and no obstructive CAD.[51] A comprehensive coronary reactivity testing uses vasoactive agents such as adenosine, acetylcholine, and nitroglycerine to detect CMD, endothelial dysfunction, and vasospasm.[15,51] In order to unify terminology and diagnostic criteria for vasomotor disorders, the Coronary Vasomotion Disorders International Study (COVADIS) Group has proposed standardized definitions and diagnostic criteria.[52,53] Dipyridamole stress echo, cardiac positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR) can also detect CMD. It is clear that a low coronary flow reserve (CFR) is associated with adverse prognosis in men and women.[54,55] Among patients with no obstructive CAD, endothelial dysfunction measured by reduced brachial flow-mediated dilation is independently associated with ischaemia on stress imaging, but not with symptoms.[56]

There are sex differences in the impact of traditional risk factors on IHD risk (e.g. diabetes is associated with a higher IHD risk in women compared to men),[57,58] thus potentially contributing to symptom pathophysiology. Women also have unique risk factors including higher rates of autoimmune/chronic inflammatory conditions that contribute to CMD.[59,60] In women with typical and atypical angina who had systemic lupus erythematosus compared to asymptomatic controls, CMD was highly prevalent as detected by CMR.[61]

Angina is associated with psychological factors

Comorbid psychological factors such as anxiety and depression are highly prevalent in female and male patients with angina, and psychological stress can contribute to and exacerbate angina.[62,63] Vaccarino *et al.*[63,64] have shown that depression is associated with chest pain, regardless of obstructive CAD severity, and in women, but not in men, angina frequency (in the past month) was associated with more mental stress ischaemia (MSI).[65] Although incidence studies have generally not found a gender difference in the link of psychological factors and CAD, the influence of various psychological stressors (such as anxiety, anger, hostility, social support) on triggering microvascular angina in women is understudied. While there is a poor relationship between angina and a positive conventional stress test for myocardial ischaemia, higher angina burden in everyday life is associated with myocardial ischaemia provoked by a mental stress test.[65,66] Mental stress ischaemia is an important prognostic marker with an estimated two-fold increase in mortality, although it is not consistently related to obstructive CAD severity, and abnormal vascular reactivity to mental stress has been implicated.[67,68] Vasoconstriction and microcirculatory dysfunction during mental stress in the peripheral circulation are also related to ischaemia with mental stress,[69] a phenomenon that is more pronounced among women.[70] In parallel, INOCA subjects have greater pulsatile arterial tonometry abnormality during a mental stress test.[71]



Take home figure Autonomic vascular reactivity to mental stress and angina. In a patient susceptible to psychological risk factors, daily life mental stress (1) may induce a state of central autonomic network dysregulation with increased activity in the dorsal anterior cortical cingulate (2) and the associated limbic, subcortical, and medullary autonomic centres, leading to increased sympathetic outflow (3). The resultant vasoconstriction (4) has been demonstrated in coronary and peripheral circulation and leads to ischaemic changes detected by ST-segment changes on the electrocardiogram (regardless of coronary artery disease status) (5a). Increased sympathetic outflow may also disrupt anti-nociceptive pathways in some patients (5b), who are more likely to be women, leading to abnormal cardiac nociception. Both of these scenarios may lead to the symptom experience of chest pain (6).

Angina and the autonomic nervous system

The central and peripheral autonomic nervous systems (ANS) play an important role in emotional regulation, pain processing, and cardiovascular sympathetic outflow to various organs (*Take home figure*). In patients previously referred to as cardiac syndrome X (CSX) in older literature, objective measures of CFR were not present, and measures of myocardial ischaemia inconsistent.[72] It is now believed that a large portion of these patients who have documented ischaemia have CMD despite absence of obstructive CAD. Compared to those with obstructive CAD, abnormal cardiac nociception indicated by higher pain with contrast injection, right ventricle pacing, and adenosine infusion, as well as pain at a lower stimulus intensity was observed in patients with CSX. Whether the exaggerated pain sensitivity is due to abnormal sympathetic activation in the heart vs. abnormal ANS processing of visceral afferent signals is not known.[73,74] Individual differences in pain sensitivity thresholds may also contribute to angina.[75]

Emerging Knowledge

Angina and visceral pain pathways

Myocardial pain signals converge with cutaneous afferent pain signals in the dorsal root ganglion, where slow conducting unmyelinated C-fibres convey dull pain, while fast conducting myelinated A-fibres conduct sharp pain.[76] How these pain signals are generated and why they lead to varying degrees of often vague, visceral sensations is not understood, but in general it is thought that ischaemic myocardial pain mediators such as adenosine, substance P, and serotonin, trigger chemosensitive receptors that transmit pain via sympathetic afferents.[74,77] The ANS

integrates these signals with resultant sympathetic/parasympathetic modulation including, blood pressure, respiration, heart rate, and rhythm changes during ischaemia.

Increased pain sensitivity may be due to abnormal cortical processing of pain signals. Rosen *et al.*[78,79] have reported brain activation in the hypothalamus, periaqueductal grey, thalami, the prefrontal cortex, and the left inferior anterior cingulate cortex (ACC) during angina in patients with ischaemia and obstructive CAD. In contrast, there was a failure of frontal cortex activation in silent ischaemia, although thalamic activation was similar to the angina group,[78] suggesting that abnormal visceral pain processing of afferent pain signals could be contributing to silent ischaemia.[79] Initial data indicate that those with MSI had greater activation in the dorsal ACC (dACC) detected by ^{15}O-water PET compared to those with no MSI.[80] The dACC has extensive connectivity to the insula, amygdala, and autonomic centres, and plays a role in emotional regulation, pain sensitivity, and autonomic cardiovascular responses. Information about relationships between dACC activation, autonomic outflow, and angina is needed.

Treating Angina—Are We Chasing Our Tails?

What do these prior and emerging findings contribute to our interpretation of contemporary understanding of chest pain and IHD in women, as well as studies of PCI for treatment of stable angina in obstructive CAD?[1–3] Specifically, the lack of consistent relation between angina and myocardial ischaemia in obstructive CAD observed in prior decades helps us understand the lack of angina relief despite PCI-related improvement in myocardial ischaemia in the ORBITA trial.[30] Prior research relating angina to the psychological factors of anxiety, depression, and mental stress help us interpret the FAME 2 trial findings that angina improved after patients were told that there was no significant lesion (FFR > 0.8), and angina also improved after patients received a stent to treat a significant lesion,[31,32] due to anxiety-related angina perception and reporting. Thus, although current guidelines recommend PCI for persistent angina in patients with optimal anti-anginal treatment,[81] it remains questionable whether PCI has a true therapeutic effect or merely a placebo effect. In the stable IHD setting, before a patient undergoes invasive coronary angiography, the possibility of recurrent symptoms post-PCI should be discussed with the patient to increase their awareness of the limitations of the procedure. We, respectively, suggest that the current controversy regarding treating angina with PCI is chasing our tails, as current data are consistent with prior knowledge, and therefore not productive. Furthermore, emerging knowledge regarding the cardiac ANS and visceral pain pathways in patients with and without obstructive CAD may offer explanatory mechanisms for these study findings.

Knowledge Gaps

While emerging data implicates mental stress, ANS, and visceral pain mechanisms for angina, a number of knowledge gaps exist. Specifically, why do women have more angina compared to men, despite paradoxically having less obstructive CAD? Are their sex differences in correlations of symptoms with objective evidence of perfusion abnormalities, including low CFR? The mechanistic pathways of how chronic stress may predispose to future development of angina, in the context of sex differences as well as social determinants of health are unclear. The contribution of ANS activation during acute mental stress with resultant haemodynamic and vascular reactivity to angina needs to be investigated with appropriate control groups. Investigation of whether visceral brain activation/deactivation patterns differ across angina and varying degrees of CAD severity, and in comparison, to asymptomatic groups with obstructive CAD, is needed. Standardized mental stress testing using mental arithmetic, anger recall, public speaking task, etc. have been used in the research realm, but have not been translated to clinical practice. Clarifying how physiologic responses to mental stress are influenced by underlying psychological risk factors (such as chronic anxiety and depression) and their contribution to angina burden will help guide novel angina treatment strategies. Blinded clinical trials that target ANS activation should be performed for angina to generate therapeutic guidelines. These mechanistic human studies would involve interdisciplinary investigation among cardiologists, biobehavioural specialists, and anaesthesia/pain specialists to improve angina treatment. An inclusive approach to management of persistent angina would include not only pharmacologic and revascularization therapies, but also lifestyle modification for risk factor control (i.e. smoking cessation, nutrition counselling, cardiac rehabilitation, stress management), along with psychological evaluation and support.

Conclusions

Ischaemic heart disease remains the leading cause of morbidity and mortality among women and men yet women are more often underdiagnosed, have a delay in diagnosis, or receive suboptimal treatment. A gender-bias with regard to lack of recognition of sex differences in presentation of IHD may in part explain these differences in women compared to men. Existing knowledge indicates that often angina does not correlate with myocardial ischaemia or obstructive CAD, and emerging knowledge supports an inclusive approach to chest pain symptoms in women, as well as a more thoughtful consideration of PCI for angina in stable obstructive CAD, to avoid chasing our tails. Emerging knowledge regarding the cardiac ANS and visceral pain pathways in patients with and without obstructive CAD offers explanatory mechanisms. Studies that targets ANS activation should be performed for the outcome of angina using interdisciplinary investigation among cardiologists, biobehavioural specialists, and anaesthesia/pain specialists to improve angina treatment.

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