Title: Stable Coronary Syndromes: The Case for Consolidating the Nomenclature of Stable Ischemic Heart Disease.

Short title: Stable coronary syndromes: a new paradigm.

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Introduction

Angina pectoris, first described by William Heberden in the Royal College of Physicians, London, in 1768, is chest pain of cardiac origin. Despite being a symptom, angina is a disease-based diagnosis (International Classification of Disease, I20). Practice guidelines use somewhat different terms. The nomenclature of the American guidelines includes '*chronic stable angina (CSA)'* (2002) and '*stable ischemic heart disease (SIHD)'* (2012), whereas the guidelines of the European Society of Cardiology (ESC, 2013) refer to '*stable coronary artery disease (SCAD)'*. Thus there are multiple terms and abbreviations for SIHD and cohesion is lacking.

By contrast, 'acute coronary syndrome' (ACS) is a unifying hierarchical term that subtends the distinct sub-groups of unstable angina and myocardial infarction and is used consistently worldwide.

The conundrum of angina in patients with no obstructive CAD

The established diagnostic pathways for patients with suspected angina have been appropriately developed to identify obstructive coronary artery disease (CAD) with a view to evidence-based treatment. In recent years, however, multiple clinical studies have disclosed that more than one third of symptomatic patients do not have obstructive CAD[1]. Further, ischemia may be substantial in this subgroup and the prognosis is not benign[2].

Exclusion of obstructive CAD in a patient with angina presents a conundrum. Angina without obstructive CAD may be frustrating for the patient and the clinician, and in the absence of a unifying diagnosis, treatment becomes empirical and potentially sub-optimal. The lack of

evidence from randomized controlled clinical trials in this sub-group underpins the heterogeneity in management.

Sex association with ischemia and no obstructive coronary disease and prognosis

'Syndrome X' is a historical term stigmatized by its associations with female sex, obesity, and psychology, leading to therapeutic nihilism in the minds of some clinicians. Although reductions in mortality attributable to coronary heart disease (CHD) have been observed in recent decades, no such decline has been observed in younger (<55 years) women[3]. The persistence of risk among younger women may be explained in part by impaired coronary flow reserve (CFR) rather than obstructive CAD[1].

Given this vexing state-of-affairs[2,3], the recent White Paper by Bairey Merz *et al*[1] is a welcome development. The authors cite a new term for the sub-group of patients with ischemia and no obstructive CAD (INOCA [Ischemia and No Obstructive Coronary Artery Disease]), the gaps in evidence and areas for future research.

Diagnostic tests for CAD and their limitations for identifying the etiology of INOCA

Historically, anatomical and functional tests were developed for the detection of obstructive CAD and validated against the coronary angiogram. Increasingly, invasive examinations include adjunctive measurements, such as fractional flow reserve (FFR), however, neither angiography nor FFR evaluate microvascular function.

Given the clinical focus on obstructive CAD, only a minority of invasive cardiologists are competent in the use of interventional diagnostic procedures, including pharmacological tests of coronary endothelial function and vasospasm by intra-coronary administration of

acetylcholine and guidewire-based tests of coronary vasoreactivity (i.e. CFR) and microvascular resistance, respectively. This gap is underpinned by the lack of evidence from randomized trials that the use of such tests improves patient wellbeing and healthcare costs. Stress magnetic resonance imaging and positron emission tomography have diagnostic utility for coronary microvascular dysfunction, but as with the invasive diagnostic tests, evidence of patient benefits from randomized trials is lacking.

An emerging focus on direct imaging of CAD is highlighted by the U.K. NICE guideline-95 update (November 2016)[4] which recommended CT coronary angiography (CTCA) as the first line diagnostic test in patients with angina but without prior CHD. NICE-95 reflects the results from recent trials involving CTCA. Compared with functional testing, the use of CTCA is associated with an increased use of evidence-based therapy and, potentially, a reduction in the risk of MI.

Adoption of CTCA as a first line test in patients with chest pain is increasing worldwide. In the U.K., the NICE-95 update has major implications not only regarding access to CTCA, but also for the management of symptomatic patients without obstructive CAD, the majority of whom are women. Some of these patients may have microvascular or vasospastic angina and the exclusion of obstructive CAD by CTCA may lead to false reassurance.

The SCOT-HEART quality of life analysis highlights this conundrum[5]. Symptoms and quality of life assessed at baseline and 6 months improved *less* in patients assigned to the CTCA-guided strategy as compared to standard care. I was a member of the Trial Steering Committee and this result was unexpected. One potential explanation could be false reassurance for those patients with INOCA, in whom angina therapy may have been

discontinued. This analysis refuted the hypothesis that symptoms and quality of life would improve with a CTCA-guided strategy and it conflicts with the NICE-95 update.

The case for unifying terminology

In summary, the conundrums relating to the lack of decline in CHD mortality in younger women, inconsistent disease nomenclature, focus on anatomical imaging, heterogeneous management of disease sub-groups (i.e. INOCA and related gaps in clinical evidence), unexpected trial results, and controversial guideline recommendations are '*on my mind*'.

The diagnostic classifier 'acute coronary syndrome' is a significant term that subtends the distinct clinical presentations of patients with acute coronary disease. Considering SIHD and its disease sub-groups, there is a critical lack of a unifying high-level classifier. In my opinion, this gap in terminology associates with some of the issues outlined above. In the absence of simple, consistent nomenclature, advances in our understanding of disease subgroups such as INOCA, which is a current hot topic in cardiology, are less well placed for translation into practice. Given the focus on obstructive CAD, this gap could potentially enhance under-recognition and under-treatment of patients with INOCA. The term 'acute coronary syndrome' has high-level, unifying significance so it seems logical to propose the term '*stable coronary syndrome'* (Figure 1). This term would sit well in the hierarchical classification of IHD and serve to highlight that angina is not synonymous with obstructive CAD and that a disorder of coronary artery function may be relevant.

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Conflict of Interest Disclosures

The author is employed by the University of Glasgow which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and treatment of angina. The companies include Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Menarini Pharmaceuticals, and Siemens Healthcare.

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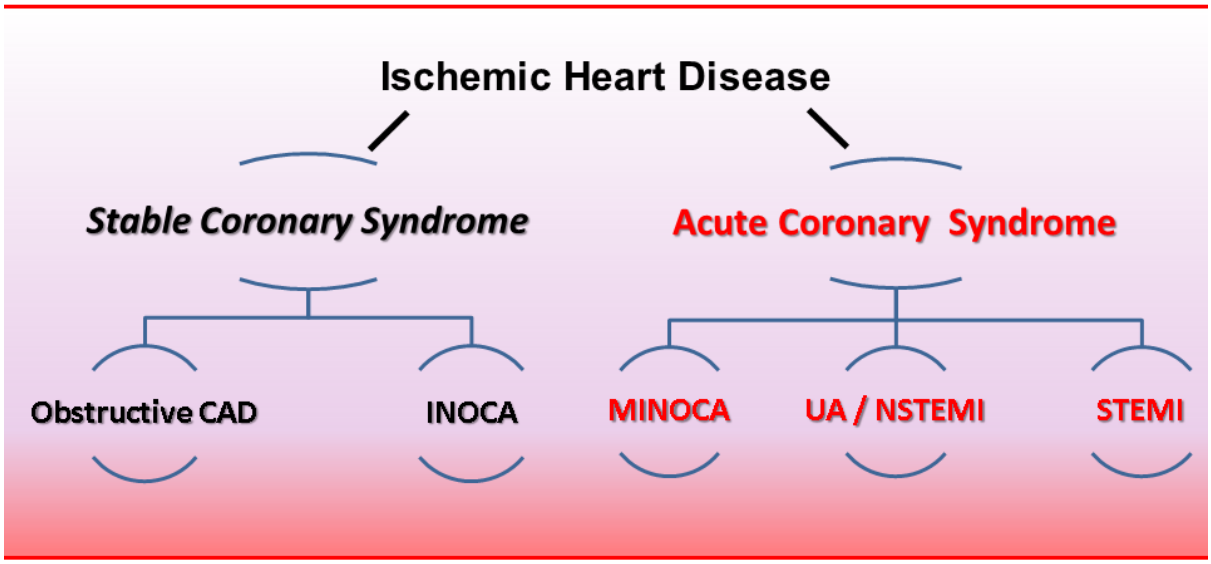
Figure Legend

A hierarchical nomenclature of diagnostic terms for coronary disease subgroups that cause ischemic heart disease.

Stable coronary syndromes and acute coronary syndromes are second order terms that broadly encompass the IHD subgroups including obstructive and non-obstructive CAD and disorders of coronary artery function including microvascular and vasospastic angina.

Key: CAD coronary artery disease; INOCA - ischemia and no obstructive coronary artery disease; MINOCA – myocardial infarction and no obstructive coronary artery disease; UA – unstable angina; NSTEMI - non-ST-segment elevation myocardial infarction; STEMI - ST-segment elevation myocardial infarction.

Figure 1.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STEMI