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Non-invasive Risk Stratification for Coronary Artery Disease: Is It Time for Subclassifications?

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Abstract

Purpose of Review Coronary artery disease (CAD) is the leading contributor to cardiovascular disease; it is the most prevalent non-communicable disease globally and has high morbidity, mortality and health care cost. Risk stratification is defined as prevention or containment of disease prior to it occurring or progressing, and non-invasive surrogates include history, examination, biomarkers and non-invasive imaging. This review aims to highlight advancement in current diagnostic strategies and explores gaps for CAD secondary to atherosclerosis and non-obstructive vascular diseases.

Recent Findings Cardiac risk scores have largely proven inadequate in risk stratifying heterogeneous patient populations. Greater emphasis should also be provided to posttest risk stratification. Non-invasive imaging with MRI is the most accurate but least cost efficacious presently due to availability and expertise. Echocardiography and nuclear imaging have good accuracy, but radiation limits the latter. Novel echocardiographic technologies may increase its appeal. Cardiac CT angiography is increasingly promising.

Summary Non-invasive and minimally invasive imaging has significantly influenced the cost-efficacy trajectory of coronary artery disease diagnosis and management. Recent studies suggest that future guidelines will incorporate more subclassifications from the findings of these novel technologies and for more diverse patient demographics.

Keywords Cost efficacy · Coronary artery disease · Minimal invasive imaging · Non-invasive imaging · Risk score · Risk stratification · Screening

Introduction

Coronary artery disease (CAD) is a broad term that incorporates atherosclerotic, non-atherosclerotic occlusive and vasospastic etiologies. Atherosclerosis, by far the commonest contributor to CAD, remains a major cause of death and disability, globally. Although its prevalence may have declined in Western countries, the effects of diet and lifestyle shifts, obesity, diabetes and ageing populations may have halted and in some case reversed this trend, particularly in developing countries [1]. There are many different approaches to prevent atherosclerosis and related mortality, including modification of risk factors, screening and early detection, to early and effective treatments. Vasospasm is largely diagnosed through exclusion of obstructive CAD and other causes are uncommon.

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Obviously, the easiest and cheapest way to (non-invasively[1]) identify asymptomatic patients at increased absolute risk for CAD is to undertake a comprehensive CAD risk assessment, incorporating risk factors, including age, gender, obesity, plasma lipid profile, blood pressure, diabetes, kidney function, family history of CAD and smoking [2–7]. This comprehensive strategy is more effective than assessing risk factors individually, due to interactions between risk factors. For example, a 'normal' LDL cholesterol level in an individual at high risk for CAD (e.g. with diabetes) does not negate the utility of lipid lowering. There are now many different scoring systems available, all of which individually have their advantages and disadvantages, especially when applied to an individual patient. However, in principle, each provides an opportunity to match the intensity of preventive strategies to the patient's individual risk to maximize the potential benefits of intervention in some individuals and, at the same time, reduce the needless cost and potential for harm from overtreatment in others. For the most part, the intensive treatment of individuals at high absolute risk of CAD obviates the utility of additional non-invasive testing. Equally, in individuals at low risk, additional non-invasive testing is unwarranted. However, between these extremes there remains a large number of individuals with borderline or intermediate risk, in whom additional non-invasive risk stratification may be warranted to *'subclassify'* risk/prognosis and direct future therapy.

In patients who are evaluated for chest pain (but do not have an acute coronary syndrome), additional non-invasive risk stratification also potentially provides new opportunities for diagnosis, prognostication, treatment modifications and improved clinical outcomes [8–10]. In particular, the need for invasive angiography, interventional procedures and/or hospitalization is substantially influenced by the presumed likelihood and severity of flow limiting stenoses (e.g. >70%). Despite this, many patients undergoing elective coronary catheterization are found to not have occlusive CAD. Towards the goal of more accurately assessing risk, non-invasive screening in stable (non-acute) CAD is increasingly used in clinical practice, including stress testing, echocardiography, CAC scores, CT and MRI stress perfusion.

Importantly, not all comparator diagnostics have been tested with other modalities in mixed populations to derive standardized pretest risk and thus follow through to posttest risk. This point is the basis for a call towards subclassifcation [8]. Numerous reviews have focused on symptoms, electrocardiography and conventional stress imaging [2–7, 11]. In this review, we will focus on the utility of advances in risk scores, non-invasive functional and anatomical imaging for CAD and the different opportunities it affords in managing atherosclerotic and vasospastic CAD; and also to subclassify patients post testing.

[1] Non-invasive strategies in this review incorporate risk scores, functional and anatomical information on CAD; imaging utilizing injected contrast, radioactive isotopes or drugs labelled 'minimally invasive' are also included.

Risk Scores

Risk scores are important key elements that enable precise diagnostic evaluation for guiding treatment and prognosis. In symptomatic patients with stable coronary artery disease, the key lies in accurate determination of the pre-test probability (PTP) to identify the next best step per se to avoid unnecessary risks and/or costs. Both the European [9] and American guidelines [6] recommend the Duke clinical score (DCS) and modified Diamond–Forrester (D–F) model [1, 8] as the preferred models to calculate PTP. More recently, the modified D–F model (basic model) was re-evaluated in an all-comer, unselected cohort of 3903 patients suspected of angina [10]. This retrospective, observational study, demonstrated a substantial overestimation of the likelihood of CAD. The inclusion of clinical risk factors (clinical model) resulted in a minor, albeit, statistically significant improvement particularly in discriminating between patients with low and moderate probability of obstructive CAD. The prognostic abilities of both the basic and clinical models were similar, demonstrating that patients with a low PTP of obstructive CAD have a good prognosis. This finding is consistent with other studies that have used the current PTP models [12, 13]. Clearly, pre-selection of patients with stable CAD for further testing remains a work in progress.

Non-invasive Anatomical Imaging of CAD with Computed Tomography

There are a number of potential markers and imaging modalities available to improve the diagnostic accuracy in stable CAD. Among the various modalities of imaging discussed in this review, stress echocardiogram and CT coronary angiography have been highlighted. Indeed, the latter has been integrated into the NICE guidelines [14, 15] as the first-line test in all patients suspected of stable CAD with the removal of the PTP model. The role of functional imaging in the NICE guidelines remains as a complementary two-tiered approach in those who have indeterminate CAD. This was based on the high sensitivity of CTCA in anatomical assessment of CAD as well as cost effectiveness [16]. Beyond these advantages, the ability for CTCA to characterize plaques and facilitate downstream preventive treatment may confer a better prognosis from the clinical standpoint. The CONFIRM registry revealed a survival benefit with the initiation of statin therapy in patients with subclinical atherosclerosis. The Prospective Multicentre Imaging Study for evaluation of chest pain (PROMISE) study compared anatomical testing to functional

testing (FT) in low to moderate risk symptomatic patients with potential CAD [13]. Both approaches were comparable with similar discriminatory abilities in predicting future cardiovascular events with FT being more specific but much less sensitive as compared to coronary artery calcium score [17]. Notwithstanding, despite the neutral impact on clinical outcomes over a median of 25 months, in the prespecified analysis of the PROMISE study, patients with high-risk plaques, with features, such as positive remodelling, low CT attenuation and "napkin-ring" sign, conferred a significant increased risk of future major adverse cardiovascular events (MACE), independent of cardiac risk factors. In fact, there is incremental value in risk assessment of this tool in women and in patients with non-obstructive CAD.

To date, the most compelling data for the role of CTCA in stable CAD emanates from the 5-year follow-up of the SCOT-HEART study [18]. This was an open-label, multicentre, parallel-group trial, that randomized 4146 patients with stable CAD to the addition of CTCA to standard care as opposed to standard care alone. It demonstrated a significant difference in clinical endpoints, primarily driven by a lower rate of nonfatal myocardial infarction, despite similar degrees of intervention in both groups. Notably, more preventive therapy was seen in the CTCA arm, which is imperative as a significant proportion of clinical events occurred in the patients with non-obstructive CAD (seen in SCOT-HEART and PROMISE). Whether CTCA remains superior to an imaging approach is still left to be seen though as the comparator to CTCA in the SCOT-HEART study was predominantly a stress test with only approximately 10% of patients undergoing stress imaging.

Comparison of the current three international guidelines (ACC/AHA, ESC and NICE) was evaluated from the cohort of the PROMISE and SCOT-HEART studies [19••]. The symptom-based strategy of NICE classified a higher proportion of low-risk patients, improving diagnostic discrimination as compared to the Bayesian risk-based approach of the American and European guidelines.

Beyond imaging means, a widely studied pivotal mechanism of atherosclerotic CAD is endothelial dysfunction. The presence of endothelial dysfunction has been shown to predict cardiovascular events independently from traditional risk factors in stable symptomatic patients with CAD [20, 21]. Moreover, the lack of improvement of this parameter with intervention is linked with a higher risk of future events [22]. Notwithstanding, endothelial function, commonly measured as reactive hyperemic index (RHI) using peripheral arterial tonometry in the iPOWER study, has not been shown to correlate consistently in women with coronary microvascular dysfunction and in women with angina with no obstructive coronary artery disease [23], which highlights the difficulty in risk stratification in the increasingly recognized cohort of patients with angina with no obstructive coronary artery disease (NOCAD).

A systematic review of ten studies, involving 53,108 patients, which showed both the development and validation of their PTP model, highlights the difficulty in generating a single higher-performing model, with considerations to the heterogeneity of populations and the availability of more contemporary tests. Any contemporary risk score needs to be based on readily available risk factors and tools that are applicable to a wide range of patients and balanced with cost-effectiveness to maintain a sustainable healthcare program. Finally, irrespective of the investigational approach, the current paradigm calls for a need to evaluate aggressive prevention strategies in this patient cohort, knowing that a substantial proportion of myocardial infarction can occur in patients with non-obstructive CAD.

Non-invasive Functional Imaging for Stable CAD

In the era of multi-modality imaging, there is a spectrum of choice to establish the diagnosis of ischemic heart disease and subsequently quantify ischemic burden, prognosis and tailor management [8, 24, 25]. Pretest probability should determine the first choice of test; however, not all groups will necessarily derive the same predictive probabilities from these binary tests [26]. Individualized models remain distant. Some advancement should be factored in as they develop.

Cardiac magnetic resonance imaging (CMRI) arguably offers the best sensitivity and specificity in terms of diagnosis and there is evidence for prognostication in term of the presence of fibrosis as evidenced by the CE-MACR 12 and MR-IMPACT 11 trial [27]. The main consideration with CMR is that the evidence of benefit arises from institutions with significant expertise and resources. Although the duration of studies was reduced sufficiently to be clinically efficient, the availability of expertise and resources are not readily available to many tertiary centres. Rebates are also a significant issue, especially in Australia, as a stress perfusion is not a rebateable item under Medicare. Additionally, the use of adenosine is not considered more physiological than exercise as a stressor for ischemia. Patients with claustrophobia and an EGFR under 30ml/min/m^2 are also excluded from this modality.

The modality of choice would thus be one that is widely available, with adequate expertise, cost effectiveness and minimal radiation, whilst maintaining its diagnostic and prognostic accuracy. Stress echocardiography is the modality that meets the criteria defined above. The NICE guidelines however suggest that CT angiography would be a first-line investigation due to its high sensitivity. The results from the latest SCOT-Heart trial [28••] would justify this decision to some extent but there is a radiation dose associated with CT angiography, and it has a poor specificity and ability to quantify ischemia, leading to increase in downstream investigations.

It could also be argued that a negative stress echocardiogram, achieving sufficient workloads, carries a good prognosis irrespective of its sensitivity, and treating the risk factors of those patients with a higher intermediate probability and a negative stress echo would suffice. A normal stress echo is associated with an annual risk of 0.4–0.9% for cardiac mortality or acute myocardial infarction—based on a total of over 11,000 patients [29]. However, it would be prudent to concentrate on improving the sensitivity of stress echocardiography to make it an ideal stand-alone first-line modality for identifying, prognosticating and tailoring treatment for stable coronary artery disease, and in conjunction, improving imaging surrogates for the coronary arterial bed, such as calcium scoring and peripheral imaging.

Technology has evolved that can improve the sensitivity of stress echocardiography to that of CT angiography. First, perfusion stress echocardiography with flash imaging (myocardial contrast echocardiography) as illustrated in an earlier version of this journal has certainly shown to have improved the sensitivity of stress echocardiography. In a study of 1252 patients undergoing dipyridamole stress echocardiography and perfusion imaging, the event free survival when there were no perfusion or wall motion abnormalities over a 25-month follow-up was in the order of 97.9%. When there were perfusion abnormalities but no wall motion abnormalities, the event free survival in that period reduced by almost 10% [30].

Another major innovation in echocardiography are 3D matrix transducers with probe dimensions similar to 2D transducers whilst maintaining a relatively high frame rate of more than 25 frames per second with single beat acquisition. This has resulted in image quality similar to 2D images but with the added benefits of 3D acquisition of avoiding the geometrical assumptions of LV volumes inherent in 2D imaging. This technology has been combined with the other major development in echocardiography which has been the evolution of deformation imaging, in particular speckle tracking. A recent study by Dugdus et al. [31] evaluated the utility of both these technological advances in stress echocardiography. In this study, 120 patients who had coronary angiography after a positive non-invasive test were evaluated with a 3D assessment of deformation using a number of parameters, including global longitudinal strain (GLS) and global area strain (GAS) at rest. Two groups were created according to Gensini score based on the invasive angiography: noncritical stenosis (Gensini: 0–19) (n = 84) and critical stenosis (Gensini ≥ 20) (n = 36). Global longitudinal strain and all other strain parameters were significantly worse in patients with the critical CAD group compared with the noncritical CAD group.

Receiver operator characteristic analyses were performed to find out ideal strain cut-off values to detect severe coronary artery disease defined as Gensini score ≥ 20. A GLS value of ≥ 10 has 88.9% sensitivity and 92.9% specificity; A GAS value of ≥ 21 has 97.2% sensitivity and 88.1% specificity to detect critical CAD.

Non-invasive left ventricular (LV) pressure-strain loop (PSL) provides a novel method of quantifying myocardial work (MW) with potential advantages over conventional global longitudinal strain (GLS) by incorporating measurements of myocardial deformation and LV pressure. In essence, the measurements would be less dependent on prevailing loading conditions. The role of myocardial works in stress echocardiography is currently being evaluated and certainly holds promise in further enhancing the diagnostic and prognostic utility of stress echocardiography. The future of stress echocardiography is a combination of contrast imaging and native imaging with 3D deformation imaging with the possible utilization of myocardial works. The use of contrast imaging would alleviate the problem of image quality and myocardial contrast enhancement enables the detection of perfusion abnormalities, in theory, at an earlier stage of the ischemic cascade. Deformation imaging and myocardial works in the setting of good image quality would enhance the detection of subclinical ischemia, possibly even at rest.

Risk Stratifying Nonobstructive CAD

Numerous mechanistic studies utilizing coronary flow reserve (CFR) assessment have demonstrated the presence of subclinical coronary microvascular dysfunction (CMVD) in asymptomatic smokers with no CAD [32], subjects with hypercholesterolemia without CAD [33–35] and in patients with diabetes mellitus [36–38]. Similarly, CMVD has been observed in obese subjects compared to non-obese participants [39] and in patients with hypertension and even borderline hypertension [40, 41]. Assessment of coronary microcirculation with CFR incorporates both the epicardial and microcirculatory function, and therefore an abnormal CFR may be due to abnormal endothelial function or CMVD or both in patients with significant cardiovascular risk factors [32, 35, 38, 42].

A study by Kaufmann et al. [32] reported normalization of CFR using vitamin C, an antioxidant agent, in smokers compared to non-smokers. This finding supported the hypothesis that the deleterious effects of smoking on vascular function might be mediated to some extent by an increase in oxidative stress. A significant inverse correlation between CFR and levels of lipid sub-fractions (LDL-cholesterol) has also been found in patients with elevated total blood cholesterol, again linking abnormal coronary vascular function with lipid profile [32, 33]. In addition, patients with diabetes mellitus have impaired endothelial function, which might increase their susceptibility to vasoconstriction, atherosclerosis and atherothrombotic sequelae [37, 43].

Clinical manifestations of CMVD without epicardial CAD include exertional angina, typical ST-segment depression on

exercise stress testing and angiographically normal epicardial coronary arteries. It has been customary to use the term "Syndrome X" to describe these manifestations following its first description by Kemp in 1973 [44]. However, another appropriate description was coined by Cannon [45], with the term "chest pain with normal coronary angiogram" (CPNCA) describing aptly their clinical presentation. Approximately 40% of patients undergoing coronary angiography with signs and symptoms of ischemia, including its demonstration via myocardial perfusion imaging, stress echocardiography or stress electrocardiography, have normal or non-obstructive CAD [46–48]. This chest pain syndrome is more prevalent among females and might have inconsistent response to nitrates. Coronary microcirculatory dysfunction is thought to be the key pathophysiologic contributor to the symptoms since these patients present with a reduced CFR and metabolic evidence of myocardial ischemia [49, 50].

The diagnostic dilemma and the economic considerations associated with evaluation of anginal symptoms in women have garnered interests in recent years [51–54]. In the Women's Ischemia Syndrome Evaluation (WISE) study [55], the relationship between CFR and late major adverse cardiovascular events was evaluated in 189 women referred for investigation of coronary ischemia. The authors found that CFR was a predictor of major adverse outcomes in these women regardless of the presence or absence of obstructive CAD or multiple cardiac risk factors. In the same study, Thomson et al. [56] reported that cardiac magnetic resonance (CMR) myocardial perfusion reserve index (MPRI) correlated well with coronary flow velocity reserve (CFVR) as measured conventionally with adenosine reactivity in women with suspected coronary ischemia and atherosclerotic risk factors. Therefore, an abnormal microvascular response to adenosine in women with underlying CMVD could also be assessed non-invasively using CMR MPRI.

The prognosis of patients with CMVD in the absence of obstructive CAD appears to be good with rates of major cardiovascular events comparable to those of the general population [57, 58]. However, in 20–30% of patients, there might be progressive worsening of symptoms, or even appearing at rest, which significantly impairs quality of life [59]. In this group of patients, particularly women [60], and those with a minimally elevated cardiac troponin [61], impaired CFR is associated with adverse cardiovascular events.

In summary, CMVD has been documented in asymptomatic individuals with cardiovascular risk factors as well as in patients with classical anginal symptoms and a normal coronary angiogram, the latter being predominantly in females. Follow-up studies suggest that CMVD predicts future cardiac events in the absence of obstructive coronary disease.

Weighting Risk — Where is the Money for the Future?

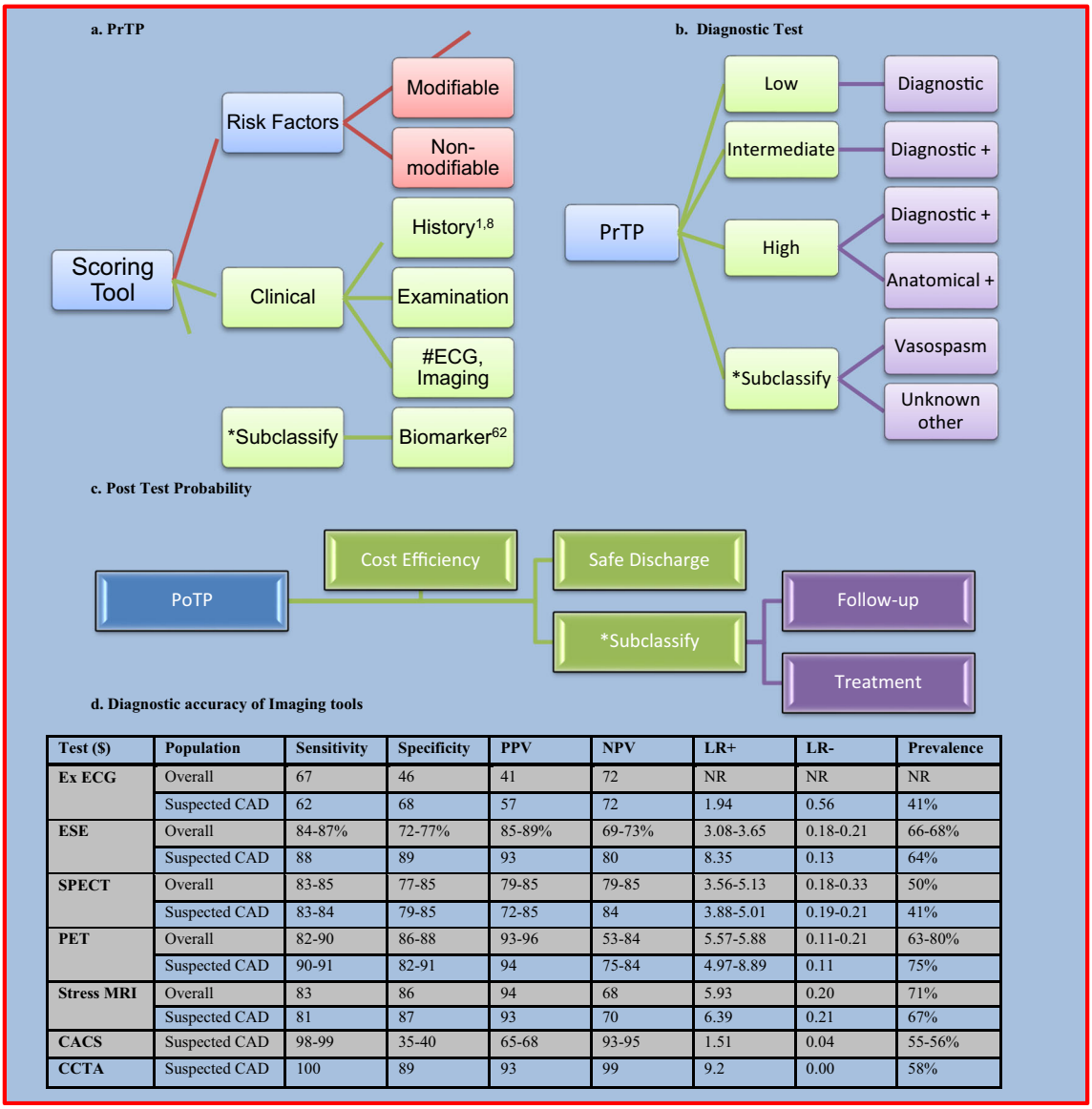
The foundations of risk stratification are to first establish evidence of CAD (prevalence) and then to establish clinically significant CAD (burden). The clinical intentions are preventive (screening), i.e. disease prior to onset 'primordial' or, prior to presentation 'primary' or to prevent progression 'secondary' prevention; and/or institute therapeutic options. Weighting risk and differences in populations need further exploration as we lay the foundations for subclassifying non-invasive strategies (Fig. 1).

The Challenge of Probability

Although there are many different tests to detect CAD (detailed above), the greatest challenge to any consideration of their potential utility of testing must begin with an understanding of their baseline risk (known as pre-test probability; PTP). In all cases above, the pretest likelihood of CHD in a population with certain characteristics influences the posttest risk of having CHD. A positive result is likely to be a true positive result (i.e. a low false-positive rate) in a population with a high pretest risk for CHD, while a negative test is likely to be falsely negative (Fig. 1). Conversely, in a population with a low pretest risk for CHD, a positive test is only weakly correlated with the presence of CHD (i.e. has a high false-positive rate), while a negative test is highly predictive of the absence of CHD. For example, a stress test result (positive versus negative) has the greatest impact to differentiate high versus low posttest probability of disease in a population with an intermediate pretest probability of disease. Thus, the probability of CHD following a test is directly related to the specific population evaluated and the results of the test. Improvements in pre-test assessment using validated risk engines will play an important role in improving the utility of non-invasive testing for CAD.

Combination Testing

The different modalities for non-invasive screening for CAD lend themselves to a combinatorial approach. In particular, the combination of functional studies (e.g. stress echo) with anatomical studies (e.g. CT angiography) offers improvements in specificity. Equally, the combination of CTCA with a simultaneous cardiac perfusion CT may fill the same role. Equally, combining CAC scoring for risk stratification followed by CCTA has been used in some studies to select patients for coronary angiography. A recent study of 23 patients inferred that measures of coronary physiology were more likely correlated with symptoms than anatomy by itself [62]. A network analysis of 18 low risk acute coronary syndrome and 12 suspected stable CAD patients support that without symptoms



d. Diagnostic accuracy of Imaging tools

Test ($)	Population	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Prevalence
Ex ECG	Overall	67	46	41	72	NR	NR	NR
	Suspected CAD	62	68	57	72	1.94	0.56	41%
ESE	Overall	84-87%	72-77%	85-89%	69-73%	3.08-3.65	0.18-0.21	66-68%
	Suspected CAD	88	89	93	80	8.35	0.13	64%
SPECT	Overall	83-85	77-85	79-85	79-85	3.56-5.13	0.18-0.33	50%
	Suspected CAD	83-84	79-85	72-85	84	3.88-5.01	0.19-0.21	41%
PET	Overall	82-90	86-88	93-96	53-84	5.57-5.88	0.11-0.21	63-80%
	Suspected CAD	90-91	82-91	94	75-84	4.97-8.89	0.11	75%
Stress MRI	Overall	83	86	94	68	5.93	0.20	71%
	Suspected CAD	81	87	93	70	6.39	0.21	67%
CACS	Suspected CAD	98-99	35-40	65-68	93-95	1.51	0.04	55-56%
CCTA	Suspected CAD	100	89	93	99	9.2	0.00	58%

Fig. 1 Subclassification of risk stratification and cost efficiency. The process of risk stratification undergoes three phases. New attempts to subclassify patients must factor in cost efficiency. Here the posttest advice on safe discharge, follow-up or instituting management requires the novel consideration. **a** PTP requires a risk scoring system and a formal consultation. Straight forward cases can be triaged in primary care, more complex cases require specialist input. An opportunity to subclassify risk based on novel use of biomarkers targeting the generic whole system and targeted physiological changes can add a new dimension to management; **b** Diagnostic modalities include functional exercise stress vs pharmacological (EST, ESE, MPI, MRI, SPECT) or anatomical invasive vs non-invasive (CorA, CCTA, CACS). Subclassification into vasospastic angina, functional chest pains, very low or very high risk or unknown are areas to explore and to add greater confidence for follow-up; **c** PoTP is the area most likely to require a novel approach. Once a test is carried out high posttest probability is required to guide reducing future MACE. Discharge documentation is critical, guideline information factoring this information could facilitate this; **d** Diagnostic accuracy of imaging tools must be factored with availability, reproducibility, cost, and risk. Only stress echocardiography meets this requirement. Radiation, cost, and availability influence other tests. CT Calcium scores and coronary angiography will play increasing roles as stand-alone or adjunct tests when we can quantify atherosclerotic burden accurately. # Uniform resting test all patients. However, it is inadequate as a screening tool, with poor sensitivity and specification for the presence and severity of underlying CAD and/or its prognosis. Indeed most coronary events occur in individuals without prior ECG abnormalities. Nonetheless, it provides an important baseline upon which future ECG may be judged. Stress ECG increases accuracy; however, pretest risk still influences prognosis, e.g. false positive in some populations at low risk, asymptomatic without known CAD. * Novel avenues for further subclassification into **a.** CAD documented/likely, risk (low to high); **b** Vasospasm, representation risk (low to high). **$** Data presented as percentage (%). CTCA low dose data provided *See appendix H reference 8 for breakdown of data source. Abbreviations*: ACS – acute coronary syndrome; CAD – coronary artery disease; CaS/CACS – coronary artery calcium score; CCTA – coronary computed tomography angiography; CorA – coronary angiography; ECG – electrocardiography; Ex ECG – exercise elctrocardiography; ESE exercise stress echocardiography; LR+ – positive likelihood ratio; LR– – negative likelihood ratio; MPI – myocardial perfusion imaging; MACE – major adverse cardiac events; MRI – magnetic resonance imaging ; N/A – not applicable; NPV – negative predictive value; NR – not reported; PET – positron emission tomography; PoTP – posttest probability; PPV positive predictive value; PrTP (PTP) – pretest probability; SPECT – single-photon emission computed tomography; vs – versus

and lower risk benefit from functional test. In symptomatic suspected stable CAD patients this strategy may reduce downstream angiography but data on MACE is unclear. It remains unclear if the additional cost involved in multiple testing will balance a reduction in unnecessary invasive angiography procedures or other investigations [63]. What is becoming clear is that functional and anatomical tests provide diagnostic capacity but also risk management information. For example, suspected CAD with a negative high workload functional test and evidence of early atherosclerosis requires additional secondary prevention considerations. Cost and radiation are issues to grapple with. Older technology providing non-invasive surrogates of vascular and coronary disease that has never seen widespread clinical utility [64, 65] may warrant revitalising particularly if matching with new advancements could improve capabilities.

Novel Thinking and Subclassification

Cost efficiency has to be at the forefront of planning. The demography in the developed world sees a diverse racial and socioeconomic population at medical encounters. The PTP may not adequately factor in risk [1]. Biomarkers that provide information on vascular health and vulnerability that are novel andhighlight risk in some groups (e.g. South Asian lipid profile highlight heightened risk within traditional models for this group) are being explored but are a long way from the bedside [66–69]. Outside these novel concepts, the greatest avenue for benefit in non-invasive imaging is subclassifying information. The first step is to determine who are at the lowest risk and when future screening is warranted; step 2 is to improve communication with primary care on patients at intermediate to high risk and instituting preventive and defining therapeutic measures; and step 3 is to accurately diagnose vasospastic angina and reduce representations. This would likely entail that individual health clusters must invest in prospective population data to feedback into pre and posttest scoring tools [3, 70] when new information on CAD burden could be relevant.

Conclusion

Many individuals with CAD have minimal or no symptoms, and their first clinical manifestation may be their last. Identifying these individuals while they are asymptomatic potentially provides an opportunity to improve their outcomes. No significant differences may be found in any one modality in comparison to another. Availability, expertise, cost and safety of reuse will determine the initial modality. Greater avenues for subclassification will develop with accurate pretest and posttest scoring based on clinical information. Several areas remain challenges. The role of risk scores in heterogeneous populations and biomarkers are inadequately tested. Presently, they provide data to predict group trends in populations but have unclear individual translational capacity. Applying greater pathophysiological associations could also be important. Finally, advanced testing can be relatively expensive. When factoring in healthcare systems with limited budgets, it would make sense for subclassification in guidelines to also incorporate strategies for basic '*more important contextual*' interventions.

Compliance with Ethical Standards

Conflict of Interest P. Iyngkaran, S. Noaman, W. Chan, G. Mahadavan, M.C. Thomas and S. Rajendran have won independent and governmental research funding. None pose a conflict of interest for this review.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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