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Risk stratification for coronary artery disease in multi-ethnic populations: Are there broader considerations for cost efficiency?

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Abstract

Coronary artery disease (CAD) screening and diagnosis are core cardiac specialty services. From symptoms, autopsy correlations supported reductions in coronary blood flow and dynamic epicardial and microcirculatory coronaries artery disease as etiologies. While angina remains a clinical diagnosis, most cases require correlation with a diagnostic modality. At the onset of the evidence building process much research, now factored into guidelines were conducted among population and demographics that were homogenous and often prior to newer technologies being available. Today we see a more diverse multi-ethnic population whose characteristics and risks may not consistently match the populations from which guideline evidence is derived. While it would seem very

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unlikely that for the majority, scientific arguments against guidelines would differ, however from a translational perspective, there will be populations who differ and importantly there are cost-efficacy questions, *e.g.*, the most suitable first-line tests or what parameters equate to an adequate test. This article reviews non-invasive diagnosis of CAD within the context of multi-ethnic patient populations.

Key words: Cost efficacy; Coronary artery disease; Coronary heart disease; Ethnicity; Outcomes; Risk stratification

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Core tip: Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Globalisation has seen an epidemiological shift in demographics and risk for populations. In planning a cost-effective health service it is important to understand demographic risk and variables in interpreting and managing CAD.

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INTRODUCTION

The lay term “Heart Attack”, implying coronary heart disease (CHD) is associated with significant anxiety among all communities. The first descriptions for ischemic heart disease (IHD) can be traced back to Homer and many other ancient civilizations. In Western medicine “Angina Pectoris” as first described by Heberden was derived from Latin “infection of the throat”, Greek “strangling” and Latin “pectus or chest”, took a century to consolidate its nature as a syndrome, by Osler and focus on the coronary arteries^[1-5]. As clinical medicine, physiology and pathology, three pillars of health sciences coalesced, clinicopathophysiology of diseases became the norm in clinical discussions. Further collaborations between cardiologists, epidemiologists and biostatistician in the 1940’s paved the way for the Framingham Study, the first to put a numerical face to coronary artery disease (CAD) by objectively quantifying risk factors^[6]. Subsequent evolutions were in diagnosis, therapies and now cost efficacy.

Australian cardiology practice today is fundamentally different, with new clinical paradigms in CAD emerging while traditional scientific collaborations have somewhat diminished. Examples include variations in symptoms as with angina equivalent symptoms, clinical impact of risk factors and epidemiology for pathological dynamism of coronary vascular tone. This manifests as presentations and rates of progression outside traditional models. These differences can be seen within racial or socioeconomic groups and more importantly between groups who have never been formally enrolled into studies but are now mainstay in cardiology clinics from migration and other factors.

When CAD is suspected referral for cardiac services is made for risk stratification. From the history, patients acquire a risk score that guides conformation *via* a physiological and anatomical test of the coronary arteries. Presently there are no conclusive guidelines that address the cost efficacy of risk stratifying multi-ethnic patients from presentation to diagnosing CAD should they not be represented in guideline derived studies. This review is focused on exploring the paradigm that may exist when treating a diverse population for CAD from the constraints of traditional evidence. The critical question is whether a one shoe fits all approach is sufficient to answer the questions in a multiethnic, broad aged and demographically diverse populations. We focus on the Health system in the Western suburbs of Melbourne.

DIVERGENT CORONARY ARTERY DISEASE EPIDEMIOLOGY IN DEVELOPED NATIONS

CAD the largest contributor to cardiovascular diseases (CVD) with 46% male and 38% female global CV deaths, is also the most prevalent non-communicable disease and greatest cause for morbidity and mortality worldwide; has common denominators in diet, obesity and physical inactivity which if eliminated can reduce risk by > 80%, including those with diabetes mellitus and stroke. The chronology of CAD from early observational studies has revealed temporal associations in its natural history, associated risk factors and with interventions (“primary”, “secondary” and even “primordial” strategies). Consequences of CAD rest with the burden of IHD and its sequelae, measured with years of life lost from death and years of disability lived with nonfatal acute myocardial infarction (MI), angina pectoris, or ischemic heart failure. Globally total age standardized IHD incidence and mortality rates have reduced, increases in the global burden of IHD has developed predominately from population growth, aging and discrepancies in regional socioeconomic development^[6,7].

The greatest trend in the West today is regional divergence where prevalence peaked in the last century, but with increases in both prevalence and burden in Asia, Middle East and lower socioeconomic regions. Since 1990 there was 35% increase in CAD related deaths worldwide to 7 million (Figure 1). Geography, ethnicity and gender are factors that influence incidence, prevalence of risk factors and overall risk. Death rates (per 100000) vary 20 times from 35 to > 733 between South Korean and Ukrainian males; and around 30 times from 11 to 313 between French and Ukrainian women^[8-15]. Community and global studies have gradually built on the evidence from Framingham Health Study (FHS) showing the “epidemiologic transition” of mortality from middle age (stage 3) to elderly (stage 4) in developed nations. The pattern of epidemiological transition can be trends, a rise and fall, continued rise or plateau^[13]. As many developed nations have absorbed a diverse ethnic and sociodemographic population it is unclear which trend could eventuate in future. There is evidence on the one hand the rise and fall pattern is stalling among young adults, but uncertain trends for Aboriginal and new migrants.

Australia has seen a national rise and fall trend for IHD deaths, for example 29637 deaths (23% of all deaths) *vs* 22983 (17% of all deaths) were reported in 1996 and 2006 respectively^[16]. Table 1 and Heart Foundation report summarizes the epidemiology in context^[17]. A divergent pattern does emerge when data is broken down into states and regions within states. Remoteness, certain ethnic groups and socioeconomic demographics do not fit into the rise and fall trend when data is looked at in totality or if mortality is reduced, IHD burden remains high, *e.g.*, Aboriginal and Torres Strait Islanders, lower socioeconomic status, younger and advanced ages^[18]. This then raises the question about fixed screening protocols for diagnostics and preventive strategies and its cost-efficacy.

EVALUATION OF CORONARY ARTERY DISEASE IN MULTIETHNIC COMMUNITIES

Medicare billing specialist reviews mandates prior primary care work-up. The volume of work leads to early triaging by general practitioners or emergency departments for first specialist encounter, where medicare funding regulations provide some basic framework. Figure 2 highlights the common pathway seen across medicare funded systems. Using a “three phase screening perspective”, this is however not a foolproof system for optimal cost-efficacy or outcomes as many aspects of each phase are not explored through a specialty lens. Let’s explore:

Clinical variables in CAD work-up

Clinical presentation: Firstly is documenting typical angina symptoms or equivalence, secondly eliciting markers of silent ischemia (discussed in risk scoring) and thirdly clinicopathophysiological correlations *e.g.*, CAD in women. Regards symptoms, chronic stable angina is the first presentation in 50% of cases, sudden cardiac death unstable angina or infarctions in 30%. The typical presentation of anginal chest pain or “anginal equivalents” include variations in pain referred between jaw and umbilicus, shortness of breath and constitutional symptoms such as nausea, fatigue, sweating or dizziness^[6,19,20]. Diamond proposed a classification of typical, atypical or non-angina, based on number of descriptors *e.g.*, substernal location, exertional and response to rest or nitroglycerin, found good angiographic correlation between men of all ages and in older women^[21]. Secondly, is silent ischemia which remains a controversial topic. On the third point, pathophysiological variations: in women for *e.g.*, plaque burden is more diffuse and less calcific, epicardial disease less likely among < 65 years of age and smaller diameter arteries with more vascular dysfunction. Clinically we see a biphasic presentation with

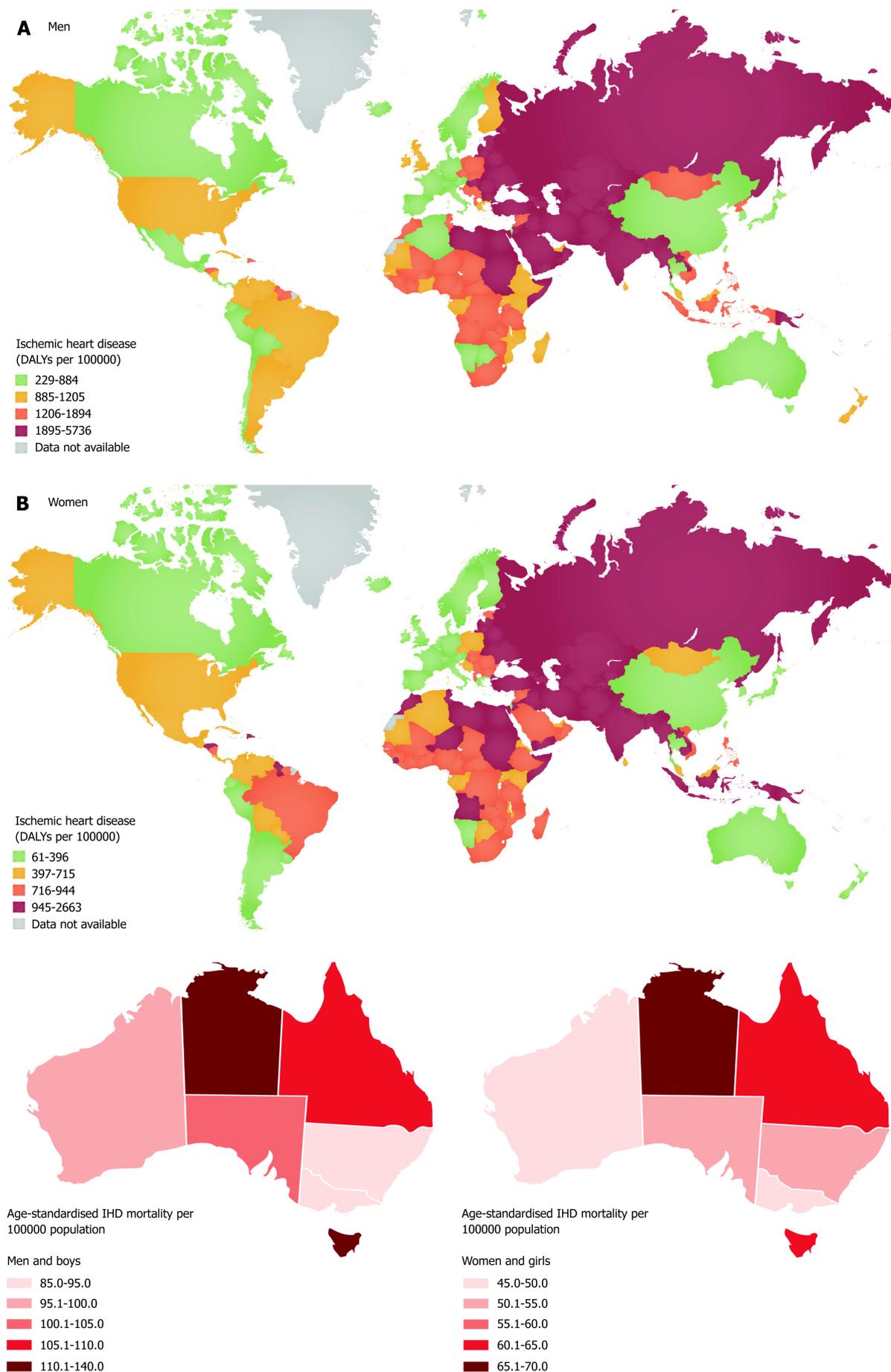


Figure 1 Ethnicity, epidemiological transition and coronary artery disease. A: The global distribution of CAD deaths. B: Mean national data may underrepresent variations within health system clusters of CAD risk, prevalence and incidences. Within developing nations, traditional and non-traditional factors contribute to risk and

may alter baseline risks associated with ethnicity and gender. When such groups' transition to developed nations such as Australia, excellent mean health care outcomes data could mask greater heterogeneity of outcomes data. These variations in epidemiological transition areas are also seen in some remote and Aboriginal populations. As demographic variations are represented variably within various health clusters this has to be factored in risk stratification. Centralized fixed guidelines and health funding models could thus be suboptimal for optimal health efficacy. (Geographical map from reference 6 and 17).

microvascular CAD at younger ages and higher associations of stress and mood changes from the history^[22]; similarly a gradient of risk is seen from Asian to African American and Indigenous patients in severity and earlier age of onset^[23-31]. Factoring these variations with language barriers can be challenging, as demonstrated by Shafiq *et al*^[32] with patient and physician discordance in symptom reporting. Such factors could even account for variations in observed management and outcomes^[33].

Risk scoring and pretest probability (PTP): From the history an assessment is made of a person's incidence or future risk of CAD. Only patients at the lowest risk of both are discharged from surveillance. Higher scores are also documented after observation of atherosclerosis and treatments such as coronary artery bypass grafting surgery or percutaneous coronary intervention. Scores determine the choice of diagnostics investigations and predict hard CAD endpoints of nonfatal or fatal MI^[6]. The FHS importantly demonstrated CVD risks with inverse relationship between various lipoproteins in cholesterol, diabetes, women and hypertension. These findings also highlighted genomic determinants and risk clusters as the foundations for multivariable or global risk assessments^[6,34-36]. Additional prospective observational studies added in other risk factors including age, gender, ethnicity, diet, cigarette use, exercise, sedentary lifestyles, excess weight and family or past history of CHD, as among the more important to shape scoring systems. Such systems have been developed for clinics (*e.g.*, Framingham Heart Disease Risk Scores) emergency departments [*e.g.*, ADAPT (Protocol for Cardiac Event Risk), Emergency Department Assessment of Chest Pain Score] or exercise (*e.g.*, Duke Treadmill Score).

Jensen *et al*^[37] explored 5 risk scores (Diamond-Forrester, Updated Diamond-Forrester, Duke, Morise, CORSCORE), all use age, sex and symptoms; Duke and Morise also use tobacco use, diabetes and hypercholesterolemia, while Duke uses MI and electrocardiogram (ECG) changes and Morise uses family history of CAD, body mass index, oestrogen and hypertension. The most efficient risk models in predicting CAD are the Duke, updated Diamond-Forrester, and CORSCORE among patients presenting with angina, while the most user friendly is updated Diamond-Forrester with the lowest number of clinical variables^[37]. Integration of this model into clinical care is discussed subsequently.

Stress testing and coronary artery evaluation

The premise of physiological testing is the ischemic cascade and the mechanisms for detecting the varying events^[38]. Stressors (mode of exercise or pharmacological agent) and diagnostic imaging modalities will contribute to the overall short or long term statistical binary classifications for the screening tests in this case sensitivity and specificity. Within this broad classification it has never actually been identified or tested if there are categories (sub-populations *e.g.*, demography) who require new observations prior to committing to the current stress guideline classification.

Ischemic cascade in physiological stress tests: The ischemic cascade describes "an assumption of linear" temporal sequence of pathophysiological changes where the preceding change triggers the subsequent in response to increasing myocardial supply-demand imbalance (Figure 3). Maznyczka *et al*^[39] proposed a more individualized concept that places the patient holistically at the center of the sequence, coining the term "ischemic constellation". This paradigm proposes no test as gold standard, that different cascade events can be abnormal at any temporal stage based on factors that can interrupt cascade linearity. These include stenosis severity or dynamism in the vascular bed, extent of stress or nature of stimulus, prior treatments, comorbidities, ischemic preconditioning and other individual factors^[39]. This would suggest that from our traditional model of PTP, symptoms, ECG and diagnostic imaging, where the latter carries greatest discriminatory capacity; in the new model under varying conditions any factor could assume greater importance.

With this in mind important points to consider: (1) PTP (a) adequacy of scoring prior to referrals; and (b) standardizing scores for fixed factors *e.g.*, age, ethnicity, family history, birthplace, *etc*; (2) stress modality (a) adequacy of stress duration and achieving > 85% mean predicted heart rates across age, gender and ethnicity. Achieving 10 METS is an accepted target, however the comfort and recovery periods

Table 1 Summary of landmark international and Australia coronary artery disease studies

Study geography	Clinical summary (Population data available on). Demography; epidemiology; morbidity; mortality; regional variations in RF and outcomes; epidemiological transition; gaps
<p>*Major international studies^[6-8]</p>	<p>Year, study, participants, sex and ethnicity:</p> <p>US studies: (1946) The minnesota businessmen study - C, 281 M, < 55 yr; (1948) Framingham heart study - ; (1984) CARDIA - AA/C, 5115 M/F, 18-30 yr; (1987) ARIC - AA/C, 15792 M/F, 45-64; (1989) Strong Heart - AI, 4549 M/F, 45-75 yr; (1989) Cardiovascular health study - AA/C, 5888 M/F, 65-102 yr; (2000) Jackson heart AA, 5302 M/F, 21-94 yr; (2000) MESA AA/C/Ch/H, 6814 M/F, 45-80; (2006) Hispanic community health study/study of latinos - H, 15079 M/F, 18-72.</p> <p>Global: 1958 The seven countries study - C, 12763 M, 40-59 yr; (1979) MONICA - ME; 15m M/F, 25-64 yr; (1999) INTERHEART - ME, 15152 M/F, age/sex matched; (2002) PURE - ME, 153996 M/F, 45-69 yr;</p> <p>Japanese: (1965) Ni-Hon-San study - J, 20k M, 45-69 yr</p> <p>Europe: UK: (1967, 1985) Whitehall, Whitehall II - C, 18403 M/10314 M-F, 40-64/35-55 yr; Iceland 1968, 2003) Rejkavik, AGES studies - C, 9141/2499 M, 34-79; Germany (1979) PROCAM - C, 4043M/1333F, 50-65</p> <p>Summary of epidemiology findings:</p> <p>Caucasian male population are baseline comparator group for epidemiology data</p> <p>High income countries:</p> <p>International trends shown strong ↓ mortality in high-income countries since 1980</p> <p>Mortality gaps exist with ethnic differences (probably genetics) either ↑ or ↓ risk or even protection.</p> <p>Globally:</p> <p>Age-standardized acute myocardial infarction incidence and angina prevalence have ↓ and ischemic heart failure prevalence has increased since 1990 (6)</p> <p>High age-standardized IHD mortality in Eastern Europe, Central Asia, and South Asia point to the need to prevent and control established risk factors in those regions and to research the unique behavioral and environmental determinants of higher IHD mortality.(7)</p> <p>Much of the dramatic CHD mortality increases in Beijing can be explained by rises in total cholesterol, reflecting an increasingly “Western” diet. Without cardiological treatments, increases would have been even greater.(6-4 Critchley J)</p> <p>Gaps in knowledge:</p> <p>Paucity of data in older > 75 yr</p> <p>Ethnic, family and true genetic contributions to CAD with improved modifiable risk factor control</p>
<p>Australia^[17,18]</p>	<p>Mortality, morbidity and cost:</p> <p>Death rates >Japan but < other high-income countries <i>e.g.</i> UK, Germany USA</p> <p>ATSI Deaths 1.5-3 x and IHD burden.0 0Smoking ATSI</p> <p>Ischaemic heart disease results in more. Australian deaths than any other single cause for both men and women.</p> <p>Death rates from heart disease are substantially higher among ATSI Australians, ranging from 1.5 to 3 times higher than in non-Indigenous Australians.</p> <p>Of all Australians aged 2 yr and over, 5% report living with heart, stroke or vascular disease. Among people aged 85 yr and over, this proportion rises to two in every five people (40%).</p> <p>In 2012-2013 the Pharmaceutical benefits scheme paid approximately \$1.8 billion for cardiovascular system medicines, representing 21% of total benefits paid in that year.</p> <p>Risk factor:</p> <p>↓ Smoking M:F18:14%: ATSI > 2x double non-Indigenous (41% daily smokers).</p> <p>< 10% of all met the NHMRC guidelines for vegetable consumption. In a national secondary school survey, 24% met recommendations for consumption of vegetables and 42% met recommendations for fruit consumption.</p>

Most Australians (58%) were either sedentary or had low levels of activity. Australians spent an average of 38.8 only 30% of children met physical activity recommendations, and only 10% met both physical activity and screen-time recommendations.

13% of men and 10% of women reported drinking alcohol at levels likely to present a risk to health. Total per capita alcohol consumption fell between the early 1970s and the early 1990s, but has been relatively steady since then.

One-third of Australians had high blood cholesterol (above 5.5 mmol/L). Almost four in every five Australians with abnormal cholesterol or triglyceride levels were not receiving treatment for it.

One in five Australians had high blood pressure and the prevalence was higher in men than women. One in four Aboriginal and Torres Strait Islander Australians had high blood pressure. The prevalence of high blood pressure rose substantially with age, from less than 10% in the 25 to 34-year age group to almost 50% in people aged 75 years and over.

More than two-thirds of men were classified as overweight or obese, as were 55% of women. One-quarter of children aged 2 to 17 years were classified as overweight or obese.

The overall prevalence of diabetes in the Australian public was more than 5%, with a further 5% at increased risk of developing diabetes.

The prevalence of mental disorders in 2007 was 17.6% in men and 22.3% in women; anxiety disorders were the most prevalent mental disorders in both sexes. Cardiovascular disease was responsible for nearly 44000 deaths in Australia in 2012, including more than 20000 deaths from ischaemic heart disease.

Common denominators in risk exist. Socioeconomic status and ethnography can contribute to this risk and needs to be factored in future risk scores. ATSI: Aboriginal and Torres Strait Islander; ET: Epidemiological transition; RF: Risk factors. *FHS: Framingham Heart Studies; NHMRC: National Health and Medical Research Council.

are not factored as risks^[106]; (b) the effects on the ischemic cascade with pharmacological stressors; and (c) Long term prognosticator of pharmacological stressors; (3) contextualizing ECG changes with risk and normal imaging: (a) strongly positive ECG change (> 2 mm) in low to intermediate risk females; and (b) marginally positive *e.g.*, > 1 mm but < 2 mm in males; (4) marginally positive imaging without symptom or ECG changes; (5) when to combine physiological test and coronary imaging modality to a risk monitoring plan at baseline; (6) lower limit criteria for classifying negative or low future risk (no cardiac follow-up required); and (7) long term planning for undifferentiated chest pains and dynamic coronary ischemia and future health services utilization.

Evidence for using the ischemic constellation in multiethnic communities: Among the six cascade events, baseline characteristics and stressor can determine which factor is more prominent with stress provoked ischemia. The most powerful test finding would be from individuals who have achieved greater than predicted exercise stress with some direct vascular atherosclerotic scoring. We cite from experience that some ethnicities especially when associated with lower/higher body mass and older may not meet the physical challenges of the treadmill to achieve generic targets. Body mass, ethnicity and older adults indexed charts are not available. Language barriers in this group could also alter the interpretation of symptoms. ECG changes could have variable importance among, troponin negative acute chest pain discharges^[40-42]. In acute chest pain presentations negative troponins could miss significant CAD^[40,43], while high sensitivity troponin assays are plagued with specificity issues^[44-51]. In summary, circumstances associated with ethnicities in some health clusters can alter the PTP, for *e.g.* difficulties with interpreting symptoms, the thresholds to provoke ischemia and constellation factors influencing the measured diagnostic parameters; greater vigilance is needed with post test decisions^[40,41,52], including those who have normal coronary angiography^[53]. Broadening decision support algorithms, presently inadequately used for more diverse demographic, could be part of future planning^[54-59].

Imaging modalities, Ca Score and computer tomography coronary angiography (CTCA): When deciding on the imaging modality several factors have to be considered, including: availability, accessibility, reproducibility, cost and safety (Table 2). ECG based exercise stress testing remains first line for younger males with low risk that are able to exercise. Direct referrals for stress echocardiography is debated presently, but evidence points to superior cost efficacy when using a patient centric approach^[60,61]. Much of the exercise and imaging quality deficits can be overcome by pharmacological agents *e.g.*, dobutamine and contrast agents^[60]. Appropriate

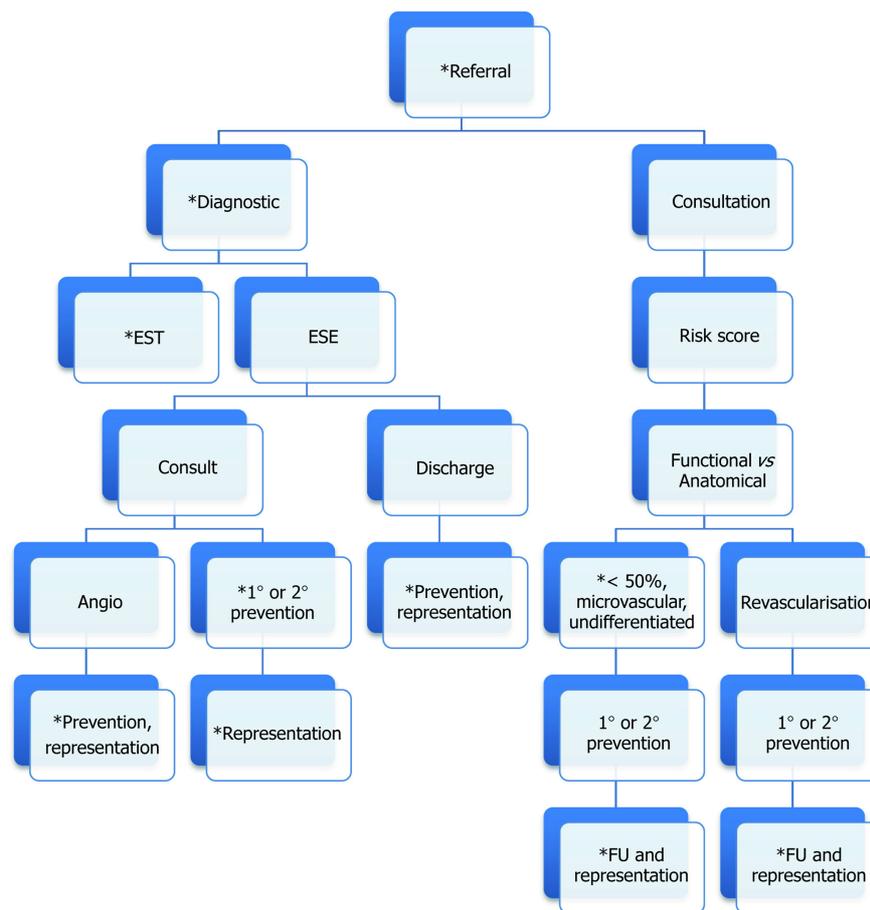


Figure 2 Triage and subsequent evaluation of suspected coronary artery disease referrals. CAD presentations to specialist are predominately referrals from general practitioners or following triage from emergency departments. Referrers either request a specialized test or a cardiac consultation. The choice between EST and ESE are not always clear. Direct specialist consultation may precipitate a more risk score guided approach. Moving down the pathway following complaints of typical symptom or positive stress test, following ascertaining anatomical information, gaps still exist for future health encounters subsequent from inconsistent classification of CAD burden probable vasospastic angina or undifferentiated cases. Direct diagnostic referrals run the highest risk of duplication for future representations. *Highlights points in the pathways where models of cost-efficacy and risk stratification can be examined further. EST: Exercise stress test; ESE: Exercise stress echocardiography; FU: Follow-up.

remuneration strategies for this have not been factored outside tertiary centers. The main advantages appear to be access, accuracy, reproducibility and cost. The access may also be the Achilles heel for cost efficacy as guidelines for repeat testing are not well regulated. SPECT has equivalent accuracy but falls short in other parameters. A main advantage could be in those patients with baseline resting wall motion abnormalities, to quantitate location and size of infarct and obtain a gated blood pool scan ejection fraction. Cardiac MRI is safe and accurate but has other access and cost issues of SPECT. With existing dilated cardiomyopathies we suggest a baseline ESE for functional assessment combined with a baseline MRI or GBPS ejection fraction. Should an MRI be available, combination with cardiac CTCA without additional functional assessment, could be considered^[61].

Ca Score statements support its use as a one off, in selected patients of low to intermediate risk to complement an existing functional assessment or modify risk to a higher or lower grade. We cannot advocate a role as a standalone investigation for CAD^[62,63]. The utility of CTCA is now clear, with ongoing research areas for risk stratification in acuity^[64,65]. As we are still unclear as to the boundaries of complimentary or additive information with functional tests and traditional risk scores, the patient cost and pretest counselling required, the role for non-specialist referrals without patients driven intent is open for further review.

Once a baseline test is done, the choice of future tests must be reproducible complimentary and provide additive information. Inter and intratest reproducibility is best achieved with stress echocardiography. All limitations of baseline test must be adequately documented for future references. The most important factor in future tests is pretest planning, *i.e.*, access to previous test findings, what additional

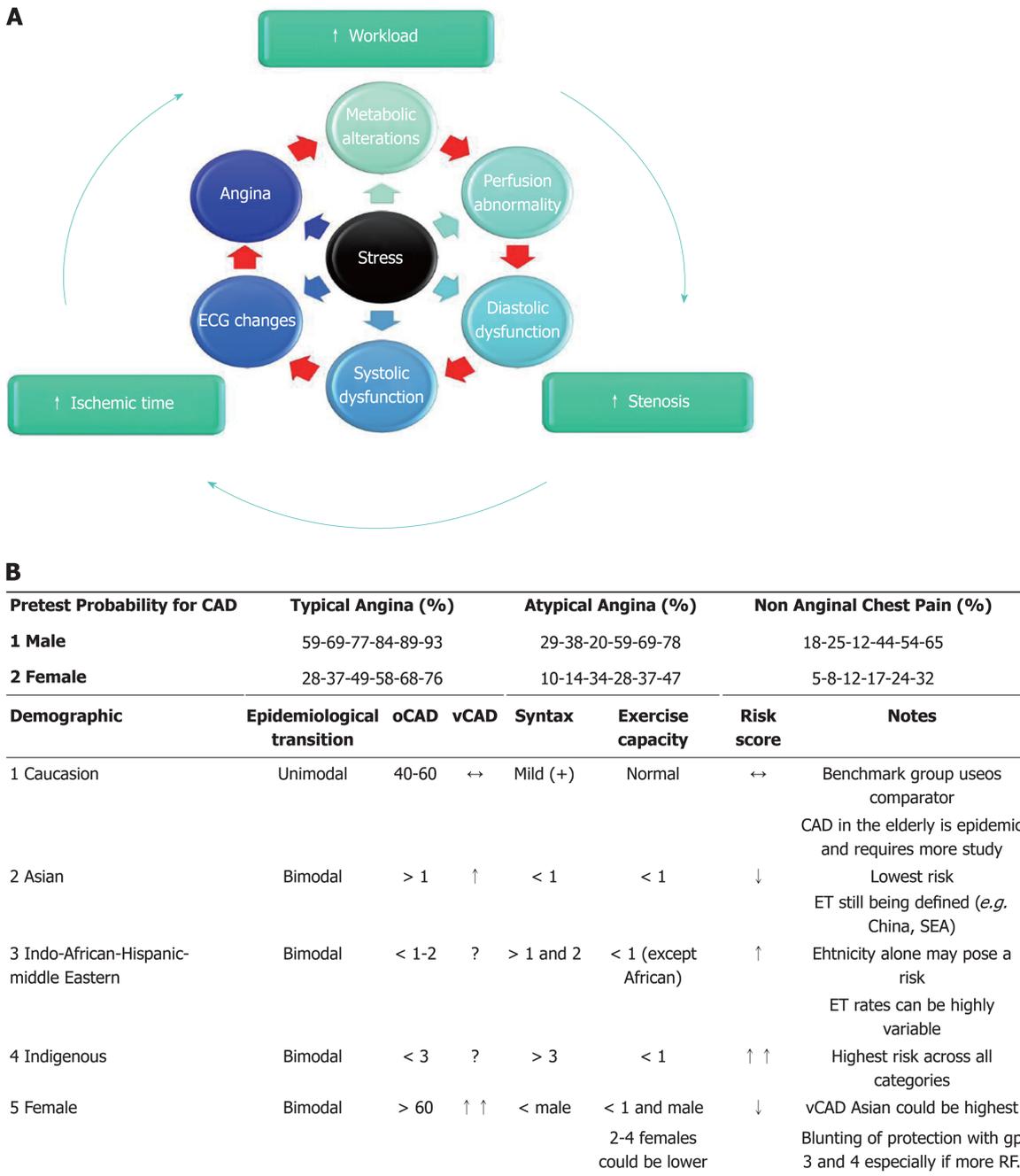


Figure 3 Ischemic Cascade and Constellation in clinical context. A: Stress creates myocardial energy imbalance leading to any of six manifestations in the ischemic cascade (red arrow) in a forward linear direction. Individual variations and combinations of workload, stenosis severity and ischemia duration (outer green arrows) that influences the order for components in the cascade, creates more realistically an 'ischemic constellation' of events, where any order for observable events is possible (multicolour arrows); B: PTP guides diagnostic workup. The probability is never 0 or 100%. With < 15 and > 85% guiding low or high risk. The actual number are for age range 30-39 years, increasing by decades, to > 80 years. Variations from the mean are determined by demography. No 1-4 represent males. Females across all groups represent the same CAD risk as the males except are relatively protected during middle ages, delaying mean onset of significant CAD. Etiological variations exist in: (1) vasospasm, being more likely in women, especially Asian. The actual rates among other non-caucasian female races are not well defined; (2) gender protection: from premature CAD in women may also be blunted in higher risk groups 2; (3) ethnicity - Aboriginal populations suffer from the greatest risk and severity of CAD, followed by 3, 1 and 2. Asians have the lowest risks; (4) developmental status - of any group also lowers mean age of onset of any ethnicity. Defining the coronary anatomy early could be one way of risk stratifying subgroups within broad ethnic based categories. oCAD: Obstructive coronary artery disease; ET: Epidemiological transition; PTP: Pre-test probability; RF: Risk factors; SEA: South East Asia; vCAD: Vasospastic coronary artery disease. (Concepts modified from ref 38, 39, 82-101).

information is required and the targets to be met. Reassessment of prognosis and diagnosis (if required must) also be documented in test or consultations reports. Any changes to baselines risk must also be recalculated.

Confounders in CAD evaluation and posttest review - Syndrome X, silent ischemia, diastolic heart failure and cardiac risk assessment in comorbidity and demography

Table 2 Sensitivity and specificity non-invasive test						
Test	Guideline indication	Sensitivity	Specificity	Stress modality	Advantage	Disadvantage
ECG	1 st L-PTP	45-50	85-90	Physical	Simple and safe	Accuracy
	2 nd L-PTP				Availability	ECG artifact
Echo	1 st L-PTP	80-85	80-88	Physical	Simple and safe	False positives
	2 nd L-PTP			Pharma*	Availability	Suboptimal image quality <i>e.g.</i> , resting wall motion defects, lung disease, respiratory artifact,
Myocardial perfusion scintigraphy (SPECT, PET)	1 st L-PTP	73-92	63-87	Physical	Accurate quantification ischemic area	Cost
	2 nd L-PTP	90%	75-87	Pharma*	Ischemia: Quantify and localize; greater spatial resolution (subendocardial) ↑ accuracy with septal defects	Availability Radiation and retesting Ischemia: ↓spatial resolution <i>e.g.</i> for subendocardial ischemia Pharma: CI, SE, ↓ sensitivity for multivessel disease ↑ acquisition time Artifacts: Lung motion, breast tissue, diaphragm attenuation
MRI Ischemia	1 st I-PTP	79-88	81-91	Pharma*	Body habitus/lung window independent	Cost
	2 nd L-PTP	67-94	61-85		Accurate No radiation Operator independence High spatial resolution Can perform absolute quantification of perfusion	Availability Expertise ↓ Gating: Rhythm and rate
CA Score CTCA	1 st L-PTP	95-99	64-83	Direct visualization coronary artery	Availability	Radiation
	2 nd I-PTP				Non-invasive Anatomical information FFR	Cost Ca score role No functional information Contrast

Guideline referral for diagnostic evaluation is guided by PTP. All males start with a PTP of > 15% and thus warrant at least a Stress ECG. Females between 30 and 39 years have PTP 10% and clinical judgement may suffice. When PTP is > 85%, *e.g.*, males > 60 years with typical symptoms, coronary imaging can be considered first line or complimentary based on clinical judgement. Females are not given a PTP > 85% and thus should at least receive a functional test. The choice of functional test is described in the body of the table. Non-imaging stress ECG has three information sources - PTP, subjective (test symptoms and hemodynamics) and solitary objective (ECG) marker of the ischemic cascade. Imaging stress testing adds baseline myocardial function to the PTP and additional objective components of the ischemic cascade improving accuracy. Greater advancement in addressing issues of access, cost and reimbursement, complementary (dual) modality testing, additional means to assess ischemic cascade components (*e.g.*, tissue strain), image quality issues (*e.g.*, contrast echo) could alter the test indication and its accuracy. PET - imaging has lower radiation, higher resolution and quantify blood flows (including microvascular), but cost and availability are issues. MRI identifies wall motion changes *via* dobutamine or myocardial perfusion by vasodilators. Exercise: treadmill; bicycle; right ventricular pacing. Pharmacological: dobutamine; adenosine; dipyridamole, ragadenoson. Imaging Sources: SPECT isotope: Technetium 99m, thallium 201. CA: Calcium; CI: Contraindication; CTCA: Computerized tomography coronary angiography; ECG: Electrocardiography; Echo: Echocardiography; FFR: Fractional flow reserve; H-PTP: High pretest probability; I-PTP: Intermediate pretest probability; L-PTP: Low pretest probability; PET: Positron emission tomography; PTP: Pretest probability; MRI: Myocardial resonance imaging; SE: Side-effects; SPECT: Single photon emission computerized tomography (Data partly synthesized from reference 38, 100, 101). *Physical exercise is the preferred stress modality. It provides higher physiological stress and workloads with greater opportunity for corroboration with patient's symptoms. Although studies have shown similar accuracy between physical and pharmacological stress test, we feel there is insufficient evidence to draw similar long term conclusions on the diverse etiologies and severity of CAD emanating from more diverse patient populations.

Typical presentations of angina or angina equivalents with or without classical findings on diagnostics can often be related to syndromes involving the coronary vasculature or heart muscle. On diastolic heart issues we refer to our recent publication^[66]. Numerous authoritative publications have explored the dynamism of the large and small coronary arteries. Important points to consider are the low rates of community and primary care recognition of this syndrome, higher frequency of representation and resource utilization, higher morbidity and prognostic considerations and lack of formally labelling patients with the diagnosis. Many of these issues can be negated by increasing first presentation diagnosis or labeling of non-cardiac chest pains following specialist encounters. Formalizing a treatment or action plan is also critical^[53,66-70].

Ambulatory silent myocardial ischemia is demonstrated in nearly 50% of stable CAD, 15% with either hypertension or 12 and 33 with diabetes alone or with another risk factor^[71-74]. Functional diagnostics induced silent ischemia; with at least mild to moderate CAD shares similar risk to symptomatic patients. As silent ischemia can occur with or without CAD the boundaries with vasospastic angina require greater exploration. In patients with risk factors identifying further fixed risk, *e.g.*, family history of premature CAD (before 60 years) in first degree relative, modifiable risk, *e.g.*, sedentary lifestyle, end organ changes, *e.g.*, proteinuria or early large or small vessel atherosclerosis, *e.g.*, retinopathy, peripheral or carotid artery disease. The choice of test favors an imaging based functional test, while imaging of a vascular bed must also be considered complimentary early in the screening process^[75-79], although improved outcomes may yet to be defined^[80,81]. Among women who are more likely to have ECG changes, prognosis is unclear and more work is needed^[82].

While the decisions for either functional or anatomical test are clear, the decisions for both are less clearly stated. Several important parameters guide the need for angiography. When PTP score approaches 85% *e.g.*, male > 60 years with typical angina. Similarly there are categories of risk at young age amongst some population with risk factor clusters *e.g.*, diabetics and chronic renal impairment^[82-98]. Should risk scoring algorithms be strengthened, more evidence develop, clearer positions for warranting both types of information could be forthcoming.

HEALTH CLUSTERS AND COST EFFICACY

It is always premature to rest when a plateau in knowledge is assumed to have been achieved. But in all developed health systems it is premature to invest public resources to understand variations in established observations that do not meet robust requirements of need, especially cost-efficiency. We accept differentials exist in phase 1-3 trials that assume largely private capital, so this argument is largely for phase 4 trials or post translational observations^[99-102]. The observations presently is "the cost efficiency of using unimodal risk stratification of CAD within health clusters that serve a multiethnic patient population with varying stages of epidemiological transition based on findings and guidelines from homogenous populations". Presently true costings can't be evaluated without further understanding of some care domains and processes within them. Broadly however, CAD assessment requires acknowledgement of four fundamental goals (Figure 4).

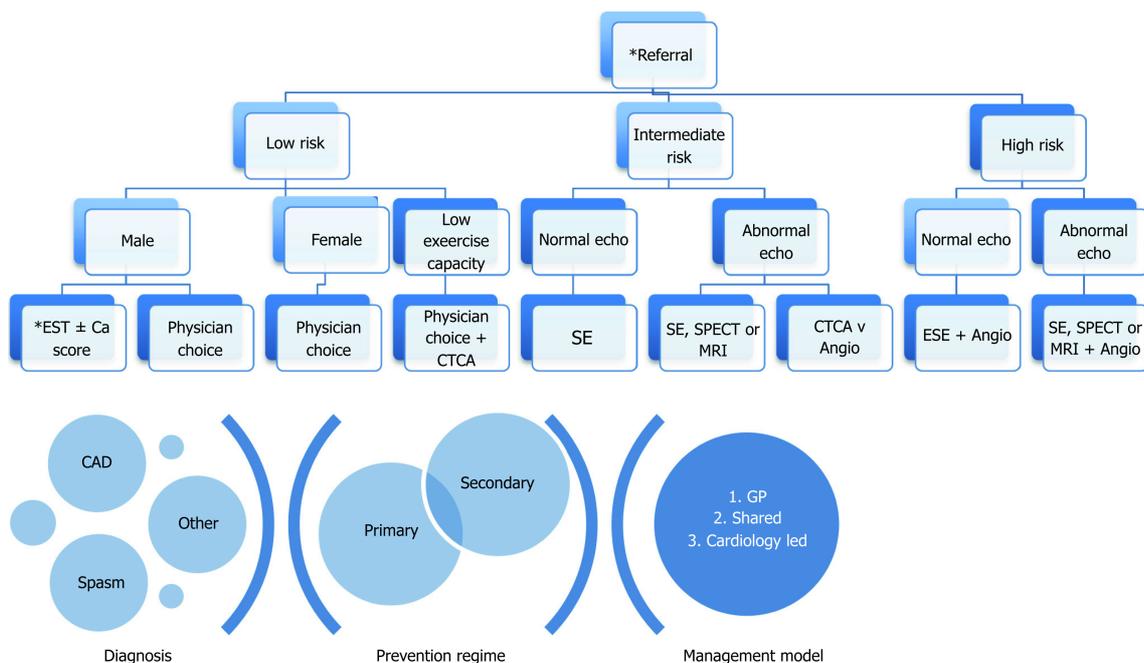


Figure 4 Theoretical Considerations for Future Cost-Efficiency. Three avenues for cost-efficacy analysis within a health cluster are identified. (1) Referral: the PTP gives a rough guide as to first choice of diagnostic test. High demand for evaluation raises an argument for observational studies for the best point of initial PTP work-up *e.g.* with GP supported education or early cardiology review; (2) Diagnostics: the combination of patient factors, cost and availability dictates stress echocardiography be the first choice of imaging modality, however more understanding of other modalities should also be encouraged; (3) Clinical Evaluation: this area is most likely to influence lifetime CAD cost-efficiency. Avenues to explore are: (a) patients and primary care preventive education after findings of minor CAD and/or with intermediate and high risk criteria factors; (b) patients at increased risk of recurrent chest pains and readmission *e.g.* vasospastic angina; (c) risk models for screening and follow-up of various ethnicities and demographics at different stages of epidemiological transition; (d) combinations of primary, specialist and tertiary care management models: the long term patient specific and health system goals once the work-up for CAD is initiated, aside from actual diagnosis of definite CAD, is prevention of disease progression or risk of future disease and preventing cost-ineffective utility of health resources especially unnecessary diagnostics and hospital beds. Physician Choice: includes any combination of investigation based on additional characteristics deemed to alter risk of accuracy of EST. Ca: Calcium; CAD: Coronary artery disease; CTCA: Computerized tomography coronary angiography; ESE/SE: Exercise stress echocardiography; PTP: Pretest probability; SPECT: Single photon emission computerized tomography.

Symptom description and risk scores the bed rock for CAD evaluation

Family history and ethnicity are examples of fixed risk that remains difficult to quantify. Clinical judgement is a difficult area to research, but plays a strong role in management. Further avenues to explore are: (A) Avenues to improve translated and cultural descriptors in history for anginal symptoms; (B) Standardizing multiethnic population level risk scores; (C) Factoring in the burden of disease in risk scores; (D) Referral forms with PTP screening tools or PTP done in waiting rooms prior to test; (E) What constitutes a baseline cardiac risk score? *e.g.*, biomarkers like hsTrop; and how often to do? Does one test supersede another? and (F) With higher risk scores do we need both functional and anatomical information?

Translating risk scores into satisfactory analysis of CAD

Without directly visualizing atherosclerosis, most conclusions are inferred. Gaps exist when CAD is not excluded and with non-critical CAD, greater risk factors or microvascular disease. (A) Redefining adequate physiological endpoints that account for the ischemic threshold, with varying grades of exercise; and (B) Visualizing alternate vascular beds as surrogate for coronary vasculature in selected cases.

Risk stratifying patients post stress testing

Once significant CAD is established management including rehabilitation and long term care pathways are well defined with solid health infrastructure in place. When patients are not cleared of CAD nor have nontraditional risks, grey areas emerge. Such areas include: (A) Factoring in the burden of disease and providing post-test risk scores; (B) Minimizing readmission and utilization of diagnostics for vasospastic CAD; (C) Licensing and return to work issues; and (D) Ensuring framework for longer term follow-up is documented, even when only a diagnostic test is requested.

Acknowledging the most cost efficacious method in achieving this goal

Ongoing health education and engagement of specialty, tertiary and regulatory bodies are important. The jurisdictions for many of these are still poorly defined. (A)

Health Clusters: (1) Jurisdictions: understanding of the boundaries, shared resources and negotiation of clinical scope could be better defined. State and federal funding tend to promote non-cooperative working relationships. Honorary acknowledgements of regional cardiologist in public institutions are examples to consider; and (2) Shared clinical and education models – research in health economics is largely a process of testing different working models. We suggest hybrid models which supports continuous information to and from all stakeholders; for providers’ flexibility of management, with accountability; and public bodies the most effective resource sharing models as important areas to explore; (B) Audit and Research Importance of audits – while regulation from authorities create a blanket rule, it is preferable that physicians using public funds should provide evidentiary data to governing bodies. Several options include: firstly, continuous professional development – to include questionnaires on selected key performance indicators across a range of issues in that community. This way accumulation of knowledge by a specialist is also transferred back to governing bodies; secondly, a mandatory requirement for audit, *via* governing body attached institutes across a range of domains at stipulated intervals. Health trainees could be assigned to assist. This will ensure a robust standard in documentation and management. As an important source for variations are referral biases, while structures have to be in place to align outcomes, punitive approaches must be avoided, as would providing sufficient time alerts to align practices; (C) Terminology - standardizing the minimum information required and the terminology to assist inter-observer interpretation. For example, define: (1) Nature of CAD - *e.g.*, atherosclerotic, vasospastic, undefined; (2) Symptom - *e.g.*, angina, angina equivalent, silent; (3) Etiology - *e.g.*, main cause, CAD in women; (4) Structure - *e.g.*, associated myopathies and anomalies; (5) Risk - *e.g.*, main etiology and future risks; and (6) Monitoring - *e.g.*, define suitable chronology of reinvestigations; and (D) Conflicting evidence in medicine - translational research questions should focus on answering many broad questions rather than, “yes” and “no” question such as mortality. We must continue to reinforce while hard major adverse cardiovascular outcome are not produced for all ethnicities, this should be a secondary outcome in phase-4 studies. The primary focus are delivery models and cost-efficiency across established health service Taxonomy domains. Nesting this question within larger studies could also broaden the funding appeal^[102-105].

CONCLUSION

CAD work-up in multiethnic populations requires a more considered approach. While it is unlikely significant CAD is missed further considerations could reveal opportunities to improve cost-efficiency through the entirety of a patient’s health journey. Established pathways provide a good foundation to work from. Fine tuning this approach based on improving the translation of: ischemic symptom, “angina and equivalents” across language and cultures; risk scores when factoring ethnicity and country of birth; observable myocardial ischemia factoring individual variations and combinations of workload, stenosis severity and ischemia duration and its influence on the ischemic constellation. We have also highlighted potential options to explore. It is also becoming apparent that new paradigms in medical practice within well-defined disease processes such as CAD are developing. Such observations, calls for greater strengthening of collaboration within health clusters for education and research, while maintaining healthy competitive clinical service models to ensure uninterrupted and efficient care for patients, from all stakeholders in public and private sectors.

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Importance of the telemedicine network for neurosurgery in Slovenia

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Abstract

The number of invasive procedures in medicine is increasing, as is the employment of new technological achievements. In the era of information-communication technology, one such achievement is also the telemedicine network. In Slovenia, it is known as the Telekap (TeleStroke) network, which was primarily designed for fast and efficient management of stroke patients. In the neurosurgical community, the system is frequently used also for conveying vital information regarding subarachnoid haemorrhage and trauma. Especially in neurosurgical emergencies, this communication system offers thorough information about the extent and location of bleeding and facilitates the preoperative planning of neurosurgical interventions. From our experience so far, the system should be expanded to other neuro-centres as well to all neurosurgery departments in order to facilitate patient management, their acute hospital care, and inter-speciality collaboration.

Key words: Telemedicine; Neurosurgery; Neurosurgical planning; Neuroimaging; Slovenia

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Core tip: The telemedicine network in Slovenia is known as the Telekap (TeleStroke) network, which was primarily designed for fast and efficient management of stroke. In the neurosurgical community, the system is frequently used for conveying information regarding subarachnoid haemorrhage and trauma. It offers thorough information about the extent and location of the pathology and facilitates the neurosurgical intervention.

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INTRODUCTION

The number of invasive procedures and the use of new technological achievements in medicine are increasing. Telemedical connections are one of such important acquisitions in the era of information-communication technology (ICT)^[1,2]. Telemedicine is defined as the use of medical data, mostly in emergencies, which emergency services are sharing between themselves by using electronic communication and with the purpose to improve healthcare, health and educational services in outpatient and emergency situations^[1,3]. Hospital and outpatient neurology is one of the emerging subspecialties in neurology that was developed to improve access to neurological care in areas without specialised neurology centres^[3-6]. Telemedical network system is not used only by neurological professions, and it is also very useful for neurosurgery.

IMPLEMENTATION OF THE TELEKAP SYSTEM IN NEUROSURGERY

In Slovenia, the telemedicine network is called Telekap (TeleStroke) and it has been used since 2015. All hospitals in the country are connected in this network, which provides continuous access to the data and connections with consulting specialists in the tertiary centre. The main idea during establishing this system was that telemedicine may provide care for all neuropathology patients in the country with quick and easy accessibility. This telemedicine network was initially designed for fast and efficient treatment of patients with a stroke. The Telekap system enables clinical and radiological assessment of location and scope of stroke, tumour, hydrocephalus, or head and spine injuries, and fast decision-making about further diagnostic procedures. It also provides triage for patients and thus enables a suitable therapy. When the patient is admitted to a peripheral hospital, the images are forwarded directly to the telemedicine centre, where neurosurgeons may plan the optimal treatment strategy. According to the conveyed images, the resuscitation and surgical team may be properly prepared for the operation during the transport of the patient. Additionally, the postoperative accommodation and care of such a patient may be forecast and organised. Increased prevalence and mortality due to stroke is partially the consequence of slow treatment due to large distances to specialised neurology centres^[7]. The time of treatment is therefore extremely important, and it affects the outcome of the treatment. The patient suffering from stroke must not only be transferred to an appropriate centre as soon as possible, and data about the disease that provide fast and expert assessment, planning, and correct action during admittance are also important. However, this is possible only if the data is promptly available. Similarity also applies for neurosurgical pathology where fast action is needed^[8,9].

The Telekap system is being used in neurology principally in relation to haemorrhagic and ischemic strokes as it provides fast informing and transfer of data from remote hospitals to centres that are specialised in stroke treatment^[5,9]. However, the telemedicine system is useful not only for informing and preparation for stroke treatment but also for other types of pathology. Beside neurology, the Telekap system is extremely valuable for neurosurgeons. They are using it frequently for acquiring significant information, mostly in relation to subarachnoid haemorrhage, tumours, and head injuries, being most frequent indications^[10].

In Slovenia there are two referral tertiary neurosurgical centres for the 1.8 million population. Due to the specifics of neurosurgical pathology, the paucity of neurosurgery experts in peripheral emergency departments, and the lacking availability of a range of effective treatments there, the patients with corresponding pathology and in need of emergency treatment are transferred to the specialist management to the either centre always when possible. On some occasions, the worsening clinical condition would direct immediate action and preclude the transport. In these sceneries, the Telekap is particularly valuable. Numerous factors have all contributed to optimal conditions for Telekap implementation in Slovenia, including the opportunity to improve access and quality of care, narrow window of time frame and treatment efficacy, the resources required for ground and helicopter

medical transportation, and the expansions and improvements of the medical care dedicated ICT. As a result, the Telekap is being used extensively in the national health care and its use is still rising.

On some occasions, the surgeons in local hospitals are capable of exerting immediate neurosurgical treatment for the patients who need urgent action and where transport would deteriorate the worsening condition due to the time required for reaching neurosurgical department^[11-13]. These are in the most cases the trauma settings with intracranial pressure (ICP) monitor placement and operations where evacuation of acute blood is needed from the brain in order to prevent a high rise of ICP and brain herniation. In such cases, only immediate surgical decompression can save the patient^[14-16]. Mostly these emergency procedures in Slovenia are connected with acute subdural, epidural, and rare superficial intracerebral hematomas and decompressive craniectomies as well as when there are difficulties encountered with the subsequent postemergency neurosurgical care.

This communication system is especially important in neurosurgery cases as it provides complete information on the extent and location of haemorrhage, and it simplifies pre-operative planning of a neurosurgical procedure. Information that is available from images on the computer system and is important for the neurosurgeon includes the type and precise location of the intracranial pathological process (injury, bleeding, ischemia, tumour, and hydrocephalus), the extent of affected brain tissue due to oedema or adjoining ischemia, and combined injuries or pathological processes which may also affect extracranial parts, such as cranial and facial bones, as well as scalp and facial soft tissues^[17,18]. Data on the optical nerve channel, eyeballs, pyramid bones, or sinuses are also extremely important, especially in the acute setting, such as head and face injuries. This information is crucial for planning surgical treatment where interdisciplinary operation is necessary, especially in patients with combined injuries. In such difficult medical emergencies, the help of maxillofacial surgeons, ophthalmologists, or otorhinolaryngologists is always welcome and leads to increased treatment quality and faster patient care^[17-19].

The Telekap has been designed to provide any patient with symptoms and signs consistent with acute neurosurgical pathology with a quick expert clinical evaluation, a review of diagnostic findings, a diagnosis, decision making, emergency treatment recommendations, and postoperative advice. It is the most reasonable to perform the Telekap consultation in collaboration with the treating physicians and nurses, as they are the ones that know the patient's condition in detail.

When the patient is accepted to a general hospital, the system submits images directly to the telemedicine centre. According to the information, neurosurgeons can optimally plan the treatment, which depends on the type of pathology. Additionally, the reanimation and surgical team can suitably prepare for the surgical procedure during the transport of the patient. It is also possible to plan and organise postoperative management of such patients, often needing intensive care and prolonged hospitalisation^[18-22].

Time is an important factor in brain injury, which may affect the final treatment outcome. The delays in providing adequate resuscitation and definitive care in a timely fashion and appropriate management are often detrimental for patients with brain injury^[19]. Thus, the telemedicine network is indispensable for neurosurgeons for the treatment of patients with urgent surgical situations, especially for those who were transferred from remote centres where time plays an important role^[22]. The Telekap can be used regardless of the hospital location, emergency department versus other unit, time of day, and proximity to the nearest neurosurgical centre. According to previous extremely positive experience, we propose that such a system should be expanded to other centres with neurological patients, and also to all neurosurgery departments in the country in order to facilitate preparation for procedures for such patients, their acute hospital treatment, and interdisciplinary collaboration. The process is still ongoing and we are expecting further expansion, modifications, and improvements of the system in the following years.

Decision making is a central function of a telestroke network. In hospitals without neurosurgical experience and neurocritical care units, the surgeon on call may perform the initial intervention. In such typical neurosurgical setting taking part in the Telekap service, medical consultations are delivered to local hospitals from specialists in the referral centre who are located at distant sites and they have unusually no connection with the patients and their treatments in the local hospitals. The referral centre is frequently an academic medical centre and provides the neurosurgical Telekap services to distant sites within its geographic region. The most numerous emergencies are those related to the high ICP for various reasons. It is essentially to release this high ICP in order to assure the best possible recovery for the patient. With the Telekap network, the operating surgeon in a distant hospital may sometime be guided with the audio-video support of a neurosurgeon. Later on, when

the decompression is achieved, the ICP rescued, and the patient stable, a transport into the tertiary centre may be organised in order to completely accomplish the surgical procedure. In case the patient requires a higher level of care following the Telestroke evaluation, a transfer to the corresponding neurosurgical center is facilitated. When the transfer is indicated, the referral centre typically receives the patient from the local hospital and can provide continuity of care, having already observed the patient virtually. Alternatively, the neurosurgeon may be transferred to the local hospital. In our clinical practice, the latter is a frequent event, where the neurosurgeon may take over the operation in the local hospital in case of difficulties and advises during the immediate postoperative care.

OUR EXPERIENCE WITH THE TELEKAP

In the period of using the Telekap system in University Medical Centre Ljubljana, we surgically treated patients at the neurosurgery department for various pathologies. Those included cerebral vascular diseases (aneurysms, arteriovenous malformations, ischemic and haemorrhagic strokes), injuries (contusions, epidural and subdural haematomas, cranial and facial fractures, and soft tissue injuries), brain oedema of various aetiologies, and primary and secondary brain tumours where oedema or bleeding occurred and the neurological status of patients deteriorated due to a sudden increase of ICP. The larger share of patients included those with ischemic and haemorrhagic strokes where surgical intervention was required by inserting a sensor for measuring ICP, external ventricular drainage, evacuation of brain haemorrhage, or decompressive craniectomy for lowering refractory increased ICP.

Worldwide, the value of telemedicine has been confirmed clinically and scientifically. In 2009, the American Heart and American Stroke Association reported about the evidence of telemedicine significance in the stroke schemes of care and made recommendations for telestroke implementation^[19,23]. The 2009 policy statement included guidelines with the recommendations that were based on class I evidence^[23]. Key recommendations emphasized the value of telestroke system to support the assessment of acute stroke severity, the equivalence to that of a bedside evaluation, the review of imaging results by remotely located stroke specialists, and urgent decisions about further treatment^[24-26]. In our experience, such evidence may directly mirror the neurosurgical practice. The Telekap proved to be an invaluable tool in the management and care of patients, as perceived by the treating surgeons and consulting neurosurgeons in the two Slovenian referral centres. As communicated in the current stroke guidelines, telestroke remains a standard care in hospitals that cannot provide an acute stroke team^[24,27]. In recent years since implementation of the Telekap in the emergency neurology services, we have successfully broadened its applications also into neurosurgical practice. We may therefore state that in Slovenia the Telekap system has developed in the last three years into a standard and indispensable tool for communication, connection, and flow of medical information between the hospitals that cannot provide a neurosurgical team and the referral centres. It now remains a standard element of the treatment strategy for neurosurgical patients from distant locations.

The monitoring of the image transmission from primary diagnostic centre (*i.e.*, emergency or radiology centre in the local hospital) as well as the flow and quality of video, audio, and Internet connectivity should be a part of technology workflow. In order to perform the consultation, surgical and postoperative guidance soundly and to achieve good treatment results, a flawless operation of all systems involved and a good technical support are mandatory^[28,29].

Considering the positive experience, we believe that it would be necessary to expand the use of Telekap also to other medical specialities in order to facilitate the flow of important medical and treatment related information. Especially, emergency medical services among the hospitals in the country may be connected, including prehospital units, interventional specialities, and traumatology, as well as paediatric units and internal medicine emergency services, in order to improve and speed up the management of urgent conditions and to improve treatment outcomes.

CONCLUSION

Progress in the treatment of intracranial pathology included the development and expansion of computer systems, networks, and applications for fast and simple informing and data transfer from the location of primary diagnostics to specialised centres. Beside technical support, which includes information communication

technology, a close cooperation of various experts is also important for the efficient operation of the entire treatment mechanism. Such a multidisciplinary team includes, in addition to neurologists and neuroradiologists, also interventional radiologists, intensive care specialists, anaesthesiologists, and neurosurgeons. It would be useful to provide such an information network, which would be intended for other specialists in medicine as well, to all hospitals and diagnostic centres in Slovenia in order to significantly improve the speed and quality of healthcare and thus improve the treatment efficacy for patients even more.

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