Cardiovascular Tests for Risk Assessment in Asymptomatic Adults and Implications for Pilots

I. Made Ady Wirawan; Robin F. Griffiths; Peter D. Larsen

BACKGROUND: This study aims to examine which marker or testing protocols have been suggested for cardiovascular disease (CVD) risk assessment in asymptomatic populations, at which CVD risk level, and how this can be implemented for CVD risk assessment in pilot populations.

METHODS: A systematic search was performed using Systematic Reviews Subset on PubMed; the OvidSP interface, including all EBM reviews and EMBASE databases; and the G-I-N International Guideline Library. From each recommendation, we extracted data on consideration of the use of a marker or test for cardiovascular risk assessment in asymptomatic populations.

RESULTS: Included were 45 guidelines, systematic reviews, or meta-analyses relevant to cardiovascular risk assessment in asymptomatic populations. The majority (9/12) of the citations recommend coronary artery calcium score (CACS) for CVD risk assessment in intermediate-risk (10-yr CVD risk score of 10–20%) asymptomatic adults. Other cardiac and vascular tests that may also be considered include the measurements of carotid-intima media thickness, supplemented by carotid plaque, and the ankle brachial index for prevention of peripheral artery disease and stroke. Stress myocardial perfusion scan is the potential cardiac functional test to be used with pilots with 5-yr risk of ≥15%. Among laboratory markers, only hs-CRP has a potency to be used in CVD risk assessment in intermediate-risk asymptomatic adults; however, the strength of the recommendation is not adequate.

DISCUSSION: Among the cardiac and vascular testing available, CACS is the most frequently suggested test. The implications of findings for CVD risk assessment in airline pilots are highlighted in this paper.

KEYWORDS: cardiovascular risk, calcium score, airline pilot, asymptomatic population, assessment tools.

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Cardiovascular disease (CVD) is an important medical condition for civil aviation authorities to consider due to the fact that CVD can cause sudden pilot incapacitation.[14] In addition, CVD has resulted in long-term disability and is the most common reason for loss of license among airline pilots.[16] Periodic medical examination in commercial pilots, including screening for CVD, is therefore aimed at assessing the risk of incapacitation in the cockpit and evaluating the functional ability of the pilots to ascertain their fitness for routine service, including in emergency situations.[40] For this purpose, the CVD risk scoring system, based on multiple traditional cardiovascular risk factors, has been applied by civil aviation authorities globally.[27]

Many risk scoring systems are currently in practice and the most widely used internationally is the Framingham risk scores.[11] Several international and national guidelines have also included risk prediction charts or tables which were derived from the Framingham function.[9] However, it has been demonstrated by previous studies that the Framingham-based risk prediction models and other risk scoring systems based on CVD risk factors have some acknowledged limitations.[10] The main limitations are related to the rule of age as the most

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heavily weighted variable[36] and the characteristics of the Framingham population that can create problems if the risk scores are applied to different populations with different baseline risk factors.[27,46] Most of the published studies show that the currently available cardiovascular risk scoring systems have similar discrimination performance limitations.[23] Although these risk scoring systems are practical and simple to apply, their diagnostic accuracies are only moderate, and some known risk factors are not incorporated.[25] Similarly, a study in a pilot population[65] found that the risk prediction charts had a modest accuracy, with an area under the receiver operating characteristics (ROC) curve of 0.72 (95% CI 0.583–0.863), a specificity of 0.73, and low sensitivity (0.53).

In addition, the methodologies for cardiovascular investigation of airline pilots following the screening using the CVD risk scores are currently suboptimal. Medical license applicants with excessive cardiovascular risk will be required to demonstrate normal myocardial perfusion by undertaking further testing, commonly through a stress electrocardiogram (ECG).[7] The main limitation of this practice is that exercise ECG has limited diagnostic accuracy in asymptomatic patients.[5] A previous study in airline pilots demonstrated that the current approach to investigate excessive cardiovascular risk relies heavily on exercise ECGs as a diagnostic test, and may not be optimal either to detect disease or to protect pilots from unnecessary invasive procedures, and a more comprehensive and accurate cardiac investigation algorithm to assess excessive CVD risk in pilots is required.[64]

Based on the above findings, there is reason to review current recommendations and guidelines on how further investigations should be performed, especially in asymptomatic populations, and how this can be implemented for CVD risk assessment in pilot populations. This study presents a systematic review that aims to examine which marker or testing protocols have been suggested for CVD risk assessment in asymptomatic populations and at which CVD risk level. Furthermore, the performance of the suggested examinations, including the area under the ROC curve (AUC), Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI) when added to the risk score model is assessed. The advantages and disadvantages of the suggested examinations are also highlighted.

METHODS

Data Sources and Searches

A systematic search was performed on 25 November 2016. The first search was performed using the Systematic Reviews Subset on PubMed (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html). This search strategy is able to identify systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines of interest. The second search strategy employed the OvidSP interface, including all evidence based medicine (EBM) reviews and EMBASE databases. The final strategy was searching national and international guidelines through the G-I-N International Guideline Library (http://www.g-i-n.net/library/international-guidelines-library). **Table I** describes the search strategies which were used to identify citations and publications of interest.

The following inclusion criteria were used: 1) guidelines, expert panel recommendations, appropriate use criteria, working group position statements, consensus statements, and systematic reviews or meta-analyses that were applicable to an asymptomatic population with no previous diagnosis of cardiovascular diseases; 2) using the English language; 3) providing recommendations on the utilization of one or more of vascular

Table I. Description of the Search Strategy Used to Identify Citations and Publications of Interest.

SEARCH A	DATABASE: PUBMED ON 25 NOVEMBER 2016	ITEMS FOUND
Filters activated	Subsets: systematic reviews, dates: publication date from 1 January 2006 to 25 November 2016	
Search terms	#1: "cardiovascular diseases"[MeSH Terms]	17,664
	#2: risk assessment (Title/Abstract) OR risk stratification (Title/Abstract) OR assessment (Title/Abstract) OR stratification (Title/Abstract) OR early detection (Title/Abstract) OR early diagnosis (Title/Abstract) OR periodic evaluation (Title/Abstract) OR periodic examination (Title/Abstract).	16,613
Combine	#1 AND #2	1999
SEARCH B	**DATABASE: (VIA OVIDSP): ALL EBM REVIEWS AND EMBASE**	**ITEMS FOUND**
Search terms	#1: exp Cardiovascular Diseases/di, dt, ep, et, ge, mo, pc, th (Diagnosis, Drug Therapy, Epidemiology, Etiology, Genetics, Mortality, Prevention & Control, Therapy).	10,409
	#2: risk assessment or risk stratification or assessment or stratification or early detection or early diagnosis or periodic evaluation or periodic examination, tw (Title/Abstract).	1,006,489
Combine	#3: #1 AND #2	2205
Limits activated	#4: limit #3 to evidence based medicine or consensus development or meta-analysis or outcomes research or "systematic review"	1624
	#5: limit #4 to yr = "2006 - 2016"	403
SEARCH C	**NATIONAL GUIDELINES VIA G-I-N INTERNATIONAL GUIDELINE LIBRARY**	**ITEMS FOUND**
Search terms and filters	•→Cardiovascular disease* AND risk assessment or risk stratification or assessment or stratification or early detection or early diagnosis or periodic evaluation or periodic examination; MeSH Term: Any Condition	64
	•→Filters: Language: English; Publication type: Guideline, Systematic review, and Evidence report; Publication status: Published; Countries: International and All Countries	
All Searches	Search A + Search B + Search C	2466

testing, cardiac testing, laboratory testing, or genomic testing for cardiovascular risk stratification.

Data Extraction and Analysis

All relevant recommendations were extracted from each included citation by one reviewer. The results obtained were then confirmed by other reviewers for completeness and accuracy. Disagreements were discussed and resolved by consensus.

From each recommendation, we extracted data on consideration of the use of a marker or test for cardiovascular risk assessment in asymptomatic populations. The strength of the recommendation was classified as follows: "A. Recommended," "B. May be recommended," "C. Insufficient evidence," and "D. Not recommended." The description of the strength of recommendation with examples of phrases is presented in **Table II**.

Recommendations for each laboratory marker, vascular, and cardiac testing were presented in a table, with the strength of each recommendation and the supporting citations. For genomic markers, the recommendations were presented descriptively.

Each potential cardiovascular marker or test was analyzed in terms of its diagnostic accuracy and reclassification performance. The overall diagnostic accuracy of a test or marker is presented by its AUC, which is the most popular metric to be used to discriminate or separate out those who will develop the event of interest from those who will not.[67]

Reclassification performance is shown by the NRI and the IDI.[48] The NRI demonstrates how much more frequently appropriate reclassification into a correct risk category occurs than inappropriate reclassification with use of the new test or marker. The IDI is a continuous version of NRI with probability differences used instead of categories, and indicates how far individuals are moving on average along the continuum of predicted risk.

RESULTS

Our initial search retrieved 2466 potentially relevant citations. After scanning titles and abstracts, 2248 citations were excluded.

Table II. Strength of Recommendation Classification.

STRENGTH OF RECOMMENDATION	EXAMPLE OF PHRASES IN RECOMMENDATION OR CONCLUSION
A. Recommended	"is recommended", "should", "is indicated", "is effective", "is beneficial", "is useful", or other phrases with the same meaning
B. May be recommended	"may/might be", "is probably", "is reasonable", "can be useful", other phrases with the same meaning
C. Insufficient evidence	"not well established", "is unclear", "is uncertain", "effectiveness is unknown", "not sufficient evidence", other phrases with the same meaning
D. Not recommended	"is not recommended", "should not", "is not indicated", "is not effective", "is not beneficial", "is not useful", "associated with harm", or other phrases with the same meaning

Then 218 citations were reviewed using full text, resulting in 173 excluded studies. Finally, 45 guidelines, systematic reviews, or meta-analyses relevant to cardiovascular risk assessment in asymptomatic populations were included. The flowchart of the selection of citations is shown by **Fig. 1**.

The 45 citations included in this study were of the following types: 16 were guidelines, expert panel recommendations, appropriate use criteria, working group position statements, or consensus statements; 26 were systematic reviews and/or meta-analyses; and 3 citations were systematic review of guidelines or recommendations.

Cardiac and Vascular Testing

The strength of recommendations on the use of cardiac and vascular testing for CVD risk assessment in asymptomatic adults is presented in **Table III**. Among the cardiac and vascular testing available, coronary artery calcium score (CACS) is the most frequently suggested test.

The strength of recommendation for CACS in the majority (9/12) of the citations is "A. Recommended" for CVD risk assessment in intermediate-risk (10-yr CVD risk score of 10–20%) asymptomatic adults. In addition, CACS may be recommended

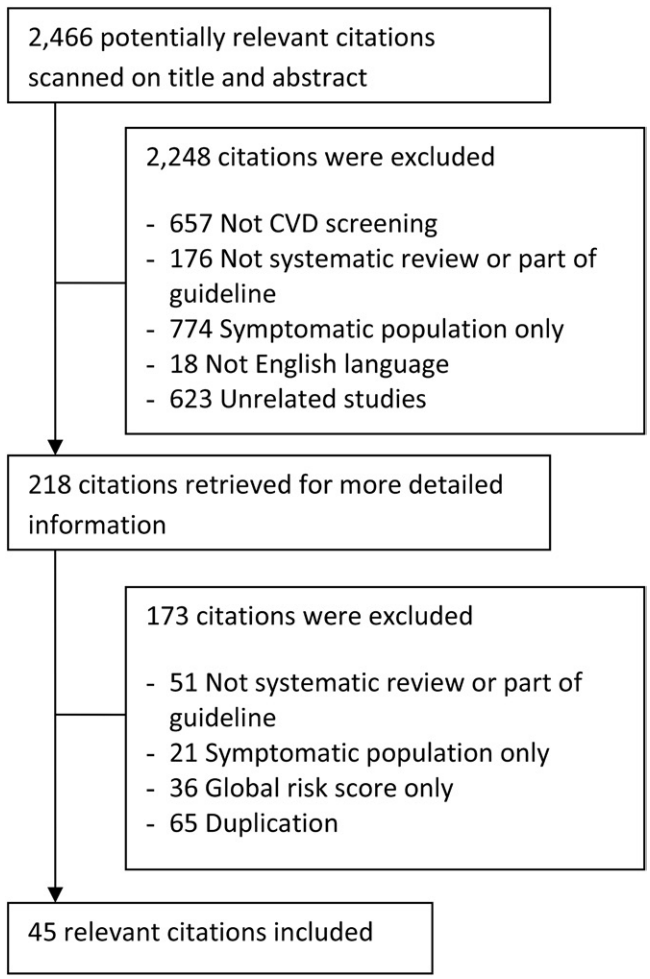

Fig. 1. Flowchart of selection of articles.

Table III. Strength of Recommendations on the Use of Cardiac and Vascular Testing for CVD Risk Assessment in Asymptomatic Adults and in Specific Conditions or CVD Risk Level.

TEST	STRENGTH OF RECOMMENDATION	N	CITATION
Resting ECG	A. Recommended in adults with hypertension/diabetes	1	Greenland et al.[21]
	B. May be recommended in other asymptomatic adults	2	Chou et al.[5], Greenland et al.[21]
	D. Not recommended	1	Lim et al.[34]
Resting echo	B. May be recommended in adults with hypertension	1	Greenland et al.[21]
	D. Not recommended in other asymptomatic adults	2	Greenland et al.[21], Lim et al.[34]
Stress ECG	B. May be recommended in intermediate-risk adults (10–20%)	2	Chou et al.[5], Greenland et al.[21]
Stress echo	A. Recommended in high-risk adults (10-yr risk of >20%)	1	Metz et al.[41]
	C. Insufficient evidence to recommend in high-risk adults	1	Douglas et al.[15]
	D. Not recommended in low-intermediate risk adults (≤20%)	3	Douglas et al.[15], Greenland et al.[21], Sicari et al.[59]
CIMT	A. Recommended in intermediate-risk adults (10–20%)	3	Greenland et al.[21], Naghavi et al.[43], Peters et al.[53]
	B. May be recommended in asymptomatic adults	2	Inaba et al.[28], Roman et al.[55]
	C. Insufficient evidence for a recommendation	2	Plantinga et al.[54], Sander et al.[56]
	C. Insufficient evidence to recommend in intermediate risks	1	Helfand et al.[24]
	D. Not recommended	1	Lim et al.[34]
Peripheral FMD	B. May be recommended for risk prediction	1	Peters et al.[52]
	C. Insufficient evidence for a recommendation	1	Peters et al.[53]
	D. Not recommended	2	Greenland et al.[21], Roman et al.[55]
Carotid plaque ultrasound	A. Recommended in intermediate-risk adults (10–20%)	1	Peters et al.[53]
	B. May be recommended to supplement CIMT	1	Inaba et al.[28]
	B. May be recommended in asymptomatic adults	1	Kwee[32]
Pulse wave velocity	B. May be recommended for risk stratification	1	Khoshdel et al.[30]
	D. Not recommended	1	Greenland et al.[21]
Ankle brachial index	A. Recommended in intermediate-risk adults (10–20%)	1	Greenland et al.[21]
	A. Recommended for stroke prevention	1	Sander et al.[56]
	B. May be recommended for risk stratification	1	Fowkes et al.[19]
	C. Insufficient evidence for a recommendation	1	Ferket et al.[18]
	C. Insufficient evidence to recommend in intermediate risks	1	Helfand et al.[24]
	D. Not recommended	1	Lim et al.[34]
Stress MPI	A. Recommended in high-risk adults (10-yr risk of >20%)	1	Metz et al.[41]
	B. May be recommended in adults with diabetes, FH-PIHD, or high-risk adults (FRS >20% or CAC score ≥400)	3	Greenland et al.[21], Hendel et al.[26], Perrone-Filardi et al.[50]
	D. Not recommended in low-intermediate risk adults (≤20%)	3	Greenland et al.[21], Hendel et al.[26], Perrone-Filardi et al.[50]
CAC scoring	A. Recommended in intermediate-risk adults (10–20%)	9	Greenland et al.[21,22], Naghavi et al.[43], Oudkerk et al.[47], Perrone-Filardi et al.[50], Peters et al.[51,53], Taylor et al.[61], Waugh et al.[63]
	B. May be recommended in low-intermediate risks (6–10%)	1	Greenland et al.[21]
	B. May be recommended in low risks (<10%) with FH-PIHD	1	Taylor et al.[61]
	B. May be recommended in diabetic asymptomatic adults	2	Bax et al.[2], Perrone-Filardi et al.[50]
	C. Insufficient evidence to recommend in intermediate risks	1	Helfand et al.[24]
	D. Not recommended in low-risk adults (<6%)	3	Greenland et al.[21], Lim et al.[34], Oudkerk et al.[47]
	D. Not recommended in low-risk adults (<10%)	1	Greenland et al.[22]
	D. Not recommended in high-risk adults (>20%)	1	Greenland et al.[22]
CCTA	D. Not recommended	3	Greenland et al.[21], Perrone-Filardi et al.[50], Taylor et al.[61]
MRI plaque	D. Not recommended	1	Greenland et al.[21]
Doppler ES	B. May be recommended in stroke risk stratification	1	King & Markus[31]
ABP	B. May be recommended	1	Conen & Bamberg[8]

ECG: electrocardiography; echo: echocardiography; CIMT: carotid intima-media thickness; FMD: flow-mediated dilation; MPI: myocardial perfusion imaging; CAC: coronary artery calcification; CCTA: coronary computed tomography angiography; MRI: magnetic resonance imaging; ES: embolic signals; ABP: ambulatory blood pressure. Risk scores: 10-yr risk from FRS (Framingham-based risk scores); FH-PIHD: family history of premature ischemic heart disease.

in low intermediate (10-yr CVD risk score of 6–10%) by one citation, may be recommended in low risk (10-yr CVD risk score <10%) with family history of premature ischemic heart disease by one citation, and may be recommended in asymptomatic adults with diabetes by two citations. Only 1/12 citations has insufficient evidence to recommend CACS for CVD risk assessment in intermediate-risk adults.

Another test that has potency to be utilized in the CVD risk assessment of asymptomatic adults is carotid intima-media thickness (CIMT). Of the nine citations that have recommendations for the application in asymptomatic populations, CIMT is recommended by three citations for CVD risk assessment in intermediate-risk adults (10-yr CVD risk score of 10–20%), and may be recommended for CVD risk assessment without specifying the population's risk level by two citations. Three citations, however, have insufficient evidence for a recommendation and one citation did not recommend the use of CIMT.

Three citations include a recommendation for the detection of carotid plaque using ultrasound. Of these, one citation recommends the use of carotid plaque screening for CVD risk assessment in intermediate-risk (CVD risk score of 10–20% over 10 yr) adults. In addition, carotid plaque may be

recommended to be used by two other citations, where one of these specifically addresses the possibility of using carotid plaque to supplement the CIMT test.

Ankle brachial index (ABI) is recommended by two of six citations, one of which recommends the use of ABI for CVD risk stratification in intermediate-risk populations, and another recommendation is for identification of subjects of increased stroke risk.

Resting electrocardiography is recommended in patients with hypertension and diabetes, and may be recommended in other asymptomatic adults by 1/3 and 2/3 citations, respectively. Stress echocardiography and stress myocardial perfusion imaging (MPI) are recommended to be applied in identifying low-risk patients by one citation. However, these two tests are not recommended to be used in low to intermediate risk populations (10-yr CVD risk <20%).

Laboratory Testing

The majority of international and national guidelines have included risk prediction charts or tables which were derived from the Framingham function,[9] which also incorporate standard laboratory markers, including total and HDL cholesterol, LDL, and markers for dysglycemia (fasting blood glucose and/or HbA1C).

In addition to the above markers, the laboratory tests that are considered for the CVD risk assessment in asymptomatic adults are presented in **Table IV**. It is indicated that only three laboratory markers are recommended to be used in cardiovascular risk assessment in asymptomatic populations, that is high-sensitivity C-reactive protein (hs-CRP), lipoprotein/apolipoprotein, and lipoprotein-associated phospholipase A2 (Lp-PLA2). Hs-CRP is recommended by 1/9 citations, lipoprotein/apolipoprotein is recommended by 1/6 citations, and Lp-PLA2 is recommended by 1/5 citations. The specific CVD risk levels for which the tests are suggested include asymptomatic intermediate-risk adults (10-yr CVD risk of 5–20%) for hs-CRP and lipoprotein/apolipoprotein, and intermediate-high-risk adults (10-yr CVD risk of ≥10%) for Lp-PLA2. In addition, hs-CRP may be recommended for CVD risk assessment in intermediate-risk patients (10-yr CVD risk of 10–20%) by 5/9 citations.

Specifically, microalbuminuria is recommended for CVD risk assessment in adults with hypertension or diabetes by 3/4 citations. This laboratory marker may be also recommended for CVD risk assessment in intermediate-risk adults (10-yr CVD risk of 10–20%) by 2/4 citations.

Genomic Testing

Genomic testing recommendations are found in five citations. Although inquiring about a family history of premature ischemic heart disease is often recommended during the initial assessment, genomic profiling is not recommended in most of the guidelines[3,21,43] and systematic reviews or meta-analyses.[37]

A population structure and meta-analysis concluded that variants on 9p21.3 are associated with ischemic stroke and

Table IV. Strength of Recommendations on the Use of Laboratory Markers for CVD Risk Assessment in Asymptomatic Adults and in Specific Conditions or CVD Risk Level.

LABORATORY MARKER	STRENGTH OF RECOMMENDATION	*N*	CITATION
hs CRP	A. Recommended in intermediate-risk adults (5–20%)	1	Davidson et al.[12]
	B. May be recommended in intermediate-risk adults (10–20%)	5	Buckley et al.[4], Greenland et al.[21], Lim et al.[34], Myers et al.[42], Naghavi et al.[43]
	B. May be recommended in intermediate-risk adults (15–20%)	1	Helfand et al.[24]
	D. Not recommended	2	Schnell-Inderst et al.[57], Shah et al.[58]
Lipoprotein/Apolipoprotein	A. Recommended in intermediate-risk adults (5–20%)	1	Davidson et al.[12]
	B. May be recommended in intermediate-high-risk (≥ 10%)	1	Lippi et al.[35]
	D. Not recommended	4	Greenland et al.[21], Helfand et al.[24], Lim et al.[34], Myers et al.[42]
Lp-PLA2	A. Recommended in intermediate-high-risk adults (≥ 10%)	1	Davidson et al.[13]
	B. May be recommended in intermediate-risk adults (10–20%)	1	Greenland et al.[21]
	B. May be recommended in intermediate-risk adults (5–20%)	1	Davidson et al.[12]
	B. May be recommended	2	Garza et al.[20], Sander et al.[56]
Natriuretic Peptide	D. Not recommended	2	Greenland et al.[21], Myers et al.[42]
Hb A1C	B. May be recommended in adults without diabetes	1	Greenland et al.[21]
Microalbuminuria	A. Recommended in adults with hypertension or diabetes	3	[2], Greenland et al.[21], Myers et al.[42]
	A. Recommended for CVD risk assessment	1	Perkovic et al.[49]
	B. May be recommended in intermediate-risk adults (10–20%)	2	Greenland et al.[21], Myers et al.[42]
Fibrinogen	B. May be recommended	1	Sander et al.[56]
Interleukin	B. May be recommended	2	Sander et al.[56], Wang et al.[62]
TNF-α	D. Not recommended	1	Sander et al.[56]
Homocysteine	D. Not recommended	5	Helfand et al.[24], Lim et al.[34], Luhmann et al.[38], Marti-Carvajal et al.[39], Myers et al.[42]
Leukocyte count	D. Not recommended	2	Helfand et al.[24], Lim et al.[34]
Periodontal disease	D. Not recommended	1	Helfand et al.[24]
Cystatin C	B. May be recommended for CVD risk assessment	1	Lee et al.[33]

Risk scores: 10-yr risk from FRS (Framingham-based risk scores); hs CRP: high-sensitivity C-reactive protein; Lp-PLA2: lipoprotein-associated phospholipase A2, lipoprotein/apoliporotein includes particle size, density, apolipoprotein B (ApoB); TNF-α: tumor necrosis factor-alpha.

coronary heart disease.[1] However, the Evaluation of Genomic Applications in Practice and Prevention Working Group found that there was inadequate evidence to suggest testing for the 9p21 genetic variant or 57 other variants in 28 genes.[3] Another meta-analysis confirms the lack of association between a candidate gene named *ESR1* rs223469 and coronary heart disease, and shows that inconsistencies between previous studies are explained by differences in their quality.[37]

Performance of Suggested Markers and Testing

Coronary artery calcium scoring. As indicated in the Table III, CACS is the most popular test for prediction of cardiovascular risk in asymptomatic populations. Ferket et al., who conducted a systematic review of guidelines on imaging of asymptomatic coronary artery disease, supported this conclusion. They found that the majority of guidelines (10/14) recommended CACS as a test to improve coronary risk assessment based on recognized risk factors.[17]

The discriminatory ability of CACS was shown in a recent systematic review of added value of CACS in risk stratification for cardiovascular events. This review found that an increase in AUC was shown by all studies when CAC was added to the risk model, ranging from 0.05 to 0.20.[51] In the Multi-Ethnic Study of Atherosclerosis, the AUC increased from 0.79 to 0.83 when CACS was added to the original multiple risk factors model.[21]

Furthermore, CACS also reclassified a significant proportion of people into correct risk categories. This was shown by an NRI that ranges from 14 to 30%, where the most obvious improvement was found in those at intermediate Framingham risk (10-yr risk of 10–20%).[51,66] This is a category that most airline pilots are likely to fall into once above the "normal' risk range.[60] It was also estimated from the Multi-Ethnic Study of Atherosclerosis that addition of coronary artery calcium measurement to the traditional risk factors model resulted in NRI in the total population of 25%, with NRI in intermediate-risk individuals of about 55%, and an IDI of 0.026.[53] This means that the evaluation of coronary calcification is useful in CVD screening, especially in subjects who are classified as intermediate risk based on the CVD risk scoring systems. High calcium scores identify subjects at high risk who will benefit from aggressive preventive interventions. Moreover, current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging stated that for both general and special populations, a zero score excludes most clinically relevant coronary artery disease.[47]

Due to limited information, however, more research is needed, especially to evaluate the impact of CACS measurement on clinical outcomes and costs.[17] The CACS measurement has also raised concerns about radiation dose for patients. The radiation dose using prospective triggering as suggested by most current recommendations, however, is considered low, with an effective dose range from 0.9 to 1.1 mSv.[21]

Carotid-intima media thickness, carotid plaque, and ankle brachial index. Another testing that is potentially used for CVD risk assessment in asymptomatic populations is the measurement of CIMT. Performance of CIMT in CVD risk stratification was shown to be adequate in a recent systematic review. However, this review found that the increase in AUC when CIMT was added to the conventional prediction models was slight, ranging from 0.00 to 0.03.[53] The results from CIMT measurement are also dependent on accurately performing the test. To achieve high-quality results, standard operating procedures, including required equipment, technical approach, and operator training and experiences, must be carefully followed.[21]

Similarly, the AUC for carotid plaque measurement when added to the traditional risk prediction model was found to be between 0.01 and 0.06.[53] In addition, a recent meta-analysis comparing the performance of CIMT and carotid plaque indicated that carotid plaque had a higher diagnostic accuracy than CIMT for the prediction of CVD events. Therefore, to increase the diagnostic performance of carotid ultrasound, CIMT measurement should be supplemented by carotid plaque assessment.[28]

Inclusion of the ABI in cardiovascular risk stratification using the Framingham risk score was highlighted in a meta-analysis of 16 population cohort studies. This study suggested that ABI would result in reclassification of the risk category and modification of treatment recommendations in approximately 19% of men and 36% of women.[19] Conflicting recommendations were, however, found in other citations, stating that ABI was not recommended and that there was insufficient evidence to recommend the use of ABI for CVD risk stratification.[18,24,34]

Stress myocardial perfusion imaging. Due to high negative predictive values, stress myocardial perfusion imaging is recommended to be used by one citation for identifying low-risk individuals among those with high risk (10-yr risk of >20%, equivalent to a 5-yr risk of ≥15–20% according to NZ-CRC). The negative predictive values for endpoints that include myocardial infarction and CVD death was 98.8%. This means that those with a normal result from a stress myocardial perfusion scan may avoid unnecessary tests and further interventions.[41] However, stress MPI is not recommended to be used for CVD risk assessment in low- to intermediate-risk asymptomatic adults.[21,26,50]

High-sensitivity C-reactive protein. Among the laboratory markers, only hs-CRP has a potency to be used in CVD risk assessment in intermediate-risk asymptomatic adults. The strength of the recommendation, however, is not adequate ("A. Recommended" by 1/9 citations and "B. May be recommended" by 5/9 citations).

A systematic review conducted for the U.S. Preventive Services Task Force indicated that addition of hs-CRP to the risk prediction model was able to reclassify 11% of men in the intermediate-risk group as high risk. However, there is a lack of information on clinical utility and harms of the testing.[4,24] An advice from an expert panel of lipid specialists on clinical utility of inflammatory markers stated that for initial clinical assessment in adults with intermediate risk (10-yr CVD risk of 5–20%), CRP is recommended to be measured routinely in men 50 yr of age and women 60 yr of age.[12]

A health technology assessment report showed that adding hs-CRP to the risk prediction models slightly increased the AUC by 0.00 to 0.027. However, despite improving risk prediction, the clinical relevance and cost-effectiveness of this improvement remain unclear.[57] Similarly, a systematic review of 31 prospective cohorts suggested that CRP does not perform better than the Framingham risk equation for discrimination. The risk stratification or reclassification improvement from addition of CRP to the global risk score models is small and inconsistent.[58]

Implications for Cardiovascular Risk Assessment in Pilots

In the medical assessment of airline pilots, the International Civil Aviation Organization (ICAO) introduced the application of the "1% rule", a rule that does not allow probability of cardiovascular mortality of an individual to exceed 1% per annum.[29] Because of the flexibility of ICAO in the application of this rule and based on comprehensive reviews, the 2% per annum risk (or 10% per 5 yr) in airline pilot assessment has been applied in some ICAO contracting countries.[29]

The Civil Aviation Authority (CAA) of New Zealand, for instance, evaluates the cardiovascular risk of all medical certificate applicants who are over 35 yr of age[7] using the adjusted Framingham based method published in the New Zealand Guideline Group (NZGG) in 2003 and updated in 2009.[6,44,45] The NZGG method states a 5-yr risk estimation and a 5-yr CVD risk of 10% (approximately 10-yr CVD risk of 20%) or higher is considered "excessive" for the purpose of the CAA medical standards.

Pilots exceeding a 5-yr risk of 10% are required to undergo further investigations and normal myocardial perfusion needs to be demonstrated to gain a medical certificate.[7] This is currently done by undergoing stress electrocardiography. If the functional test shows either an ambiguous or a positive result, the pilot will be considered for further testing and a coronary angiography is commonly required.[6,7]

The present review shows that the strength of recommendation for stress ECG is classified as B (may be recommended). Two references support the idea that stress ECG may be useful for CVD risk assessment in intermediate-risk populations (10-yr CVD risk of 10–20%).[5,21] The performance of stress ECG was assessed in a review of the evidence for the U.S. Preventive Services Task Force.[5] Pooled analyses showed that abnormalities on stress ECG, including ST-segment depression with exercise, failure to reach maximum target heart rate, or low exercise capacity, are associated with an increased risk for subsequent cardiovascular events, with pooled hazard ratio ranges from 1.4 to 2.1 after adjustment for traditional risk factors. However, this review found that no study estimated how accurately stress ECG plus traditional risk factor assessment classified patients into groups of low, intermediate, or high risk compared with classification on the basis of traditional risk factor assessment alone. No study also provided sufficient data for risk stratification tables to estimate the NRI.[5]

A marker or testing will be considered a useful tool in CVD risk stratification if it has good performance in reclassifying a substantial proportion of originally intermediate-risk persons as high-risk and, therefore, resulting in better clinical management to reduce the risk for CVD events.[24] Data on Table III indicates that some testing might be useful to be applied for CVD risk stratification in asymptomatic adults at intermediate risk (10–20%, 10-yr risk). This intermediate-risk level is equivalent to a 5-yr risk score of 5–10% and 10–15% when assessed using the New Zealand cardiovascular risk charts. This is important given the fact that almost half of the cardiovascular events occurred in pilots whose previous 5-yr CVD risk was in the 5–10% range.[65] Reclassification of pilots at those CVD risk levels into correct risk categories is of utmost importance in primary prevention in pilot populations.

Another consideration is that while CACS provides very helpful risk stratification information in intermediate risk individuals, with the evolution of coronary computed tomography angiographic (CCTA) technology, CCTA radiation exposure can be as low as 1–3 mSv, and CCTA can provide both angiographic and derived coronary calcium score. The problem with nuclear perfusion imaging is that it becomes abnormal only with obstructive or flow limiting coronary disease, and many coronary events in an aircrew population occur as a result of plaque rupture in nonobstructive arteries. Many agencies are now using combined CCTA/CACS as the preferred screening modality for intermediate or high risk (>2%/yr) aircrew, and reserve MPI only for individuals with obstructive disease found on CCTA.[21,50,61]

This systematic review found that coronary artery calcium score (CACS) measurement is the most frequently suggested test to be used for CVD risk stratification in asymptomatic adults. Considering its overall diagnostic performance and reclassification performance, CACS is the most promising test to be included in the CVD risk assessment of airline pilots. Based on the reclassification performance, CACS is useful to be applied in asymptomatic people with intermediate risk, which is equivalent to a 5-yr risk of 5–10% and 10–15% according to the New Zealand cardiovascular risk charts. Other cardiac and vascular tests that may also be considered include the measurement of CIMT supplemented by carotid plaque and ABI for prevention of peripheral artery disease and stroke. Stress myocardial perfusion scan is the potential cardiac functional test to be used in high-risk pilots (5-yr risk of ≥15%) to detect low-risk pilots and avoid unnecessary tests and further interventions.

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