

## Estimating Cardiovascular Risk in the 21<sup>st</sup> Century: Role of Serological Markers and Imaging as new Tools for Risk Stratification.

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### Abstract

Cardiovascular diseases continue to be the primary cause of death worldwide, thus making their high burden a call for adequate prevention strategies. Estimating individual risk of suffering cardiac or cerebral vascular events allows the implementation of disease-modifying measures. Risk stratification charts based on traditional risk factors (sex, age, smoking, hypercholesterolemia, diabetes mellitus and hypertension) are the most recommended methods, given their easy use, high applicability and predictive value. Nevertheless, intermediate risk patients undergoing further stratification may require additional tools, such as serological markers and imaging. This review focuses on the utility and applicability of various tools designed for cardiovascular risk assessment.

**Keywords:** Cardiovascular risk; risk assessment; serological markers; cardiovascular imaging; cardiovascular disease; cardiovascular risk stratification; atherosclerosis

### Abbreviations:

AHA = American Heart Association

ACC = American College of Cardiology

BNP = B natriuretic peptide

CACS = Coronary Artery Calcification Score

CRP = C - Reactive Protein

CT = Computed tomography

CV = Cardiovascular

CVD = Cardiovascular Disease

CVDs = Cardiovascular Diseases

CVR = Cardiovascular Risk

Lp(a) = Lipoprotein (a)

RF = Risk Factors

### Introduction

Cardiovascular diseases (CVDs) continue to be the primary cause of death worldwide. Even though the general mortality rates have decreased, they are on the rise in underdeveloped and developing countries [1]. The consequent high disease burden calls for adequate prevention strategies, especially considering the early onset of atherosclerosis of coronary and cerebral arteries during childhood and that its late manifestations only permit symptomatic or palliative management, rather than a curative approach [2]. Estimating individual cardiovascular risk (CVR) allows for disease-modifying measures to be taken in order to prevent its unfavorable consequences.

Most CVR estimation tools take traditional risk factors (RF) into account (sex, age, smoking, hypercholesterolemia, diabetes mellitus and hypertension), since they have been linked to 90% of all acute myocardial infarctions [3]. However, the evaluation of said RF not always accurately predicts the risk of cardiovascular (CV) events to occur in the future. This need for optimizing prediction has led to the design of various tools aimed at determining the 5- or 10-year risk of suffering a CV event. To many clinicians, the role and utility of such tools is not free of controversy [4].

Ideally, in order to command early interventions and preventive strategies, screening should identify individuals who are at risk but are not yet known for having complications of coronary and brain atherosclerotic disease.

Due to high inter-population variability, the local incidence and prevalence of cardiovascular risk factors and events should be determined for each population.

In order to estimate CVR, many algorithm-based stratification charts and computational programs have been created as a result of several observational studies of asymptomatic individuals at risk around the world. Among others, the most popular tools are Framingham's 2008 and the American Heart Association's 2013 charts, as well as the Systematic Coronary Risk Estimation (SCORE) elaborated by the Task Force of European Society of Cardiology and other societies [5, 6]. These charts, recommended by most international primary care guidelines, result in overall or absolute CVR based on traditional risk factors [6, 7]. To aid in decision making, they have been adapted in many different countries according to local epidemiology, but they can also under- or overestimate individual risk, since the precise capability to distinguish between people who will or will not present a CV event is lacking.

In Chile, Kunstmann and collaborators [8] were able to obtain local epidemiological data by close follow-up of approximately 12,000 people for nearly 10 years, comprising 37,470 person years of observation; a representative sample of the national situation. Furthermore, they applied both Framingham's original chart, a locally adapted version of it and the European algorithm to their study population. They observed significant differences regarding high and low risk estimations. After 5 years of observation, both Framingham's chart and the European SCORE overestimated overall risk in contrast to the Chilean adjusted version, but had a better performance when it came to differentiating between those who would or would not suffer a CV event.

Individuals with known cardiovascular disease (coronary heart disease, peripheral arterial disease, cerebrovascular disease) or diabetes mellitus, must be immediately labeled as high risk and therefore require no further investigation before defining treatment.

## Role Of Serological Markers In The Estimation Of Cardiovascular Risk

Many new strategies have been developed in attempt to further optimize risk stratification, such as the presence of plasmatic biomarkers. Many quantifiable molecules involved in multiple pathways of the pathophysiology concerning cardiovascular diseases have been submitted to evaluation, but only few have proven to add more value than the already existing estimation methods.

Erythrocyte sedimentation rate and C-reactive protein (CRP) are commonly measured to detect inflammation [9]. Since endothelial disease involves an inflammatory process, these markers could play a theoretically useful role. However, their limited specificity for evaluating vascular and cardiac injury has prevented their use to become universally accepted. CRP measurement is not recommended in asymptomatic patients of either low or high risk, but it is in those of intermediate risk. This mediator is linked to various metabolic and inflammatory pathways, including some associated to the formation of unstable atherosclerotic plaques [9]. The American Heart Association (AHA), along with the American College of Cardiology (ACC) consider CRP to be a valid marker for atherosclerotic disease that should be measured only in selected patients [10].

Conversely, elevated serum fibrinogen has demonstrated a high predictive value in acute myocardial and cerebral vascular injuries [11]. Markers for ischemia, such as troponins, have shown high sensitivity regarding myocardial infarction. Similarly, D-dimer (a metabolite of fibrin) is known for its use in ruling out venous thromboembolic disease.

Homocysteine, related to thrombus generation, is considered a second line CVR marker when elevated, but its reduction is not associated with a consequent decrease in risk [1].

Phospholipase A2-related lipoprotein (Lp(a)) is a precise marker for plaque rupture and atherothrombotic events. Its measurement could prove useful in secondary prevention in patients who are at high risk of CV event recurrences, but its high cost prevents its use in first line evaluation [1]. AHA/ACC 2019 guidelines suggest that it could be considered when there is family history of premature atherosclerotic disease, in which high levels should prompt a higher risk stratification [10].

Furthermore, other serological markers have shown risk-enhancing associations, such as cystatin-C and higher rates of renal failure [4].

## Role Of Imaging In The Estimation Of Cardiovascular Risk

Imaging has proven to improve CVR assessment and is therefore recommended in several guidelines, such as those by the AHA/ACC 2019 and the 2016 European Task Force, among others [2, 10].

### 1. Cardiac computed tomography

It is a non-invasive test that evaluates cardiac anatomy. When assessing CVR it can be employed in two ways: one being computed tomography (CT) angiography, and second, Coronary Artery Calcification Score (CACS).

#### CT angiography

This imaging technique allows for visualization of the coronary arteries, comprising wall, arterial lumen and atherosclerotic plaque characteristics. This type of study may be recommended in symptomatic patients with low or intermediate pre-test risk of coronary disease [12].

On the other hand, it has not been proven to be superior to routinely implemented functional stress testing in asymptomatic patients. It is for this reason that it plays no present role in determining CVR in such patients [12].

If CT angiography were to be used in conjunction with myocardial scintigraphy and serological markers, the combined high-yield performance could be an important tool for assessing risk in terms of anatomy, physiology and functionality.

However, such code of action still requires further investigation in order to be recommended accordingly.

### Coronary Artery Calcification Score - CACS:

Coronary artery calcification points towards underlying atherosclerosis and has been directly associated to increasing CVR. The CACS quantifies the amount of coronary calcium to improve detection of subclinical coronary involvement and to assess CVR even further [13].

Although this can and should be considered a strong complement for initial CVR estimation, it is not recommended for follow-up evaluations due to the irreversible nature of these injuries (fibrous and calcified plaques will not be removed by statins). Its use in routine screening is not recommended. A significant limitation to this test is that only about 20% of atherosclerotic plaques are calcified and therefore a large number of them remain undetected.

Both European and American guidelines include this method for risk stratification in patients with low and especially intermediate risk [12, 14]. Early detection of subclinical disease through this method improves myocardial infarction and death prediction and can therefore be relevant in guiding therapy. For example, a recent recommendation states that in intermediate risk patients, a positive result should prompt statin therapy initiation [10].

### 2. Magnetic resonance imaging (MRI)

This technique contributes to both anatomical and functional cardiac assessment, especially in myocardopathies, aortic disease and in terms of myocardial perfusion stress testing [4]. Its use in risk estimation is still limited, although new data has shown promising evidence for its utility in molecular imaging.

### 3. Carotid ultrasound imaging

Ultrasound of carotid arteries can reveal stenosis, thus making evident an atherosclerotic process that could otherwise remain undiagnosed. In spite of this, evidence has failed to support its use in universal screening. Conversely, it can be beneficial in intermediate risk patients without known CVD, in whom diagnosis of subclinical findings would prompt timely treatment initiation [1].

Further attempts to clarify its utility in risk stratification have found this technique to contribute to the determination of overall atherosclerotic plaques and burden (e.g. total volume of plaques in both carotid and femoral arteries), rather than the independent finding of carotid disease, and shows higher correlation with CVR [15].

### 4. Myocardial scintigraphy

It is a non-invasive diagnostic tool that combines the infusion of a tracer with nuclear imaging, therefore permitting evaluation of myocardial perfusion while resting as well as during cardiac stress. It is generally deemed useful when testing for coronary disease in intermediate and high-risk patients [1].

### 5. Coronariography

An invasive procedure in which peripheral arterial access is obtained in order to infuse contrast medium into the coronary arteries and thus show their precise distribution, lumen and stenosis if present. It is performed in patients that are already at high risk, making it a fundamental tool in defining the need for revascularization (secondary prevention) [16].

## Discussion

Proper CVD prevention heavily relies on timely identification of individuals who are at significant risk of suffering cardiac or cerebral vascular injuries within the next 5 to 10 years [13]. Analyses of traditional risk factors combined with serological markers and imaging pose a considerable challenge. The large offer of tools and currently available evidence remain difficult to translate into actual clinical benefit and cardiovascular risk estimation.

A recent study by Lemos and collaborators [17] evaluated multiple variables in risk estimation. Five clinical parameters were chosen (left ventricular hypertrophy shown on electrocardiogram, coronary artery calcification score (CACS), B natriuretic peptide (BNP), high sensitivity cardiac troponin and CRP).



They studied two population-based cohorts of people without CVD, provided by the Multi-Ethnic Study of Atherosclerosis (MESA; n=6,621) and the Dallas Heart Study (DHS; n=2,202). These groups were followed for 10 years. Cardiovascular events (acute myocardial injury, cerebral strokes, coronary and peripheral revascularization, heart failure, atrial fibrillation and death related to any of these causes) were registered, resulting in 1,026 and 179 events in the MESA and DHS groups, respectively. Of the five parameters, all but CRP proved to be associated with overall CVD. CACS was the best predictor of coronary disease in both cohorts.

All parameters were related to heart failure development, especially BNP, serum troponins and left ventricular hypertrophy. Thus, this multimodal approach improved overall CVR estimation in individuals with unknown history of CVD in both groups, but single parameters affected certain cardiovascular events to differing extents. This implies that at least some tools provide beneficial information regarding specific cardiovascular complications. A multimodal strategy would hereby increase heterogeneity of risk stratification (e.g. distinguishing high risk of suffering myocardial ischemic injuries from that of the appearance of heart failure)

MARKER/IMAGE	INDICATION	PROS	CONS
Charts for CV risk estimation	Patients at risk of a CV event (without known CVD or diabetes mellitus diagnose).	Easy applicability, widely studied.	Charts should be designed based on local prevalence of diseases. If not, risk may be under/overestimated.
C- reactive protein	Symptomatic patients of intermediate CV risk.	Inflammation marker.	Limited specificity.
Phospholipase A2-related lipoprotein	Patients with premature atherosclerotic disease.	Precise marker for plaque rupture and atherothrombotic events.	High cost.
CT angiography	Symptomatic patients of intermediate CV risk.	Visualization of the coronary arteries, comprising wall, arterial lumen and atherosclerotic plaque characteristics.	High cost. Patient is exposed to radiation.
Coronary artery calcification score	Asymptomatic patients of intermediate CV risk.	Early detection of subclinical disease. Good clinical correlation with CV risk.	Not useful for follow-up evaluation (only useful for initial diagnose). Only considers calcified plaques.
Magnetic resonance imaging	Main utility in mycardiopathies. Functional and structural myocardial evaluation.	High quality image.	Limited contribution for CV risk assessment High cost.
Carotid ultrasound imaging	Detection of atherosclerotic disease in intermediate-risk patients.	Easy access. Non-invasive.	Late detection. Limited contribution for CV risk assessment.
Myocardial scintigraphy	Symptomatic patients of intermediate to high CV risk.	Non-invasive. Myocardial perfusion evaluation.	High cost.
Coronariography	High CV risk patients.	Defines management, determining need for revascularization. Useful in advanced disease of high-risk patients.	Invasive. Limited contribution in early detection or primary prevention.

**Table 1:** Summary of pros and cons of new tools developed for CVR assessment.

## Conclusion

Given their overall high applicability and practical use, risk stratification charts continue to be the most recommended estimation method. However, intermediate risk patients may require additional testing.

Cardiovascular risk estimation should be approached integrally, establishing overall risk and using more sophisticated diagnostic tools as long as they are ordered and analyzed within an individual's context and with clear impact on treatment decisions.

Adding novel diagnostic methods to optimize risk estimation could increase the financial burden and hinder clinical practice, as well as reducing access to other necessary healthcare measures. Medical criterion thus calls for patient-centered rather than disease- and/or technology-driven attention.

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