INNOVATION FOREVER
Open Access

Innovation Discovery

ISSN 2959-5150 (Online)

Review

Conventional and Non-conventional Risk Factors: A Need for an Innovative Integration in Cardiovascular Disease

Ettore Luisi[1], Achille Solimene[1], Chiara Serpico[1], Luigi Marotta[1], Gisella Titolo[2], Mariarosaria Morello[1], Silvia Caiazza[1], Saverio D'Elia[2,3], Paolo Golino[1,4], Francesco S. Loffredo[1,4], Francesco Natale[4,5], Giovanni Cimmino[1,3*]

[1]*Department of Translational Medical Sciences, Section of Cardiology, University of Campania Luigi Vanvitelli, Naples, Italy*
[2]*Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy*
[3]*Cardiology Unit, Azienda Ospedaliera Universitaria Luigi Vanvitelli, Naples, Italy*
[4]*Vanvitelli Cardiology and Intensive Care Unit, Monaldi Hospital, Naples, Italy*
[5]*Department of Life Science, Health, and Health Professions, Link Campus University, Rome, Italy*

[*]***Correspondence to: Giovanni Cimmino, MD, PhD, Associate Professor of Medicine,*** *Department of Translational Medical Sciences, Section of Cardiology, University of Campania Luigi Vanvitelli, Naples 80131, Italy; Email: giovanni.cimmino@unicampania.it*

Abstract

Cardiovascular disease (CVD) remains the most important cause of morbidity and mortality worldwide, despite major advances in prevention and treatment strategies. Traditional risk scores based on conventional risk factors have improved cardiovascular prevention but are insufficient for residual risk, particularly that driven by inflammation, endothelial dysfunction, thrombosis, metabolic alterations, and chronic comorbidities such as chronic kidney disease. In this narrative review, we discuss the limitations of current cardiovascular risk assessment models and explore the added value of non-conventional biomarkers, including inflammatory, endothelial, thrombotic, and metabolic markers, as well as emerging diagnostic technologies. We analyze the growing role of point-of-care testing (POCT) in enabling rapid, decentralized, and dynamic biomarker assessment, and we examine how artificial intelligence (AI)-based approaches can integrate heterogeneous clinical, biological, and technological data. Evidence suggests that multimodal, AI-driven models outperform traditional algorithms in identifying high-risk individuals and refining personalized prevention strategies. We propose an innovative framework for cardiovascular prevention based on the integration of clinical data, biomarkers, POCT, and AI, aiming to move from static risk estimation toward a dynamic and personalized cardiovascular risk assessment paradigm.

Keywords: artificial intelligence, cardiovascular mortality, guidelines, cardiovascular prevention, emerging risk factors, endothelial dysfunction, therapeutic targets, chronic kidney disease

Received: December 29, 2025
Revised: March 13, 2026
Accepted: March 30, 2026
Published: March 31, 2026

Copyright © 2026 The Author(s). Published by Innovation Forever Publishing Group Limited. This open-access article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0), which permits unrestricted use, sharing, adaptation, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Luisi E, Solimene A, Serpico C, Marotta L, Titolo G, Morello M, Caiazza S, D'Elia S, Golino P, Loffredo FS, Natale F, Cimmino G. Conventional and Non-conventional Risk Factors: A Need for an Innovative Integration in Cardiovascular Disease. *Innov Discov*, 2026; 3(1): 5.

1 INTRODUCTION

Cardiovascular risk stratification is traditionally based on the identification and quantification of well-established clinical risk factors, such as dyslipidemia, hypertension, smoking, diabetes mellitus, and obesity, integrated into validated risk scores. Although these tools have contributed substantially to primary and secondary prevention, a significant proportion of cardiovascular events still occurs in individuals classified as low or intermediate risk, highlighting the existence of residual risk that is not adequately explained by conventional models. Growing evidence indicates that inflammation, endothelial dysfunction, thrombosis, metabolic imbalance, and organ-specific conditions such as chronic kidney disease (CKD) play a key role in cardiovascular disease (CVD). In parallel, advances in biomarker research, point-of-care testing (POCT) technologies, and artificial intelligence (AI) have created new opportunities to refine risk prediction. This article reviews conventional and non-conventional cardiovascular risk factors, discusses the clinical relevance of emerging biomarkers and POCT, and explores how AI can integrate these dimensions into a

more comprehensive and personalized cardiovascular risk assessment strategy.

2 CONVENTIONAL CARDIOVASCULAR RISK FACTORS

Cardiovascular disease is currently the leading cause of death worldwide. Its incidence remains high, primarily due to risk factors that, while well-known, are not always adequately managed and treated.

A distinction is made between modifiable and non-modifiable risk factors. Modifiable risk factors include low-density lipoprotein (LDL) cholesterol and other lipoproteins containing apolipoprotein B, high blood pressure, cigarette smoking, diabetes mellitus, obesity, and physical inactivity. Non-modifiable risk factors include age and family history[1,2].

LDL cholesterol has a proven causal role in the development of atherosclerosis. Numerous genetic, observational, and clinical studies have shown that reducing its levels leads to a proportional reduction in cardiovascular risk. Non-high-density lipoprotein (HDL) cholesterol, which includes all atherogenic lipoproteins, is also an equally valid indicator[3-5].

High blood pressure is another important factor[6,7]. The risk of coronary heart disease (CHD), heart failure (HF), and stroke increases linearly even from relatively low levels, and lowering blood pressure brings significant benefits, especially in high-risk individuals[8].

Cigarette smoking remains one of the most harmful habits[9,10]. It is responsible for half of preventable deaths in smokers and reduces life expectancy by approximately ten years[11]. The cardiovascular risk is five times higher in smokers under the age of fifty, and the damage is even more severe in women[12].

Diabetes mellitus, both type 1 and type 2, doubles the risk of cardiovascular events[13-18]. Women with type 2 diabetes have a particularly high risk of stroke. The association with other risk factors such as dyslipidemia and high blood pressure creates a complex and dangerous clinical picture[19].

Finally, physical inactivity[20,21] and the resulting adiposity[22,23], measured by body mass index and waist circumference, are closely linked to both ASCVD and type 2 diabetes. The lowest mortality is observed in subjects with a BMI between 20 and 25 kg/m², while higher values progressively increase the risk[24].

To stratify cardiovascular risk in different patients, scores that integrate all risk factors have been developed.

Systematic Coronary Risk Evaluation 2 (SCORE2) is the new algorithm developed by the European Society of Cardiology in 2021 to estimate 10-year cardiovascular risk (fatal and non-fatal events) in patients aged 40 to 69 without known cardiovascular disease or diabetes. It represents an evolution of the previous SCORE because it also includes non-fatal events, making the assessment more realistic and thus allowing it to guide clinical decisions and any changes in lipid-lowering or antihypertensive therapy in high-risk individuals. The risk factors included in the calculation are: age, gender, cigarette smoking, systolic blood pressure, total cholesterol, and HDL. A score is assigned to each of these factors to obtain a 10-year risk percentage using risk cards. A score of <5% indicates low risk, 5-10% moderate risk, 10-15% high risk, and >15% very high risk. SCORE2 is calibrated for different European regions, as data indicate a different incidence of cardiovascular events between countries. Four risk groups have been identified. Low-risk groups include France, Belgium, and Spain; moderate-risk groups include Italy and Germany; high-risk groups include Poland and Hungary; and very high-risk groups include Eastern European countries, Russia, and North Africa.

One limitation of SCORE2 is its inapplicability to elderly patients over 70 years of age or those with diabetes[25]. For this reason, two additional scores have been developed: SCORE2-OP and SCORE2-diabetes. SCORE2-OP (Older Persons) estimates 10-year cardiovascular risk in elderly subjects (≥70 years). It was developed to reduce overestimation or underestimation of risk, given that, after age 70, it increases naturally. The variables considered are the same as the SCORE2, but with thresholds and risk curves adapted to the elderly. The SCORE2-OP is also calibrated for different European areas (low, moderate, high, and very high risk), to reflect epidemiological differences between countries[26].

SCORE2-Diabetes, on the other hand, is a calculation algorithm to more accurately stratify the 10-year cardiovascular risk for patients with type 2 diabetes mellitus, under 70 years of age, without known atherosclerotic cardiovascular disease, and without severe target organ damage. Diabetic patients already have a 2-4 times higher cardiovascular risk than other patients. Therefore, using SCORE2 could lead to an underestimation of risk. In addition to the SCORE2 variables, glycated haemoglobin (HbA1c), renal function (eGFR), and diabetes duration have been added. SCORE2-Diabetes has made cardiovascular prevention in diabetics more personalized, avoiding treating all patients as automatically high risk and distinguishing those who require more aggressive strategies such as the use of hypoglycemic drugs with proven cardiovascular protection (such as SGLT2 inhibitors or GLP-1 agonists)[27] (Table 1).

In conclusion, the main modifiable risk factors for

Table 1. SCORE2, SCORE2-OP and SCORE2-Diabetes Overview

	SCORE2	SCORE2-OP	SCORE2-Diabetes
Target population	Adults 40-69 years without CVD	Adults ≥70 years without CVD	Adults with type 2 diabetes and no CVD
Purpose	Estimates 10-year risk of fatal and non-fatal cardiovascular events	Estimates 10-year risk in older adults	Estimates 10-year risk specifically for patients with diabetes
Required variables	Age, sex, smoking, SBP, total cholesterol, HDL	Age, sex, smoking, SBP, total cholesterol, HDL	Age, sex, smoking, SBP, total cholesterol, HDL, HbA1c, eGFR
Risk regions	4 European regions (low, moderate, high, very high)	4 European regions	4 European regions
Clinical use	Primary prevention in middle-aged adults	Primary prevention in older adults	More accurate risk stratification in diabetic patients

ASCVD are well known and extensively documented. Their management requires an integrated approach, combining primary prevention, early diagnosis, and targeted treatment. The use of these scores makes it easier for both physicians and patients to decide on the best intervention strategy to reduce cardiovascular risk.

3 NON-CONVENTIONAL CARDIOVASCULAR RISK FACTORS

3.1 Endothelial, Inflammatory and Thrombotic Biomarkers

Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are immunoglobulin superfamily proteins that are critically involved in endothelial activation, by mediating leukocyte adhesion and trans-endothelial migration[28-30]. ICAM-1 is constitutively expressed on endothelial and immune cells, interacting with integrins (CD11/CD18) and ligands such as fibrinogen and macrophage adhesion ligand-1, thereby supporting leukocyte recruitment, T-cell activation, and phagocytosis[29,31,323]. VCAM-1 is inducible under inflammatory stimuli, including tumor necrosis factor-alpha (TNF-α), oxidative stress, and altered shear stress, and promotes leukocyte adhesion, cytoskeletal remodeling, and extravasation; inflammatory cytokines further enhance its expression, creating a feedback loop that sustains vascular inflammation[33-35].

Circulating levels of ICAM-1 and VCAM-1 are increased and mirror an underlying state of endothelial dysfunction associated with chronic vascular inflammation in individuals with HF with preserved ejection fraction (HFpEF). Soluble ICAM-1 correlates with coronary artery calcification and subclinical atherosclerosis, while soluble VCAM-1 predicts cardiovascular morbidity and atrial fibrillation (AF)[36,37]. Adipose tissue expansion and adipokine dysregulation exacerbate endothelial dysfunction and insulin resistance, promoting vascular narrowing. Furthermore, ICAM-1 and VCAM-1 activate inflammatory and profibrotic pathways — including NF-κB, Akt/mTOR, ERK, STAT3, and TGF-β/Smad — driving inflammation, fibrosis, hypertrophy, and adverse cardiac remodeling. Although these associations support their strong pathophysiological relevance, ICAM-1 and VCAM-1 currently lack validated clinical cut-off values for cardiovascular risk stratification and are not endorsed by major cardiovascular prevention guidelines for routine risk assessment[1,38]. Moreover, given their elevation across a broad spectrum of inflammatory and systemic disorders, their limited specificity restricts their clinical applicability. Therefore, these molecules should be regarded primarily as mechanistic indicators of endothelial activation rather than validated clinical risk markers.

Evidence from genetic[59,40], epidemiological[41,42], and mechanistic studies[43,44], along with clinical trials using canakinumab[45,46] and colchicine[47,48] indicates that inhibiting the interleukin (IL)-6 pathway could reduce CVD risk independently of traditional factors. Importantly, a distinction should be made between therapeutic pathway validation and biomarker validation. While the CANTOS trial demonstrated that targeting upstream inflammation reduces recurrent cardiovascular events[46], this does not imply that IL-6 measurement itself is clinically validated for cardiovascular risk stratification. Subsequent analyses confirmed that IL-6 reduction correlates with improved outcomes[49], yet current prevention guidelines do not recommend routine IL-6 testing for cardiovascular risk assessment[1,38]. Atherosclerosis, a leading cause of CVD, develops through the accumulation of ApoB-containing lipoproteins, especially LDL cholesterol, in the arterial wall[50]. Their retention and modification trigger chronic low-grade inflammation, which can be worsened by conditions like dyslipidemia, hypertension, diabetes, smoking, and sedentary lifestyle[51]. Multiple immune cells, including macrophages, neutrophils, and lymphocytes, participate in this inflammatory process by releasing cytokines such as TNF-α, TGF-β, IFN-γ, and various interleukins (IL-1, -2, -4, -6, -7, -10, -12, -13, -17, -21)[52].

IL-6 is a key mediator in the development and progression of atherosclerotic CVD and is produced by both immune and vascular cell types[53]. It amplifies inflammation by recruiting more immune cells and stimulating additional cytokine release, leading to

endothelial activation and increased adhesion molecule expression[54,55]. IL-6 further contributes to plaque expansion by enhancing foam cell formation, stimulating smooth muscle cell proliferation and migration, and promoting extracellular matrix synthesis[56]. Furthermore, it weakens plaques by reducing collagen synthesis and fibrous cap stability while increasing tissue factor (TF) expression, creating a higher risk of rupture and thrombosis[56,57]. These mechanisms indicate that inhibiting IL-6 signaling could serve as a promising strategy for the prevention and treatment of atherosclerosis.

Nevertheless, IL-6 measurement is not currently recommended for routine cardiovascular risk assessment due to lack of standardized thresholds, assay harmonization, and robust evidence of incremental predictive value beyond established risk scores[1,38,58]. Thus, IL-6 remains a biologically relevant inflammatory mediator rather than a clinically endorsed predictor of cardiovascular risk.

TNF-α is a major cytokine that plays a central role in the inflammatory processes driving atherosclerosis[59]. Elevated TNF-α levels have been identified as independent predictors of first-time cardiovascular events[60] and are associated with recurrent coronary events following myocardial infarction (MI)[61]. TNF-α also correlates with the progression of early carotid atherosclerosis[62] and appears linked to common CHD risk factors, particularly in men with premature MI[63]. Environmental factors, such as smoking and obesity, may further modulate TNF-α levels. Smoking not only increases CVD risk[64] but also influences TNF-α concentrations in healthy individuals[65]. Moreover, TNF-α is secreted by adipocytes, and increased adiposity correlates with higher TNF-α levels and an elevated risk of CHD[66-68].

Monocytes, macrophages and, potentially, adipocytes secrete cytokines such as IL-6 and TNF-α[69,70], which contribute to insulin resistance by directly affecting the insulin receptor[71]. Both TNF-α and IL-6 show positive associations with adiposity, especially visceral fat, and are linked to insulin resistance as well as other cardiovascular risk factors.

They also boost hepatic fatty acid synthesis and stimulate lipolysis, leading to elevated serum concentrations of triglycerides and fatty acids. Although IL-6 concentrations can rise acutely in response to exercise[72,73], improvements in body composition through energy restriction and increased physical activity reduce TNF-α and IL-6 concentrations in adolescents and children. Inflammatory marker levels may be influenced by age, with IL-6, TNF-α[70], ICAM-1[74], and E-selectin[75] typically higher in healthy children compared to adults, whereas CRP tends to increase with age. Sex differences are evident in post pubertal children, with obese males exhibiting higher E-selectin and VCAM-1 levels than females[76]. These findings suggest caution when interpreting inflammatory markers in childhood and highlight the need for further research. Although randomized clinical trials such as COLCOT and LoDoCo2 demonstrated that colchicine reduces cardiovascular events in selected high-risk populations, the magnitude of absolute risk reduction was modest and dependent on the specific clinical context[47,48]. These findings highlight the therapeutic potential of targeting inflammation in atherosclerosis; however, they do not provide evidence that circulating levels of upstream cytokines, such as IL-6 or TNF-α, can be used as reliable indicators for individual patient risk assessment.

Galectin-3 (Gal-3) is a 26kDa glycoprotein-binding lectin secreted primarily by activated cardiac macrophages, playing a pivotal role in the induction and development of atherosclerosis[77]. Gal-3 contributes to plaque development and vascular injury through multiple interrelated mechanisms, including the promotion of inflammation, oxidative stress, lipid accumulation, and migration of vascular cells. It also modulates endothelial cell function by impairing endothelial progenitor cells (EPCs), which are essential for repairing damaged blood vessels and promoting angiogenesis[78,79]. Moreover, Gal-3 promotes fibroblast activation, resulting in extracellular matrix accumulation and tissue fibrosis, which, along with its pro-inflammatory actions, contribute to adverse ventricular remodeling and the progression of HF[80]. Experimental studies in NADPH oxidase 4/low-density lipoprotein receptor double knockout (Nox4-/-/Ldlr-/-) mice have demonstrated that progressive endothelial dysfunction is associated with amplified atherosclerotic plaque burden and higher Gal-3 expression compared with Ldlr-/- mice, highlighting the role of Gal-3 in plaque progression and vascular injury[81].

Clinical evidence suggests that plasma Gal-3 levels can serve as a predictor of cardiovascular mortality in high-risk patients undergoing coronary angiography[77]. Elevated Gal-3 levels are independent risk factors for coronary artery disease and mid-term all-cause mortality in MI patients, with concentrations above 8.7ng/mL indicating higher risk[82]. Gal-3 is also upregulated in HF and serves as a biomarker for diagnosis and prognosis, including in patients with HFpEF[83,84]. Increased Gal-3 levels are associated with higher mortality in acute and chronic HF, with diagnostic odds ratios ranging from 2.30 to 2.36[85]. Although approved by the FDA in 2010 for HF risk stratification, current evidence suggests Gal-3 should be used alongside other clinical parameters rather than as a sole prognostic marker.

The coagulation cascade is primarily initiated by

TF, a transmembrane glycoprotein also known as thromboplastin. In physiological conditions, TF is constitutively present in subendothelial compartments, particularly in vascular smooth muscle cells, where it is spatially segregated from circulating blood[86]. Conversely, endothelial cells and monocytes do not display TF under resting conditions; nevertheless, exposure to inflammatory signals or pathological stimuli can rapidly induce both TF expression and its procoagulant function in these cell types[97].

Beyond its role in hemostasis, TF has emerged as an important contributor to CVD. Elevated plasma concentrations of TF antigen have been reported in hypertensive patients compared with normotensive individuals, and pharmacological treatment with different classes of antihypertensive agents is able to reduce these levels[88]. A central mechanism underlying this association involves angiotensin II, which stimulates TF expression in monocytes, endothelial cells, and vascular smooth muscle cells via activation of the angiotensin II type I receptor[89,90]. In agreement with this mechanism, inhibition of the renin-angiotensin system through angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type I receptor antagonists leads to a reduction in circulating TF activity in hypertensive patients[91,92]. Notably, ACE inhibitors also suppress endotoxin-driven TF expression in monocytes, highlighting anti-inflammatory effects that are independent of blood pressure control.

Alterations in metabolic homeostasis further modulate TF expression. In human endothelial cells, high glucose levels amplify TF induction triggered by thrombin, while increased glucose intake has been shown to upregulate TF expression in circulating monocytes from healthy subjects[93]. Moreover, hyperglycemia promotes the generation of advanced glycation end-products, which stimulate TF expression in endothelial cells through engagement of the receptor for advanced glycation end-products and subsequent activation of NF-κB dependent signaling pathways[94,95].

As atherosclerosis develops, TF expression increases progressively in response to both lipid accumulation and chronic vascular inflammation. Oxidized low-density lipoprotein enhances TF expression in endothelial cells, monocytes, and macrophages, whereas high-density lipoprotein exerts an inhibitory effect on thrombin-induced TF expression[96,97]. Consistent with these experimental observations, elevated plasma TF activity has been documented in patients with high LDL cholesterol levels[98]. During plaque progression, infiltrating monocytes differentiate into macrophages and foam cells, thereby reinforcing the inflammatory microenvironment within the arterial wall[99]. Pro-inflammatory mediators, including tumor necrosis factor-α and several interleukins, further enhance TF expression. While TF expression is largely confined to monocytes in the early phases of atherogenesis, it later becomes detectable in foam cells, endothelial cells, and vascular smooth muscle cells[100].

In acute coronary syndromes, the local inflammatory response at sites of coronary artery occlusion is characterized by marked elevations in cytokine levels, which strongly induce TF expression in vascular cells[101]. Additional contributions to circulating TF derive from activated platelets and leukocytes, leading to increased TF levels in the blood of affected individuals[102]. Accordingly, patients presenting with unstable angina show significantly higher plasma TF concentrations than those with stable angina, and elevated TF levels are associated with an increased risk of future cardiovascular events[103]. (Table 2). Although TF plays a key mechanistic role in plaque destabilization and thrombus formation, its measurement is not standardized and has not been prospectively validated to provide additional prognostic information beyond established cardiovascular risk markers[58,104]. Consequently, TF should be considered primarily as an indicator of prothrombotic and inflammatory activity rather than a clinically actionable risk biomarker.

Collectively, these endothelial, inflammatory and thrombotic biomarkers delineate biologically coherent and therapeutically targetable pathways in cardiovascular disease. However, pathophysiological relevance should not be conflated with clinical validity: in the absence of standardized measurement, reproducible cut-off values, and robust evidence of incremental predictive performance beyond established risk models, these biomarkers remain indicators of disease biology rather than fully validated tools for individual cardiovascular risk stratification.

3.2 Non-Conventional Cardiovascular Risk Factors: Lipoprotein(a), Uric Acid, Hyperhomocysteinemia, and Vitamin D

Non-conventional cardiovascular risk factors are increasingly recognized for their role in CVD beyond traditional markers like dyslipidemia and hypertension.

Among these, Lipoprotein(a), uric acid, and hyperhomocysteinemia have substantial evidence linking them to CVD risk, while the role of vitamin D is less directly addressed in the current literature.

Elevated Lp(a) is a genetically determined, independent, and causal risk factor for atherosclerotic CVD, CHD, and calcific aortic valve stenosis. The risk increases continuously with higher Lp(a) levels, with no clear threshold, and is independent of other lipid levels or traditional risk factors. Guidelines recommend at least one lifetime measurement of Lp(a) in adults, especially those at intermediate or high risk. Emerging therapies targeting Lp(a), including inclisiran, and antisense

Table 2. Endothelial, Inflammatory and Thrombotic Biomarkers overview

Biomarker	Main Cellular Sources	Main Mechanisms	Clinical Relevance	References
ICAM-1	Endothelial, immune cells	Leukocyte adhesion and transmigration; endothelial activation	Marker of endothelial dysfunction; associated with subclinical atherosclerosis and HFpEF	[28-33]
VCAM-1	Activated endothelial cells	Inflammation-induced leukocyte adhesion and extravasation	Predictor of cardiovascular morbidity and atrial fibrillation	[34-38]
IL-6	Macrophages, endothelial and vascular cells, adipocytes	Amplifies inflammation; promotes plaque growth and instability	Causal mediator of atherosclerotic CVD; therapeutic target	[39-50]
TNF-α	Macrophages, adipocytes	Vascular inflammation; insulin resistance; dyslipidemia	Independent predictor of cardiovascular events and atherosclerosis	[51-62]
Galectin-3	Activated macrophages	Inflammation, fibrosis, endothelial dysfunction	Predictor of cardiovascular mortality and heart failure progression	[63-71]
Tissue factor	Vascular cells, monocytes, platelets	Initiates coagulation; inflammation-driven expression	Associated with plaque instability and thrombotic risk	[72-87]

oligonucleotides such as pelacarsen, have demonstrated promising effects in lowering Lp(a)[105-110]. Elevated uric acid is associated with hypertension, metabolic syndrome, coronary artery disease, stroke, and increased CVD mortality. The relationship is observed even at high-normal uric acid levels.

While most studies support uric acid as a risk marker, causality remains debated. Mechanisms include oxidative stress, endothelial dysfunction, and inflammation. Uric acid to HDL-C ratio is a strong predictor of CVD risk and mortality in older adults[111-115]. Elevated homocysteine is recognized as a risk factor for CVD, stroke, and atherosclerosis.

However, lowering homocysteine with B vitamins has not consistently reduced CVD risk in clinical trials, leading to debate about its causal role[116-118].

In accordance with current studies, screening may be considered in patients without other risk factors, and B vitamin deficiencies should be corrected especially in patients with intermediate/major hyperhomocysteinemia[117].

Numerous large observational studies and meta-analyses show that low vitamin D levels are linked to higher risk of CVD, including coronary artery disease, MI, HF, stroke, and cardiovascular mortality; additionally, studies reflect that hypovitaminosis D predisposes acute myocardial infarction (AMI) patients to post-infarction complications and cardiac remodeling[119-122].

The association appears particularly strong in certain populations, such as those with hypertension, diabetes, or older adults[120,123]. Biological mechanisms support a possible causal link, including effects on inflammation, endothelial function, and the renin-angiotensin-aldosterone system[121-123].

In conclusion, non-conventional cardiovascular risk factors, such as lipoprotein(a), uric acid, hyperhomocysteinemia, and vitamin D should be considered an integral component in the prevention and management of CVD.

4 FOCUS ON CKD

CKD is characterized by a glomerular filtration rate <60mL/min/1.73m² for > 3 months or by kidney damage which can be assessed by albuminuria (defined as albumin-to-creatinine ratio > 30 mg/g)[124]. Elevated levels of albuminuria increase the risk of mortality. The incidence and prevalence of CKD are increasing because of aging populations, increasing prevalence of type 2 diabetes, hypertension and underestimation of CKD early stages. CKD is associated with CVD because of vasculature damage related to kidney mediators and hemodynamic alterations[125]. Traditional cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and smoking have an important role also in CKD progression through the involvement of large kidney vessels (determining kidney arteries stenosis) and smaller vessels (causing nephroangiosclerosis). Furthermore, CKD also correlates to non-traditional cardiovascular risk factors such as inflammation and vascular calcification (due to an increase in calcium-phosphorus cells concentrations and a change in their phenotype from contractile to a synthetic one). Finally, uremic cardiomyopathy in CKD is characterized by myocardial fibrosis and left ventricular hypertrophy[126,127] (Figure 1).

According to traditional risk scores such as SCORE2 and SCORE2-OP, patients with moderate and severe CKD belong to high and very high risk of CVD categories

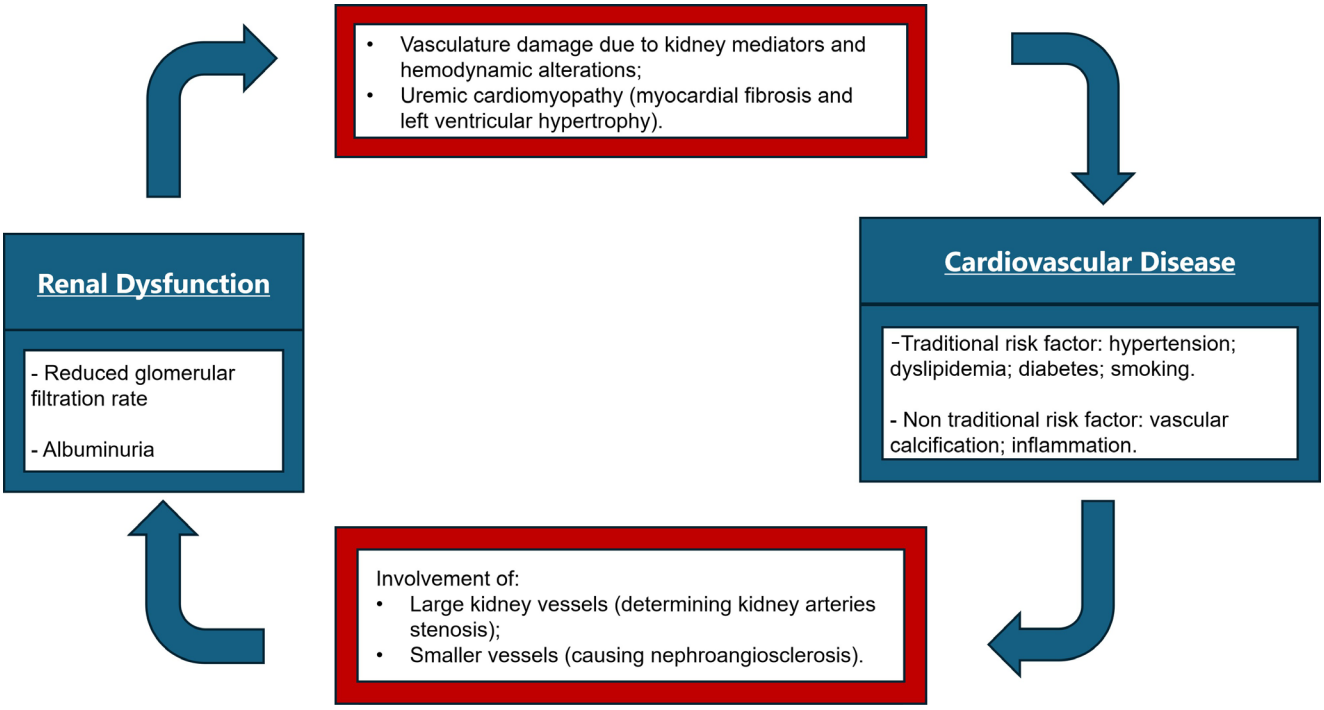


Figure 1. Renal Dysfunction and Cardiovascular Disease Relation. Renal system and cardiovascular system are strictly linked. In case of dysfunction of one of them, the other one is also involved.

respectively[128]. These scores fail to apply efficient CVD preventive therapies in CKD patients, because of the presence of specific functional and anatomical alterations[129]. A recent study proposed a new risk score, called "CKD Add-on" that adds to traditional prediction models GFR measure and albuminuria. CKD Add-on increases the efficacy of CVD risk prediction compared to SCORE2 and SCORE2-OP alone[128].

Nowadays, computational models such as AI and regression-based methods represent a possibility to improve screening strategies to prevent or accelerate diagnosis of CVD in CKD.

Type 4 cardiorenal syndrome can be defined as cardiovascular involvement in CKD which is characterized by: sudden cardiac death (SCD), arrhythmias, ischemic heart disease and HF[130].

Many studies demonstrated that computational models could predict SCD from one day after hemodialysis until 2.5years of follow-up.

Furthermore, automated learning models for arrhythmias prediction in CKD mainly focused on predicting new onset of incident AF and arrhythmic events during dialysis.

As regards ischemic heart disease, an AI models predicts the number of events at 2.5years of follow-up in hemodialysis patients.

Automated learning models can predict HF incidence, outcome and therapy efficacy. For example, an ongoing clinical trial is evaluating AI tools to predict safety and efficacy of low dose angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers in CKD patients affected by HF with reduced ejection fraction (HFrEF).

Finally, computational solutions can also predict major adverse cardiovascular events (MACE) in CKD patients.

IA models allow the analysis of a large number of data and identify complex patterns that may not be easily evident for human observers. For this reason, using these tools it is possible to generate new CV risk score systems and personalize therapies for each specific patient[129,131].

5 ROLE OF POCT

In modern medicine, increasingly oriented towards personalization and prevention, integrating risk factors-both traditional and emerging-requires diagnostic tools capable of providing rapid, precise, and immediately actionable information. In this scenario, POCT has proven to be a crucial innovation, enabling decentralized diagnostics and supporting timely clinical decisions[132-135]. POCT represents a true shift from centralized laboratory diagnostics, moving the focus towards more patient-centered care, particularly important in evaluating cardiovascular, inflammatory, and thrombotic risk[136,137]. Thanks to advances in biomarker detection, microfluidics, and AI, POCT is transforming risk stratification and disease management[138-141]. However, it is important to acknowledge that POCT devices may have limitations, such as lower analytical precision compared to

centralized laboratories and variability between different platforms[133,138].

Beyond analytical accuracy, several practical and systemic challenges must also be considered when implementing POCT in routine clinical practice. First, cost-related issues remain significant. Although POCT may reduce hospital length of stay and improve clinical efficiency, the initial investment required for device acquisition, maintenance, quality control procedures, and consumables can be substantial. In some healthcare systems, reimbursement policies are not yet fully adapted to decentralized diagnostic models, potentially limiting large-scale adoption. Therefore, comprehensive cost-effectiveness analyses are essential, taking into account both direct and indirect healthcare savings[142,143].

Second, adequate training and competency assessment of healthcare personnel are crucial to ensure reliable results. Unlike centralized laboratory diagnostics performed by specialized laboratory professionals, POCT is often conducted by nurses, physicians, or other non-laboratory staff who may not have specific training in laboratory medicine. This decentralization increases the risk of pre-analytical and analytical errors if standardized training programs, certification processes, and continuous quality assurance measures are not rigorously implemented[144,145]. International standards such as ISO 22870 and ISO 15189 emphasize the importance of structured governance, operator training, and quality management systems for POCT implementation.

Finally, regulatory aspects and quality assurance systems represent additional important challenges. POCT devices must comply with national and international regulatory frameworks to ensure analytical performance, clinical validity, and patient safety. However, approval pathways may vary across geographic regions, potentially causing delays in commercialization and clinical implementation. Moreover, ensuring consistency and harmonization between POCT results and those obtained from centralized laboratories is essential to avoid discrepancies that could influence clinical decision-making[146].

Addressing these economic, educational, and regulatory considerations is fundamental to maximizing the clinical benefits of POCT while maintaining high standards of diagnostic accuracy and patient safety.

5.1 POCT for Inflammatory, Cardiac, and Thrombotic Biomarkers

Inflammation, cardiac muscle damage, and thrombosis are fundamental processes underlying many acute and chronic diseases, particularly cardiovascular conditions. POCT platforms capable of detecting inflammatory biomarkers (such as C-reactive protein, interleukins, and procalcitonin), cardiac biomarkers (including troponins and natriuretic peptides), and thrombotic markers (like D-dimer and fibrin degradation products) allow clinicians to obtain clinically meaningful data within minutes[136-138,147]. Immediate availability of these biomarkers in clinical and outpatient settings improves early diagnosis, risk stratification, and monitoring of disease progression or treatment response. Furthermore, POCT facilitates the integration of traditional biomarkers with emerging, non-conventional indicators, enabling a more complete and dynamic assessment of patient risk[136,137]. This approach is particularly advantageous in emergency medicine, primary care, and resource-limited settings, where rapid decisions can significantly impact clinical outcomes[133,136].

5.2 Microfluidic Platforms

Microfluidic technologies are central to the evolution of POCT, as they allow miniaturization and integration of complex laboratory processes into compact devices[139,140,148,149]. These platforms manipulate tiny volumes of biological samples within microscopic channels, promoting rapid reactions, reduced reagent consumption, and highly sensitive analyses[139,148]. Microfluidic POCT devices can analyze multiple biomarkers simultaneously from a single drop of blood, supporting multiplexed diagnostics and providing a more comprehensive patient risk assessment[140,141,149]. Their portability, scalability, and compatibility with large-scale production make them ideal for widespread clinical adoption, with benefits in sustainability and cost reduction. Moreover, microfluidic platforms integrate well with novel biosensors and nanomaterials, further enhancing detection of both traditional and innovative risk factors[148,149].

5.3 POCT Combined with AI for Real-Time Decision Support

The integration of POCT with AI represents one of the most promising frontiers in diagnostic innovation[147,150]. AI algorithms can analyze POCT-generated data in real time, integrating biomarker levels with clinical parameters, patient history, and even environmental or behavioural factors[147]. This synergy enables advanced decision support systems capable of predicting risk, suggesting diagnostic pathways, and guiding personalized therapeutic interventions[150-152]. In cardiovascular and inflammatory diseases, AI-enhanced POCT can support early warning systems, improve triage accuracy, and reduce diagnostic uncertainty. Ultimately, the union of POCT and AI transforms raw diagnostic data into clinically useful information, promoting a predictive, personalized, and truly patient-centred healthcare model[147,150-152].

6 INTEGRATING AI WITH NON-CONVENTIONAL CARDIOVASCULAR RISK FACTORS AND BIOMARKERS: A NEW PARADIGM

In recent years, cardiovascular risk stratification has progressively moved beyond a purely clinical framework

toward a biologically informed perspective. Despite the widespread use of traditional risk scores, a substantial proportion of cardiovascular events continues to occur in individuals classified as low or intermediate risk, highlighting the concept of residual risk, particularly its inflammatory component[153-155]. Non-conventional biomarkers reflecting inflammation, endothelial dysfunction, thrombosis and metabolic imbalance have therefore gained increasing attention as potential tools to refine cardiovascular risk assessment.

However, these biomarkers rarely act as isolated predictors. Inflammatory mediators, endothelial activation markers and metabolic factors interact within complex, non-linear biological networks that are difficult to capture using conventional statistical models. AI and machine-learning approaches offer a conceptual shift in this context, as they are specifically designed to manage high-dimensional data and identify hidden interactions among variables without prespecified assumptions of linearity or independence[156]. Recent studies have shown that AI-based models integrating non-traditional biomarkers outperform classical risk scores in terms of discrimination and reclassification, particularly in biologically heterogeneous and high-risk populations[157].

Among emerging biomarkers, Gal-3 represents a paradigmatic example of biological complexity. Originally introduced as a prognostic marker of fibrosis and HF, Gal-3 is now recognized as a multifunctional protein involved in immune modulation, inflammation, endothelial activation and thrombotic pathways. The recent comprehensive review by Morello et al.[80] clearly highlights Gal-3 as a molecular link between cardiovascular disease and immune dysregulation, emphasizing its active role in endothelial dysfunction and pro-thrombotic signaling rather than a purely observational biomarker. These context-dependent effects make Gal-3 particularly suitable for AI-driven integration, where its contribution can be interpreted in relation to coexisting inflammatory and metabolic signals.

A similar complexity characterizes hyperhomocysteinemia, a well-established but still controversial cardiovascular risk factor. Experimental and clinical evidence indicates that elevated homocysteine levels promote oxidative stress, endothelial dysfunction and activation of pro-thrombotic pathways. Recent work by Cimmino, D'Elia and colleagues has contributed to clarifying the mechanistic links between homocysteine metabolism, vascular injury and cardiovascular risk[158]. Notably, the same group has demonstrated a protective role of vitamin D against IL-6-mediated pro-atherothrombotic effects in human endothelial cells[159]. These multifaceted effects further support the need for analytical frameworks capable of integrating homocysteine within broader biological networks rather than evaluating it as a single linear predictor.

Despite growing interest, the current literature remains fragmented. Most AI-based cardiovascular prediction models rely on limited biomarker panels, retrospective datasets and often exclude endothelial and thrombotic markers that are central to vascular vulnerability. This limitation is particularly evident in conditions such as CKD, where inflammation, metabolic disturbances and endothelial dysfunction coexist and traditional risk algorithms consistently underperform[160]. In this setting, AI should not be regarded merely as a technical refinement, but as a necessary tool to translate biological complexity into clinically meaningful risk stratification.

In this framework, AI does not simply improve risk prediction accuracy, but fundamentally changes the way cardiovascular risk is conceptualized, shifting from isolated predictors to interacting biological systems. Overall, integrating AI with non-conventional cardiovascular biomarkers marks a transition from static, factor-based risk estimation toward a dynamic, systems-level understanding of cardiovascular disease. Future research should prioritize biologically grounded, multimodal models that balance predictive accuracy with interpretability, paving the way for truly personalized cardiovascular prevention.

In this perspective, interpretability and explainability are not merely technical refinements but essential requirements for clinical translation. While complex machine-learning models may achieve superior predictive performance, their adoption in cardiovascular prevention depends on the ability of clinicians to understand how specific variables contribute to individual risk estimation[161,162]. Highly complex deep-learning architectures, often described as "black box" systems, may generate accurate predictions without transparent reasoning pathways, potentially limiting clinician trust and clinical accountability. Explainable AI approaches, including feature attribution methods and model-agnostic explanation tools, may help clarify the relative contribution of non-conventional biomarkers such as Gal-3, homocysteine, inflammatory cytokines or thrombotic markers within multidimensional risk profiles. This transparency is particularly important when integrating biologically interconnected pathways, where nonlinear interactions may otherwise obscure mechanistic plausibility and clinical reasoning[162]. Furthermore, the integration of AI into cardiovascular risk stratification raises relevant ethical and medico-legal considerations. Risk prediction models trained on retrospective or demographically homogeneous datasets may inadvertently introduce algorithmic bias, limiting generalizability across diverse populations and potentially amplifying existing health disparities. External validation in independent and geographically heterogeneous cohorts is therefore indispensable before clinical implementation.

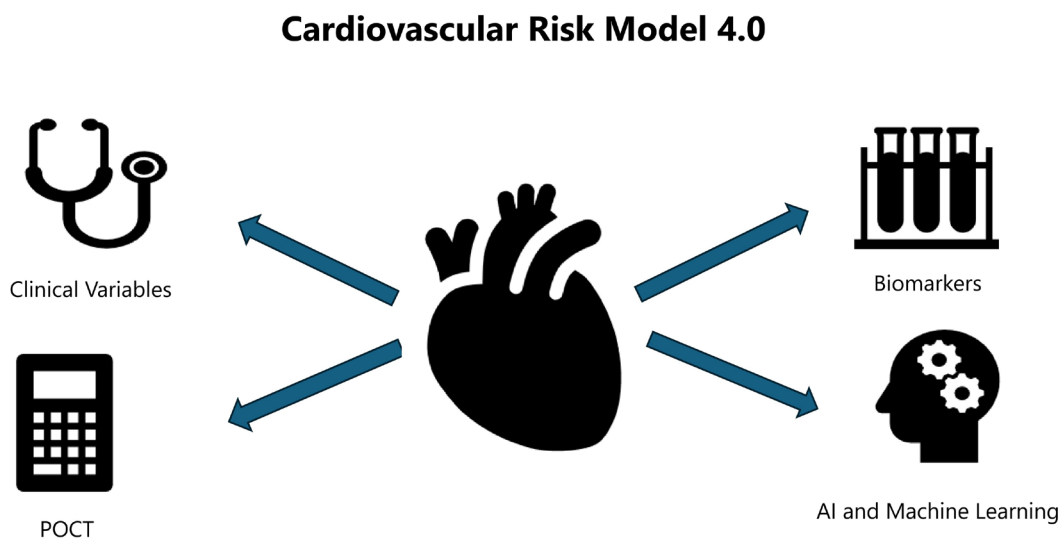


Figure 2. Cardiovascular Risk Model 4.0. The synergistic integration of clinical variables, biomarkers, POCT, and AI-driven cardiovascular risk stratification.

In addition, questions regarding accountability remain central: AI systems should function as decision-support tools rather than autonomous decision-makers, with final responsibility residing in clinical judgment. Continuous performance monitoring, recalibration strategies, and regulatory oversight are essential to ensure safety, equity, transparency, and medico-legal sustainability in real-world application[163].

7 WHAT IS NEW IN THIS REVIEW?

The novelty of this review lies in highlighting the structural limitations of traditional risk models, the inadequacy of linear statistical approaches, and the transformative potential of integrating AI with POCT in clinical practice[164-170]. Conventional models, such as Framingham, SCORE, or QRISK, rely on a fixed set of well-known variables and often assume linear relationships, overlooking patient-specific dynamics. This limits their ability to integrate emerging biomarkers, non-conventional signals, or complex interactions among risk factors, reducing predictive accuracy in diverse and high-risk populations[168]. Many traditional models are based on linear regression or proportional hazard models, which cannot capture non-linear interactions, hidden patterns, or dynamic risk clusters[164]. In cardiovascular diseases, often multifactorial and involving inflammatory and thrombotic processes, the relationships between biomarkers and clinical outcomes are inherently non-linear[167]. Therefore, linear statistical approaches are insufficient for precise risk stratification. The use of AI applied to POCT data is not merely an incremental improvement; it represents a true paradigm shift[165,166] AI algorithms can analyze biomarker data in real time, integrating patient history, environmental, and behavioral factors, enabling personalized and predictive decision-making directly at the point of care. For example, deep learning models applied to ECGs[166] or machine learning models developed from the UK Biobank[165] can predict cardiovascular risk beyond conventional scores. This approach transforms isolated diagnostic measurements into dynamic, continuous, patient-centered risk assessments, fundamentally shifting the paradigm from static evaluation to predictive, personalized healthcare. In summary, this review demonstrates how integrating AI and POCT can overcome the limitations of traditional risk models, paving the way for more precise, dynamic, and personalized cardiovascular risk management.

8 CONCLUSION

A contemporary approach to cardiovascular prevention requires moving beyond isolated clinical variables toward an integrated, data-rich model. The combination of traditional clinical data with non-conventional biomarkers reflecting inflammation, endothelial dysfunction, thrombosis, and metabolic alterations provides a more meaningful representation of cardiovascular risk. POCT plays a crucial role by allowing rapid, repeatable, and context-specific biomarker assessment, thereby transforming risk stratification into a dynamic process. AI further enhances this framework by integrating heterogeneous data sources, identifying complex non-linear interactions, and supporting individualized risk prediction. We propose an innovative "Cardiovascular Risk Model 4.0", based on the synergistic integration of clinical variables, biomarkers, POCT, and AI-driven cardiovascular risk stratification. This model shifts cardiovascular prevention from a static, population-based paradigm to a dynamic, personalized, and systems-oriented approach, with the potential to improve early detection, optimize preventive strategies, and ultimately reduce residual cardiovascular risk (Figure 2).

Acknowledgements

We would like to thank our nurses and collaborators that every day with passion and dedication help us in taking care of our patients.

Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

The data for this manuscript are derived from publicly available published clinical trial and study results from 1975 to 2025.

Author Contribution

Cimmino GC and Luisi EL contributed to the conceptualization and methodology; Luisi EL, Morello MM, Titolo GT, D'Elia SD, Marotta LM, Solimene AS, Caiazza SC and Serpico CS contributed to the resources and data curation; Luisi EL, Morello MM, Titolo GT, Marotta LM, Solimene AS, Caiazza SC, Serpico CS, Loffredo FL and Natale FN wrote the original draft; Golino PG and Cimmino GC reviewed and edited the manuscript; Golino PG and Cimmino GC supervised the study. All authors have read and approved the final version of the manuscript.

Abbreviation List

ACE, Angiotensin-converting enzyme
AF, Atrial fibrillation
AI, Artificial intelligence
AMI, Acute myocardial infarction
ARBs, Angiotensin receptor blockers
CHD, Coronary heart disease
CKD, Chronic kidney disease
CVD, Cardiovascular disease
EPCs, Endothelial progenitor cells
Gal-3, Galectin-3
HbA1c, Glycated hemoglobin
HF, Heart failure
ICAM-1, Intercellular adhesion molecule-1
LDL, Low-density lipoprotein
MACE, Major adverse cardiovascular events
MI, Myocardial infarction
POCT, Point-of-care testing
SCORE2, Systematic Coronary Risk Evaluation 2
TF, Tissue factor
VCAM-1, Vascular cell adhesion molecule-1

References

[1] Visseren FLJ, Cannon CP, Ference BA et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*, 2021; 42: 3227-3337.[DOI]

[2] Cannon CP. Cardiovascular disease and modifiable cardiometabolic risk factors. *Clin Cornerstone*, 2007; 8: 11-28.[DOI]

[3] Ference BA, Cannon CP, Visseren FLJ et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*, 2017; 38: 2459-2467.[DOI]

[4] Raja V, Ference BA, Cannon CP et al. Non-HDL-cholesterol in dyslipidemia: Review of the state-of-the-art literature and outlook. *Atherosclerosis*, 2023; 383: 117312.[DOI]

[5] Kopin L, Lowenstein CJ. Dyslipidemia. *Ann Intern Med*, 2017; 167: ITC81-ITC96.[DOI]

[6] Roccella EJ, Bowler AE. Hypertension as a risk factor. *Cardiovasc Clin*, 1990; 20: 49-63.

[7] Hengel FE, Sommer C, Wenzel U. Arterielle Hypertonie - Eine Übersicht für den ärztlichen Alltag. *DMW Deutsche Medizinische Wochenschrift*, 2022; 147: 414-428.[DOI]

[8] Whelton SP, Cannon CP, Visseren FLJ et al. Association of Normal Systolic Blood Pressure Level With Cardiovascular Disease in the Absence of Risk Factors. *JAMA Cardiol*, 2020; 5: 1011.[DOI]

[9] Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. *J Am Coll Cardiol*, 2004; 43: 1731-1737.[DOI]

[10] Benowitz NL, Liakoni E. Tobacco use disorder and cardiovascular health. *Addiction*, 2022; 117: 1128-1138.[DOI]

[11] Duncan MS, Cannon CP, Visseren FLJ et al. Inclusion of Smoking Data in Cardiovascular Disease Risk Estimation. *JAMA Cardiol*, 2022; 7: 195.[DOI]

[12] Doll R, Peto R, Boreham J et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*, 2004; 328: 1519.[DOI]

[13] Henning RJ. Type-2 Diabetes Mellitus and Cardiovascular Disease. *Future Cardiol*, 2018; 14: 491–509.[DOI]

[14] Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. *Curr Cardiol Rep*, 2019; 21: 21.[DOI]

[15] Petak S, Sardhu A. The Intersection of Diabetes and Cardiovascular Disease. *Methodist Debakey Cardiovasc J*, 2018; 14: 249.[DOI]

[16] Berry J, Keebler ME, McGuire DK. Diabetes Mellitus and Cardiovascular Disease. *Herz*, 2004; 29: 5.[DOI]

[17] Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacol Res*, 2016; 113: 600–609.[DOI]

[18] Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. *Circ Res*, 2020; 126: 1477–1500.[DOI]

[19] Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*, 2010; 375: 2215–2222.[DOI]

[20] Lavie CJ, Ozemek C, Carbone S et al. Sedentary Behavior, Exercise, and Cardiovascular Health. *Circ Res*, 2019; 124: 799–815.[DOI]

[21] Hamer M, O'Donovan G, Murphy M. Physical Inactivity and the Economic and Health Burdens Due to Cardiovascular Disease: Exercise as Medicine, 2017: 3-18.[DOI]

[22] Elagizi A, Kachur S, Carbone S et al. A Review of Obesity, Physical Activity, and Cardiovascular Disease. *Curr Obes Rep*, 2020; 9: 571-581.[DOI]

[23] Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. *Circ Res*, 2016; 118: 1752-1770.[DOI]

[24] Abarca-Gómez L, Cannon CP, Ference BA et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*, 2017; 390: 2627-2642.[DOI]

[25] Hageman S, Cannon CP, Ference BA et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*, 2021; 42: 2439-2454.[DOI]

[26] de Vries TI, Cannon CP, Ference BA et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur Heart J*, 2021; 42: 2455-2467.[DOI]

[27] Marx N, Cannon CP, Ference BA et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur*

Heart J, 2023; 44: 4043-4140.[DOI]

[28] Sans M, Cannon CP, Ference BA et al. VCAM-1 and ICAM-1 mediate leukocyte-endothelial cell adhesion in rat experimental colitis. *Gastroenterology*, 1999; 116: 874-883.[DOI]

[29] Mukhopadhyay S, Malik P, Arora SK et al. Intercellular adhesion molecule-1 as a drug target in asthma and rhinitis. *Respirology*, 2014; 19: 508-513.[DOI]

[30] Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol*, 2020; 108: 787-799.[DOI]

[31] Singh M, Cannon CP, Ference BA et al. Gene regulation of intracellular adhesion molecule-1 (ICAM-1): A molecule with multiple functions. *Immunol Lett*, 2021; 240: 123-136.[DOI]

[32] van de Stolpe A, van der Saag PT. Intercellular adhesion molecule-1. *J Mol Med*, 1996; 74: 13-33.[DOI]

[33] Kong DH, Kim Y, Kim M et al. Emerging Roles of Vascular Cell Adhesion Molecule-1 (VCAM-1) in Immunological Disorders and Cancer. *Int J Mol Sci*, 2018; 19: 1057.[DOI]

[34] Zhong L, Simard MJ, Huot J. Endothelial microRNAs regulating the NF-κB pathway and cell adhesion molecules during inflammation. *FASEB J*, 2018; 32: 4070-4084.[DOI]

[35] Carr RM. VCAM-1: closing the gap between lipotoxicity and endothelial dysfunction in nonalcoholic steatohepatitis. *J Clin Invest*, 2021; 131: 6.[DOI]

[36] Troncoso MF, Cannon CP, Ference BA et al. VCAM-1 as a predictor biomarker in cardiovascular disease. *Biochim Biophys Acta Mol Basis Dis*, 2021; 1867: 166170.[DOI]

[37] Gross MD, Cannon CP, Ference BA et al. Circulating Soluble Intercellular Adhesion Molecule 1 and Subclinical Atherosclerosis: the Coronary Artery Risk Development in Young Adults Study. *Clin Chem*, 2012; 58: 411-420.[DOI]

[38] Arnett DK, Cannon CP, Ference BA et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary. *J Am Coll Cardiol*, 2019; 74: 1376-1414.[DOI]

[39] Cai T, Cannon CP, Ference BA et al. Association of Interleukin 6 Receptor Variant With Cardiovascular Disease Effects of Interleukin 6 Receptor Blocking Therapy. *JAMA Cardiol*, 2018; 3: 849.[DOI]

[40] The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet*, 2012; 379: 1214-1224.[DOI]

[41] Papadopoulos A, Cannon CP, Ference BA et al. Circulating Interleukin-6 Levels and Incident Ischemic Stroke. *Neurology*, 2022; 98: 10.[DOI]

[42] Kaptoge S, Cannon CP, Ference BA et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J*, 2014; 35: 578-589.[DOI]

[43] Kobara M, Cannon CP, Ference BA et al. Antibody against interleukin-6 receptor attenuates left ventricular remodelling after myocardial infarction in mice. *Cardiovasc Res*, 2010; 87: 424-430.[DOI]

[44] Akita K, Cannon CP, Ference BA et al. An Interleukin-6 Receptor Antibody Suppresses Atherosclerosis in Atherogenic Mice. *Front Cardiovasc Med*, 2017; 4.[DOI]

[45] Ridker PM, Cannon CP, Ference BA et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*, 2018; 391: 319-328.[DOI]

[46] Ridker PM, Cannon CP, Ference BA et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med*, 2017; 377: 1119-1131.[DOI]

[47] Tardif JC, Cannon CP, Ference BA et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*, 2019; 381: 2497-2505.[DOI]

[48] Nidorf SM, Cannon CP, Ference BA et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*, 2020; 383: 1838-1847.[DOI]

[49] Ridker PM, Cannon CP, Ference BA et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J*, 2018; 39: 3499-3507.[DOI]

[50] Nayor M, Brown KJ, Vasan RS. The Molecular Basis of Predicting Atherosclerotic Cardiovascular Disease Risk. *Circ Res*, 2021; 128: 287-303.[DOI]

[51] Henein MY, Vancheri S, Longo G et al. The Role of Inflammation in Cardiovascular Disease. *Int J Mol Sci*, 2022; 23: 12906.[DOI]

[52] Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. *Int J Mol Sci*, 2024; 25: 1082.[DOI]

[53] Su JH, Cannon CP, Ference BA et al. Interleukin-6: A Novel Target for Cardio-Cerebrovascular Diseases. *Front Pharmacol*, 2021; 12.[DOI]

[54] Didion S. Cellular and Oxidative Mechanisms Associated with Interleukin-6 Signaling in the Vasculature. *Int J Mol Sci*, 2017; 18: 2563.[DOI]

[55] Alfaddagh A, Cannon CP, Ference BA et al. Inflammation and cardiovascular disease: From mechanisms to therapeutics. *Am J Prev Cardiol*, 2020; 4: 100130.[DOI]

[56] Katkenov N, Mukhatayev Z, Kozhakhmetov S et al. Systematic Review on the Role of IL-6 and IL-1β in Cardiovascular Diseases. *J Cardiovasc Dev Dis*, 2024; 11: 206.[DOI]

[57] Ridker PM. Inhibiting Interleukin-6 to Reduce Cardiovascular Event Rates. *J Am Coll Cardiol*, 2021; 77: 1856-1858.[DOI]

[58] Hlatky MA, Cannon CP, Ference BA et al. Criteria for Evaluation of Novel Markers of Cardiovascular Risk. *Circulation*, 2009; 119: 2408-2416.[DOI]

[59] Hansson GK. Immune Mechanisms in Atherosclerosis. *Arterioscler Thromb Vasc Biol*, 2001; 21: 1876-1890.[DOI]

[60] Cesari M, Cannon CP, Ference BA et al. Inflammatory Markers and Onset of Cardiovascular Events. *Circulation*, 2003; 108: 2317-2322.[DOI]

[61] Ridker PM, Rifai N, Pfeffer M et al. Elevation of Tumor Necrosis Factor-α and Increased Risk of Recurrent Coronary Events After Myocardial Infarction. *Circulation*, 2000; 101: 2149-2153.[DOI]

[62] Skoog T. Plasma tumour necrosis factor-α and early carotid atherosclerosis in healthy middle-aged men. *Eur Heart J*, 2002; 23: 376-383.[DOI]

[63] Jovinge S, Cannon CP, Ference BA et al. Evidence for a role of tumor necrosis factor α in disturbances of triglyceride and glucose metabolism predisposing to coronary heart disease. *Metabolism*, 1998; 47: 113-118.[DOI]

[64] Reuterwall C, Cannon CP, Ference BA et al. Higher relative, but lower absolute risks of myocardial infarction in women than in men: analysis of some major risk factors in the Sheep study. *J Intern Med*, 1999; 246: 161-174.[DOI]

[65] Haddy N. IL-6, TNF-α and atherosclerosis risk indicators in a healthy family population: the STANISLAS cohort. *Atherosclerosis*, 2003; 170: 277-283.[DOI]

[66] Sethi JK, Hotamisligil GS. The role of TNFα in adipocyte metabolism. *Semin Cell Dev Biol*, 1999; 10: 19-29.[DOI]

[67] Dandona P, Weinstock R, Thusu K et al. Tumor Necrosis Factor-α in Sera of Obese Patients: Fall with Weight Loss. *J Clin Endocrinol Metab*, 1998; 83: 2907-2910.[DOI]

[68] Zinman B, Hanley AJG, Harris SB et al. Circulating Tumor Necrosis Factor-α Concentrations in a Native Canadian Population with High Rates of Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab*, 1999; 84: 272-278.[DOI]

[69] Heilbronn L, Campbell L. Adipose Tissue Macrophages, Low Grade Inflammation and Insulin Resistance in Human Obesity. *Curr Pharm Des*, 2008; 14: 1225-1230.[DOI]

[70] Sack U, Burkhardt U, Borte M et al. Age-Dependent Levels of Select Immunological Mediators in Sera of Healthy Children. *Clin Diagn Lab Immunol*, 1998; 5: 28-32.[DOI]

[71] Mendall MA, Cannon CP, Ference BA et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart*, 1997; 78: 273-277.[DOI]

[72] Tirakitsoontorn P, Nussbaum E, Moser C et al. Fitness, Acute Exercise, and Anabolic and Catabolic Mediators in Cystic Fibrosis. *Am J Respir Crit Care Med*, 2001; 164: 1432-1437.[DOI]

[73] Nemet D, Oh Y, Kim HS et al. Effect of Intense Exercise on Inflammatory Cytokines and Growth Mediators in Adolescent Boys. *Pediatrics*, 2002; 110: 681-689.[DOI]

[74] Lee S, Bacha F, Gungor N, Arslanian S. Comparison of Different Definitions of Pediatric Metabolic Syndrome: Relation to Abdominal Adiposity, Insulin Resistance, Adiponectin, and Inflammatory Biomarkers. *J Pediatr*, 2008; 152: 177-184.e3.[DOI]

[75] Ponthieux A, Herbeth B, Droesch S et al. Biological determinants of serum ICAM-1, E-selectin, P-selectin and L-selectin levels in healthy subjects: the Stanislas study. *Atherosclerosis*, 2004; 172: 299-308.[DOI]

[76] Kapiotis S, Cannon CP, Ference BA et al. A Proinflammatory State Is Detectable in Obese Children and Is Accompanied by Functional and Morphological Vascular Changes. *Arterioscler Thromb Vasc Biol*, 2006; 26: 2541-2546.[DOI]

[77] Maiolino G, Cannon CP, Ference BA et al. Galectin-3 Predicts Long-Term Cardiovascular Death in High-Risk Patients With Coronary Artery Disease. *Arterioscler Thromb Vasc Biol*, 2015; 35: 725-732.[DOI]

[78] Chen X, Cannon CP, Ference BA et al. Galectin-3 exacerbates ox-LDL-mediated endothelial injury by inducing inflammation via integrin β1-RhoA-JNK signaling activation. *J Cell Physiol*, 2019; 234: 10990-11000.[DOI]

[79] Pei C, Wang X, Lin Y et al. Inhibition of Galectin-3 Alleviates Cigarette Smoke Extract-Induced Autophagy and Dysfunction in Endothelial Progenitor Cells. *Oxid Med Cell Longev*, 2019; 2019: 1-13.[DOI]

[80] Morello M, Cannon CP, Ference BA et al. Galectin-3: A Multitasking Protein Linking Cardiovascular Diseases, Immune Disorders and Beyond. *Targets*, 2025; 3: 34.[DOI]

[81] Langbein H, Cannon CP, Ference BA et al. NADPH oxidase 4 protects against development of endothelial dysfunction and atherosclerosis in LDL receptor deficient mice. *Eur Heart J*, 2016; 37: 1753-1761.[DOI]

[82] Lisowska A, Cannon CP, Ference BA et al. Predictive value of Galectin-3 for the occurrence of coronary artery disease and prognosis after myocardial infarction and its association with carotid IMT values in these patients: A mid-term prospective cohort study. *Atherosclerosis*, 2016; 246: 309-317.[DOI]

[83] Yin QS, Shi B, Dong L, Bi L. Comparative study of galectin-3 and B-type natriuretic peptide as biomarkers for the diagnosis of heart failure. *J Geriatr Cardiol*, 2014; 11: 79-82.[DOI]

[84] Dumic J, Dabelic S, Flögel M. Galectin-3: An open-ended story. *Biochim Biophys Acta Gen Subj*, 2006; 1760: 616-635.[DOI]

[85] Chen YS, Cannon CP, Ference BA et al. Using The Galectin-3 Test to Predict Mortality in Heart Failure Patients: a Systematic Review and Meta-Analysis. *Biomark Med*, 2016; 10: 329-342.[DOI]

[86] Mackman N, Morrissey JH, Fowler B, Edgington TS. Complete sequence of the human tissue factor gene, a highly regulated cellular receptor that initiates the coagulation protease cascade. *Biochemistry*, 1989; 28: 1755-1762.[DOI]

[87] Wilcox JN, Smith KM, Schwartz SM, Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci U S A*, 1989; 86: 2839-2843.[DOI]

[88] Felmeden DC, Cannon CP, Ference BA et al. Relation of thrombogenesis in systemic hypertension to angiogenesis and endothelial damage/dysfunction (a Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT]). *Am J Cardiol*, 2003; 92: 400-405.[DOI]

[89] Taubman MB, Marmur JD, Rosenfield CL et al. Agonist-mediated tissue factor expression in cultured vascular smooth muscle cells. Role of Ca2+ mobilization and protein kinase C activation. *J Clin Invest*, 1993; 91: 547-552.[DOI]

[90] He M, He X, Xie Q et al. Angiotensin II induces the expression of tissue factor and its mechanism in human monocytes. *Thromb Res*, 2006; 117: 579-590.[DOI]

[91] Koh KK, Cannon CP, Ference BA et al. Angiotensin II type 1 receptor blockers reduce tissue factor activity and plasminogen activator inhibitor type-1 antigen in hypertensive patients: a randomized, double-blind, placebo-controlled study. *Atherosclerosis*, 2004; 177: 155-160.[DOI]

[92] Soejima H, Cannon CP, Ference BA et al. Angiotensin-converting enzyme inhibition reduces monocyte chemoattractant protein-1 and tissue factor levels in patients with myocardial infarction. *J Am Coll Cardiol*, 1999; 34: 983-988.[DOI]

[93] Boeri D, Almus FE, Maiello M et al. Modification of Tissue-Factor mRNA and Protein Response to Thrombin and Interleukin 1 by High Glucose in Cultured Human Endothelial Cells. *Diabetes*, 1989; 38: 212-218.[DOI]

[94] Bierhaus A, Cannon CP, Ference BA et al. Advanced Glycation End Product-Induced Activation of NF-κB is Suppressed by α-Lipoic Acid in Cultured Endothelial Cells. *Diabetes*, 1997; 46: 1481-1490.[DOI]

[95] Bierhaus A, Cannon CP, Ference BA et al. Advanced Glycation End Product (AGE)-Mediated Induction of Tissue Factor in Cultured Endothelial Cells Is Dependent on RAGE. *Circulation*, 1997; 96: 2262-2271.[DOI]

[96] Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. *Nature*, 2008; 451: 904-913.[DOI]

[97] Wada H, Cannon CP, Ference BA et al. Effect of lipoproteins on tissue factor activity and PAI-II antigen in human monocytes and macrophages. *Int J Cardiol*, 1994; 47: S21-S25.[DOI]

[98] Sambola A, Cannon CP, Ference BA et al. Role of Risk Factors in the Modulation of Tissue Factor Activity and Blood Thrombogenicity. *Circulation*, 2003; 107: 973-977.[DOI]

[99] Hansson GK. Inflammation, Atherosclerosis, and Coronary Artery Disease. *N Engl J Med*, 2005; 352: 1685-1695.[DOI]

[100] Thiruvikraman SV, Guha A, Roboz J et al. In situ localization of tissue factor in human atherosclerotic plaques by binding of digoxigenin-labeled factors VIIa and X. *Lab Invest*, 1996; 75: 451-461.

[101] Maier W, Cannon CP, Ference BA et al. Inflammatory Markers at the Site of Ruptured Plaque in Acute Myocardial Infarction. *Circulation*, 2005; 111: 1355-1361.[DOI]

[102] Suefuji H, Cannon CP, Ference BA et al. Increased plasma tissue factor levels in acute myocardial infarction. *Am Heart J*, 1997; 134: 253-259.[DOI]

[103] Soejima H, Cannon CP, Ference BA et al. Heightened Tissue Factor Associated With Tissue Factor Pathway Inhibitor and Prognosis in Patients With Unstable Angina. *Circulation*, 1999; 99: 2908-2913.[DOI]

[104] Pearson TA, Cannon CP, Ference BA et al. Markers of Inflammation and Cardiovascular Disease. *Circulation*, 2003; 107: 499-511.[DOI]

[105] Clair V, Zirille FM, Gill E. Rethinking cardiovascular risk: The emerging role of lipoprotein(a) screening. *Am J Prev Cardiol*, 2025; 21: 100945.[DOI]

[106] Arnold N, Cannon CP, Ference BA et al. Lipoprotein (a) and incident coronary heart disease in the community: impact of traditional

cardiovascular risk factors. *Eur J Prev Cardiol*, 2025.[DOI]

[107] Kim JA, Kim NH. Lipoprotein(a) and Cardiovascular Risk in Asian Populations: A Comprehensive Review. *J Lipid Atheroscler*, 2025; 14: 174.[DOI]

[108] Reyes-Soffer G, Cannon CP, Ference BA et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*, 2022; 42.[DOI]

[109] Doherty S, Cannon CP, Ference BA et al. Lipoprotein(a) as a Causal Risk Factor for Cardiovascular Disease. *Curr Cardiovasc Risk Rep*, 2025; 19: 8.[DOI]

[110] Nordestgaard BG, Cannon CP, Ference BA et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*, 2010; 31: 2844-2853.[DOI]

[111] Gagliardi ACM, Miname MH, Santos RD. Uric acid: A marker of increased cardiovascular risk. *Atherosclerosis*, 2009; 202: 11-17.[DOI]

[112] Yu W, Cheng JD. Uric Acid and Cardiovascular Disease: An Update From Molecular Mechanism to Clinical Perspective. *Front Pharmacol*, 2020; 11.[DOI]

[113] Cui Y, Zhang W. Long-term cardiovascular risk and mortality associated with uric acid to HDL-C ratio: a 20-year cohort study in adults over 40. *Sci Rep*, 2025; 15: 14242.[DOI]

[114] Ndrepepa G. Uric acid and cardiovascular disease. *Clin Chim Acta*, 2018; 484: 150-163.[DOI]

[115] Feig DI, Kang DH, Johnson RJ. Uric Acid and Cardiovascular Risk. *N Engl J Med*, 2008; 359: 1811-1821.[DOI]

[116] Cao X, Cannon CP, Ference BA et al. Dysregulated homocysteine metabolism and cardiovascular disease and clinical treatments. *Mol Cell Biochem*, 2025; 480: 4907-4920.[DOI]

[117] Guéant JL, Guéant-Rodriguez RM, Oussalah A et al. Hyperhomocysteinemia in Cardiovascular Diseases: Revisiting Observational Studies and Clinical Trials. *Thromb Haemost*, 2023; 123: 270-282.[DOI]

[118] Paganelli F, Cannon CP, Ference BA et al. Hyperhomocysteinemia and Cardiovascular Disease: Is the Adenosinergic System the Missing Link? *Int J Mol Sci*, 2021; 22: 1690.[DOI]

[119] Kheiri B, Abdalla A, Osman M et al. Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. *Clin Hypertens*, 2018; 24: 9.[DOI]

[120] Wang TJ, Cannon CP, Ference BA et al. Vitamin D Deficiency and Risk of Cardiovascular Disease. *Circulation*, 2008; 117: 503-511.[DOI]

[121] Balasubramanian A, Cannon CP, Ference BA et al. Association of Vitamin D Deficiency as an Independent Risk Factor for Myocardial Infarction and Its Therapeutic Implications: A Systematic Review. *Cureus*, 2025.[DOI]

[122] Cosentino N, Cannon CP, Ference BA et al. Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. *Nutrients*, 2021; 13: 3603.[DOI]

[123] Grant WB, Boucher BJ, Cheng RZ et al. Vitamin D and Cardiovascular Health: A Narrative Review of Risk Reduction Evidence. *Nutrients*, 2025; 17: 2102.[DOI]

[124] Drawz P, Rahman M. Chronic Kidney Disease. *Ann Intern Med*, 2015; 162: ITC1-ITC16.[DOI]

[125] Zoccali C, Cannon CP, Ference BA et al. Diagnosis of cardiovascular disease in patients with chronic kidney disease. *Nat Rev Nephrol*, 2023; 19: 733-746.[DOI]

[126] Jankowski J, Floege J, Fliser D et al. Cardiovascular Disease in Chronic Kidney Disease. *Circulation*, 2021; 143: 1157-1172.[DOI]

[127] Alhaj E, Alhaj N, Rahman I et al. Uremic Cardiomyopathy: An Underdiagnosed Disease. *Congest Heart Fail*, 2013; 19.[DOI]

[128] Matsushita K, Cannon CP, Ference BA et al. Including measures of chronic kidney disease to improve cardiovascular risk prediction by SCORE2 and SCORE2-OP. *Eur J Prev Cardiol*, 2023; 30: 8-16.[DOI]

[129] Burlacu A, Iftene A, Popa IV et al. Computational Models Used to Predict Cardiovascular Complications in Chronic Kidney Disease Patients: A Systematic Review. *Medicina*, 2021; 57: 538.[DOI]

[130] Di Lullo L, House A, Gorini A et al. Chronic kidney disease and cardiovascular complications. *Heart Fail Rev*, 2015; 20: 259-272.[DOI]

[131] Simeri A, Cannon CP, Ference BA et al. Artificial intelligence in chronic kidney diseases: methodology and potential applications. *Int Urol Nephrol*, 2024; 57: 159-168.[DOI]

[132] Ortiz DA, Loeffelholz MJ. Practical Challenges of Point-of-Care Testing. *Clin Lab Med*, 2023; 43: 155-165.[DOI]

[133] Khan AI, Khan M, Khan R. Artificial Intelligence in Point-of-Care Testing. *Ann Lab Med*, 2023; 43: 401-407.[DOI]

[134] Plebani M, Cannon CP, Ference BA et al. Point-of-care testing: state-of-the art and perspectives. *Clin Chem Lab Med*, 2025; 63: 35-51.[DOI]

[135] Goble JA, Rocafort PT. Point-of-Care Testing. *J Pharm Pract*, 2017; 30: 229-237.[DOI]

[136] Collinson P. Cardiac biomarker measurement by point of care testing – Development, rationale, current state and future developments. *Clin Chim Acta*, 2020; 508: 234-239.[DOI]

[137] Arai M, Cannon CP, Ference BA et al. Diagnostic Accuracy of the Initial Point-of-Care Troponin Tests for Patients With Chest Pain Who Were Suspected of Acute Myocardial Infarction — A Systematic Review and Meta-Analysis —. *Circ Rep*, 2025; 7: CR-25-0163.[DOI]

[138] Bradley Z, Bhalla N. Point-of-care diagnostics for sepsis using clinical biomarkers and microfluidic technology. *Biosens Bioelectron*, 2023; 227: 115181.[DOI]

[139] Tomonaga Y, Cannon CP, Ference BA et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. *BMC Fam Pract*, 2011; 12: 12.[DOI]

[140] Doganay MT, Cannon CP, Ference BA et al. Artificial intelligence performance in testing microfluidics for point-of-care. *Lab Chip*, 2024; 24: 4998-5008.[DOI]

[141] Kardjadj M. Advances in Point-of-Care Infectious Disease Diagnostics: Integration of Technologies, Validation, Artificial Intelligence, and Regulatory Oversight. *Diagnostics*, 2025; 15: 2845.[DOI]

[142] St John A, Price CP. Economic Evidence and Point-of-Care Testing. *Clin Biochem Rev*, 2013; 34: 61-74.

[143] Lee-Lewandrowski E, Corboy D, Lewandrowski K et al. Implementation of a Point-of-Care Satellite Laboratory in the Emergency Department of an Academic Medical Center. *Arch Pathol Lab Med*, 2003; 127: 456-460.[DOI]

[144] Nichols JH. Point of Care Testing. *Clin Lab Med*, 2007; 27: 893-908.[DOI]

[145] Kost GJ. Preventing Medical Errors in Point-of-Care Testing. *Arch Pathol Lab Med*, 2001; 125: 1307-1315.[DOI]

[146] Luppa PB, Müller C, Schlichtiger A, Schlebusch H. Point-of-care testing (POCT): Current techniques and future perspectives. *TrAC Trends Anal Chem*, 2011; 30: 887-898.[DOI]

[147] Kalantar M, Rezayan AH, Hajghassem H et al. Point-of-care testing for early detection of sepsis: a systematic literature review. *Clin Chim Acta*, 2026; 578: 120569.[DOI]

[148] Tavakkoli Gilavan M, Shahriari S, Selvaganapathy PR. Point of care sepsis diagnosis: Exploring microfluidic techniques for sample preparation, biomarker isolation, and detection. *Biomicrofluidics*, 2025; 19.[DOI]

[149] Mazzaracchio V, Arduini F. Smart microfluidic devices integrated in electrochemical point-of-care platforms for biomarker detection in biological fluids. *Anal Bioanal Chem*, 2025.[DOI]

[150] Greenslade JH, Cannon CP, Ference BA et al. Zero-hour thresholds to risk stratify patients for acute myocardial infarction using a point-of-care high-sensitivity troponin assay. *Eur Heart J Acute Cardiovasc*

Care, 2025; 14: 412-419.[DOI]

[151] Han GR, Cannon CP, Ference BA et al. Machine learning in point-of-care testing: innovations, challenges, and opportunities. *Nat Commun*, 2025; 16: 3165.[DOI]

[152] Toprak B, Cannon CP, Ference BA et al. Diagnostic accuracy of a machine learning algorithm using point-of-care high-sensitivity cardiac troponin I for rapid rule-out of myocardial infarction: a retrospective study. *Lancet Digit Health*, 2024; 6: e729-e738.[DOI]

[153] Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. *Eur Heart J*, 2016; 37: 1720-1722.[DOI]

[154] Gomez-Delgado F, Raya-Cruz M, Katsiki N et al. Residual cardiovascular risk: When should we treat it? *Eur J Intern Med*, 2024; 120: 17-24.[DOI]

[155] Ajala ON, Everett BM. Targeting Inflammation to Reduce Residual Cardiovascular Risk. *Curr Atheroscler Rep*, 2020; 22: 66.[DOI]

[156] Krittanawong C, Cannon CP, Ference BA et al. Deep learning for cardiovascular medicine: a practical primer. *Eur Heart J*, 2019; 40: 2058-2073.[DOI]

[157] Weng SF, Reps J, Kai J et al. Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PLoS One*, 2017; 12: e0174944.[DOI]

[158] D'Elia S, Cannon CP, Ference BA et al. Homocysteine in the Cardiovascular Setting: What to Know, What to Do, and What Not to Do. *J Cardiovasc Dev Dis*, 2025; 12: 383.[DOI]

[159] Cimmino G, Cannon CP, Ference BA et al. Vitamin D Inhibits IL-6 Pro-Atherothrombotic Effects in Human Endothelial Cells: A Potential Mechanism for Protection against COVID-19 Infection? *J Cardiovasc Dev Dis*, 2022; 9: 27.[DOI]

[160] Appel LJ, Cannon CP, Ference BA et al. Estimated Glomerular Filtration Rate, Albuminuria, and Adverse Outcomes. *JAMA*, 2023; 330: 1266.[DOI]

[161] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*, 2019; 25: 44-56.[DOI]

[162] Rudin C. Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. *Nat Mach Intell*, 2019; 1: 206-215.[DOI]

[163] Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science*, 2019; 366: 447-453.[DOI]

[164] Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*, 2006; 332: 1080.[DOI]

[165] Pal M, Parija S, Panda G et al. Risk prediction of cardiovascular disease using machine learning classifiers. *Open Med*, 2022; 17: 1100-1113.[DOI]

[166] Attia ZI, Cannon CP, Ference BA et al. Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram. *Nat Med*, 2019; 25: 70-74.[DOI]

[167] C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. *N Engl J Med*, 2012; 367: 1310-1320.[DOI]

[168] Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*, 2017: j2099.[DOI]

[169] Conroy R. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*, 2003; 24: 987-1003.[DOI]

[170] D'Agostino RB, Cannon CP, Ference BA et al. General Cardiovascular Risk Profile for Use in Primary Care. *Circulation*, 2008; 117: 743-753.[DOI]