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REVIEW ARTICLE

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Acute Vascular Events: Cellular and Molecular Mechanisms

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Abstract

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. An estimated 17.9 million individuals died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke. Cardiometabolic risks, such as hypertension, excess weight, obesity, type 2 diabetes, and vascular diseases, contribute significantly to the progression of coronary artery disease. Known sequelae of events that lead to these cardiometabolic diseases include oxidative stress, inflammation, development of dysfunction of vascular adipose tissue, altered blood pressure and blood lipids, altered glucose metabolism, hardening of the arteries, endothelial dysfunction, development of atherosclerotic plaques, and activation of platelet and coagulation pathways. The Framingham Heart Study Group has developed a Risk Score that estimates the risk of developing heart disease in a 10-year period. This group of experts has developed mathematical functions for predicting clinical coronary disease events. These prediction capabilities are derived by assigning weights to major CVD risk factors such as sex, age, blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein cholesterol, smoking behavior, and diabetes status.

Currently, there is a growing interest in the use of artificial intelligence and machine learning applications. AI-based mimetic pattern-based algorithms seem to be better than the conventional Framingham Risk Score, in predicting clinical events related to CVDs. However, there are limitations to these applications as they do not have access to data on the specific factors that trigger acute vascular events, such as heart attack and stroke.

This overview briefly discusses some salient cellular and molecular mechanisms involved in precipitating thrombotic conditions. Further improvements in emerging technologies will provide greater opportunities for patient selection and treatment options. Several clinical studies have demonstrated that most CVDs can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical activity, and harmful use of alcohol. Early detection and better management of the modifiable risks seem to be the only way to reduce, reverse, or prevent these diseases. (**International Journal of Biomedicine. 2023;13(3):9-16.**)

Keywords: cardiovascular disease • artificial intelligence • thrombosis • risk factors

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Abbreviations

AI, artificial intelligence; **AA**, arachidonic acid; **CVD**, cardiovascular disease; **CAD**, coronary artery disease; **CCTA**, coronary computed tomography angiography; **CRP**, C-reactive protein; **FRS**, Framingham Risk Score; **ML**, machine learning; **T2D**, type 2 diabetes; **VT**, venous thrombosis.

Introduction

Metabolic diseases, such as hypertension, excess weight, obesity, T2D, and vascular diseases, have increased in incidence and prevalence to epidemic proportions worldwide in the last four decades.[1-3] Metabolic diseases are a cluster of disease conditions or related risk factors of altered metabolism that contribute to the development of atherosclerotic vascular diseases.[4] Despite the advances in diagnosing the risk factors and managing various metabolic diseases, atherosclerotic cardiovascular disease (CVD) outcome remains the leading cause of morbidity and mortality.[5] CVDs are the leading cause of death globally, taking an estimated 17.9 million lives each year.[6] According to a 'News Release' from the American Heart Association (July 21, 2021), heart diseases are likely to remain the number one killer in the U.S. indefinitely due to long-term

COVID-19 impact. The trend is likely to continue for years to come, as the long-term impact of the novel coronavirus will directly affect vascular health.[7-11] This trend can be disrupted by developing early diagnostic capabilities for the modifiable risks and introducing robust management of identified risks.[12]

The Framingham Risk Score (FSR) is a simplified tool for the assessment of risk level for developing CVD over a 10-year period.[13] The FRS considers six coronary risk factors: age, gender, total cholesterol (TC), high-density lipoproteins cholesterol (LDL), smoking habits, and systolic blood pressure. FRS seems to be the most applicable method for predicting a person's chance of developing CVD in the long term.[14-16] An international team of experts studied the effect of each additional risk-modifying characteristic using Fine and Gray models and reported that the coronary calcium score was the single strongest added predictor of risk.[17] There is considerable interest in the level of C-reactive protein (CRP), as a valuable test for predicting the risk of atherosclerotic vascular disease.[18] Amplifying this finding, a news report had the following headline, "The Heart Disease Test That Could Save Your Life." Furthermore, the article described CRP as an "easy new way to help predict your risk of heart attack and stroke." However, a recent study by Hickam and associates from the University of Toronto concludes, "the evidence base supporting the inclusion of CRP in vascular disease risk assessment is tenuous, incomplete, and conflicting."[19] We agree with this conclusion.

A search on the internet on the topic of: "Acute Vascular Events", reveals a few reports, one on the use of heart rate variability by Wang and associates from China,[20] and the other on using machine learning (ML), using the MESA study data.[21] The authors of the MESA study concluded that ML in conjunction with deep phenotyping improves prediction accuracy in cardiovascular event prediction in an initially asymptomatic population. They, too, concluded that artificial intelligence (AI) approaches and deep learning applications will improve risk prediction through multimodal data integration. A multinational research team has identified several limitations in this approach, such as difficulties incorporating AI into clinical practice and the lack of standardization in clinical health data.[22] Having said that, we would like to inform the readers that it is not that simple to predict acute vascular events, as the data processed by such advanced applications assume that all the biomarkers needed for risk stratification and risk prediction are available. Let us just ask the same question we asked on the internet, -'Risk Factors for Prediction of Acute Vascular Events', to the 'all-knowing' ChatGPT (Open AI). The answer lists 10 risk factors: age, gender, smoking, blood pressure, cholesterol, diabetes, family history, obesity, physical inactivity, and stress. None of these risk factors trigger the acute events, although they all contribute their share to the progression of vascular disease. This overview will briefly review the cellular and molecular mechanisms that promote acute vascular events, such as heart attacks and stroke.

Metabolic Diseases and Atherosclerotic Vascular Disease

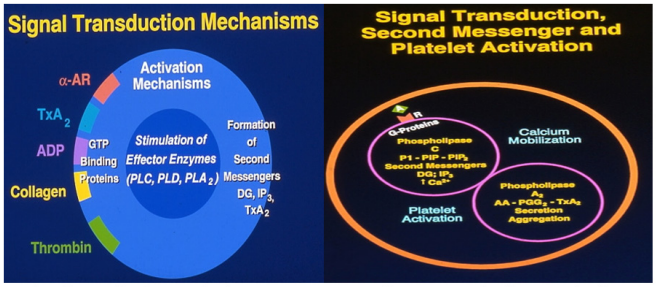
The fact that in 2014, 6090, and 2015, 5524 articles were published related to metabolic vascular syndrome indicates the role of metabolic diseases in promoting atherosclerotic vascular disease.[23] The metabolic syndrome has been described as a cluster of five pre-morbid metabolic-vascular risk factors or diseases (with the 'deadly quartet' - hyperglycemia, visceral obesity, dyslipidemia, and hypertension) associated with increased CVD. However, the sequelae of risks that promote atherosclerotic CVD include oxidative stress, inflammation, hyperglycemia, dyslipidemia, hypertension, excess weight, obesity, T2D, narrowing of the arteries, endothelial dysfunction, subclinical atherosclerosis, activation of platelets and coagulation pathways. In routine clinical settings, hyperglycemia, visceral obesity, dyslipidemia, and hypertension provide the basis for integrated diagnostics, management, and prevention of these disorders. The exact mechanisms involved in how these metabolic diseases initiate and promote atherosclerosis of the vasculature are not clear at this time. However, oxidative stress, increased reactive oxygen species, and low-grade inflammation, especially in dysfunctional adipose tissue of the vessels, seem to play a very important role in the pathophysiology of atherosclerosis. A pro-inflammatory state and dysfunctional adipose tissue shift the endothelium toward reduced vasodilation and consequent thrombotic condition.[24]

Historical Perspective of Platelet Activation

Blood platelets interact with various soluble agonists, such as epinephrine, adenosine diphosphate, and many insoluble cell matrix components, including collagen, laminin, and biomaterials used to construct invasive medical devices. These interactions stimulate specific receptors and glycoprotein-rich domains (integrins and nonintegrin) on the plasma membrane and lead to the activation of intracellular effective enzymes. Most of the regulatory events appear to require free calcium. Ionized calcium is the primary bioregulator, and a variety of biochemical mechanisms are modulated by the level and availability of free calcium. Major enzymes regulating free calcium levels via second messengers include phospholipase C, phospholipase A2, and phospholipase D, together with adenylyl cyclase and guanylyl cyclases (Fig 1A). G-Protein beta gamma dependent activation of phospholipase C results in the hydrolysis phosphatidyl inositol 4, 5 bisphosphate and formation of second messengers 1, 2-diacylyglycerol and inositol 1, 4, 5 trisphosphates (IP3), Diglyceride induces activation protein kinase C, whereas IP3 mobilizes calcium from internal membrane stores.

Elevation of cytosolic calcium stimulates phospholipase A2 and liberates arachidonic acid. Free arachidonic acid is transformed to a novel metabolite thromboxane A2 by fatty acid synthetase (COX-1, cyclooxygenase). Thromboxane A2 is the major endogenous metabolite of this pathway and plays a critical role in platelet recruitment, granule mobilization, and secretion of granule contents (Figure 1 A & B). Secretion of granules promotes p-selectin expression (adhesion protein) on the platelet membrane. In addition, activation of platelets also promotes the expression of acidic lipids on the membrane and tissue factor expression, thus making these cells procoagulant. Although platelets that are not activated can bind surface-bound fibrinogen, they cannot bind circulating soluble fibrinogen. Agonist-mediated activation of platelets promotes the expression of an epitope on glycoprotein IIb/IIIa receptors.

Activation of this receptor is essential for the binding of circulating fibrinogen. Fibrinogen forms a bridge between individual platelets and facilitates thrombus formation. Von Willebrand factor (vWF) binds platelet GP Ib-IX complex under high shear conditions. Up-regulation of signaling pathways will increase the risk for clinical complications associated with acute coronary events. In a short overview like this, it is hard to cover all aspects of platelet activation mechanisms, and readers are urged to refer to comprehensive reviews on this topic.[25-31]



A. *Signal transduction mechanisms.* **B.** *Second messengers leading to activation.*

Fig. 1. *Platelet activation mechanisms.*

Factors Promoting Thrombotic Events

An Internet search on 'risk factors for arterial thrombosis' lists the following risks: smoking, diabetes, high blood pressure, high cholesterol, lack of activity and obesity, and family history of arterial thrombosis. Arterial thrombosis is the cause of myocardial infarction and stroke, while venous thrombosis (VT) leads to venous thromboembolism. Furthermore, arterial thrombi are rich in platelets, and venous thrombi are rich in fibrin. Arterial thrombosis occurs in places of high shear flow, while VT occurs in areas of low shear blood flow.[32] Even when one searches response for 'risk factors that trigger heart attack and stroke, ' the information on the internet does not cover the mechanisms that promote these acute events. The internet response is that 'leading risk factors for heart disease and stroke are high blood pressure, high low-density lipoprotein (LDL) cholesterol, diabetes, smoking, obesity, unhealthy diet, and physical inactivity." We asked the same question to ChatGPT. The reply was the same ten risks that we mentioned in the introduction. Since I was to provide my input, I mentioned. "Your Open AI is not ready to answer such complex questions. It is still looking at half a century-old Framingham Risk Score. None of the above ten risk factors trigger acute vascular events such as heart attack or stroke. Narrowing of the artery, atherosclerotic plaque buildup, vascular dysfunction, and activation of platelet and coagulation pathways are some of the major contributors to acute vascular events". I got an apology, and the chat assistant rephrased what I listed as probable causes for acute vascular events.

Cellular and Molecular Mechanisms that Promote Acute, Arterial, and Vascular Events

The endothelium, a monolayer of endothelial cells, covers the entire inner surface of the blood vessels and, as such, is in contact with the blood and the circulating cells (Fig 2). The surface of the endothelium is covered by glycocalyx, a mosaic of glycoproteins, proteoglycans, and glycosaminoglycans. The vessel wall is covered with more than a trillion endothelial cells. The wall of blood vessels is comprised of three layers: a) the innermost tunica intima, made up of endothelial cells and sub-endothelial connective tissue; b) the intermediate, tunica media, mainly made up of smooth muscle cells; and c) the outer, tunica adventitia, made up of collagen. Principal endothelial-derived procoagulant molecules include thrombin, vWF, tissue factor expression, vascular cell adhesion molecule-1(VCAM-1), altered CD39/CD73 expression, plasmin activator inhibitor-1(PAI-1), ADAMTS-13. Anticoagulant molecules include nitric oxide, prostacyclin, thrombomodulin, heparin sulfate, urokinase plasmin activator (u-PA), tissue plasminogen activator (t-PA), C-terminal metalloproteinase with multiple functions (ADAMTS-18), endothelial protein C receptor (EPCR) and tissue factor pathway inhibitor (TFPI).

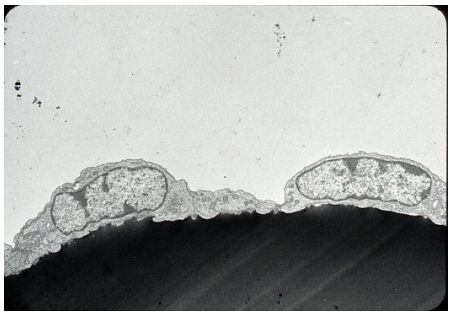


Fig. 2. *Scanning electron micrograph of endothelial cells. (Courtesy: Professor (Late) James G White, University of Minnesota)*

Endothelium prevents the development of thrombotic conditions by providing a surface that discourages the attachment of platelets and clotting proteins (Fig. 3).

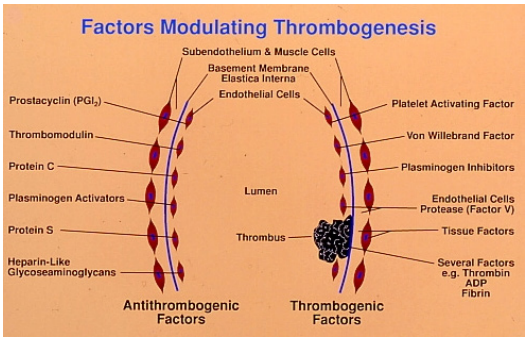


Fig. 3. *Molecular mechanisms involved in thrombogenesis. (Personal collection; source unknown)*

Following endothelial injury or dysfunction of endothelial cells, circulating platelets get activated and promote expression of cell surface adhesion molecules. These conditions also promote leukocyte rolling and tethering onto the endothelium, which initiates inflammatory responses that promote thrombosis. Alteration in the production of vessel wall prostacyclin (PGI_2)

or increased thromboxane production by circulating platelets, as well as lowered nitric oxide (NO) production, induce endothelial dysfunction. Vessel wall damage due to atherosclerosis, hypertension, vascular abnormalities, or dysfunction enhances platelet adhesion and interaction with the endothelium (Fig 4). Endothelial dysfunction is common in hypertensive subjects, diabetics, and metabolic syndrome.

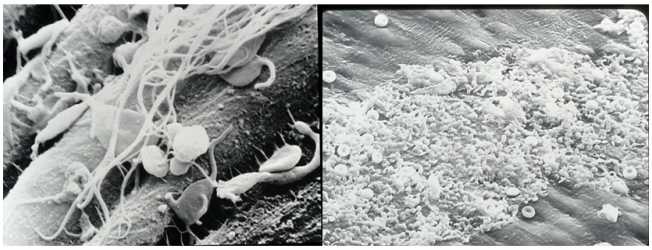


Fig. 4. *Platelet Interaction with dysfunctional (A) and denuded endothelium (B).*

(Courtesy: Professor (Late) James G White, University of Minnesota)

The activated renin-angiotensin system, together with increased oxidized lipids, may play a role in the enhanced vascular oxidative stress. These events promote the development of inflammation of the vasculature. Inflammation enhances the formation of reactive oxygen species (ROS), damaging the vessel walls. In an earlier study, we demonstrated the role of hyperglycemia in precipitating acute vascular events.[33] In brief, the pathogenesis of arterial thrombosis involves damage of the vessel wall, alterations in the production of vasodilators and vasoconstrictor molecules, development of atherosclerosis, plaque formation, and activation of platelet and coagulation pathways. To maintain an antithrombotic surface, the healthy endothelium secretes various anticoagulant molecules. However, when the surface is damaged or dysfunctional, it releases procoagulant molecules.

The endothelial barrier to prevent platelet interactions with the subendothelium depends upon the stable cell-cell junctions (Fig. 2). ACE2 on the endothelium converts angiotensin II to angiotensin-(1–7), which, as a ligand, binds to the G-protein-coupled receptor MAS, thus modulating anti-inflammatory and antithrombotic signaling pathways. Furthermore, as we have described earlier, it produces natural anticoagulant and anti-fibrinolytic molecules. A healthy endothelium produces PGI2 and nitric oxide to prevent platelet adhesion and activation.

In an earlier section, we have described molecular mechanisms involved in platelet activation. In brief, agonists interact with preferred receptors on the plasma membrane. In Figure 5 above, we have used thrombin as the agonist, interacting at the specific receptor site and inducing activation of phospholipase C, which in turn promotes the formation of active biological molecules, inositol trisphosphate (IP_3), and diglyceride (DG). Inositol trisphosphate mobilizes cytosolic calcium from membrane stores, and diglyceride activates protein kinase C. Elevation of cytosolic calcium stimulates phospholipase A2 and induces the release of arachidonic acid (AA) from membranes. Free AA is converted to prostaglandin endoperoxides G2 and H2 by cyclooxygenase (COX1). These endoperoxide molecules are further converted to thromboxane A2 (TxA2) by platelets and to prostacyclin (PGI_2) by vessel wall enzymes. Thromboxane A2 is the most potent platelet agonist, and PGI_2 is a potent antagonist. Endogenously generated thromboxanes act at the specific receptor sites on the platelet membranes and activate the GP IIb /IIIa receptors. Activated GPIIb/IIIa receptors recognize soluble fibrinogen and interact with other activated platelets to form platelet aggregates (Fig 6).

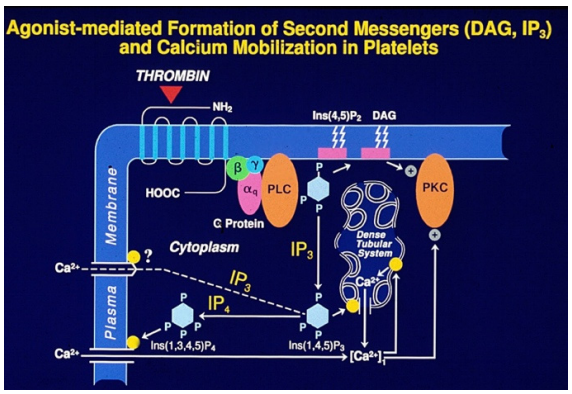


Fig. 5. *Molecular mechanisms involved in platelet activation.*

(Personal Collection: Prepared by University of Minnesota Artists)

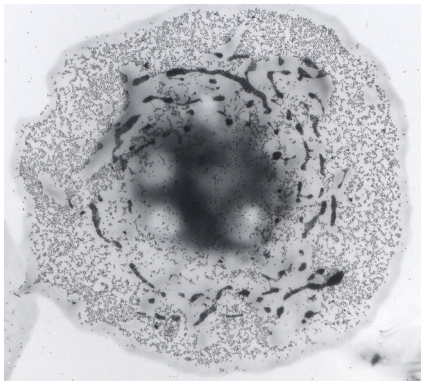


Fig. 6. *Scanning electron micrograph of spread platelets showing fibrinogen binding to activated platelets (Arteriosclerosis.1990;10:738-744).*

(Courtesy; Professor (Late) James G White, University of Minnesota)

Studies at the University of Minnesota by Professor James White and Gines Escolar demonstrated that fibrinogen gold (Fgn/Au) and platelet glycoproteins (GPIIb /IIIa) receptor complexes were moved from peripheral margins toward centers of surface-activated platelets.[27] The authors concluded that "GP11b-111a receptors remain randomly dispersed from the edge on fully activated spread platelets".

To study the role of free fatty acids in platelet physiology and pharmacology, we did a one-of-a-kind study in 1980 using a drug-induced diabetic rat model. Diabetic subjects are known to have hyperfunctional platelets. In these studies, rats were rendered diabetic by injection of streptozotocin. We followed the ability of platelets and vessel wall tissues to make prostanoids using radiolabeled AA in the control and diabetic rats. We evaluated the release and conversion of free fatty

acids to thromboxane and prostacyclin by monitoring their stable metabolites. A schematic pathway of results obtained in these studies is presented in Figure 7. Conversion of AA to pro-aggregatory thromboxane was higher in the diabetic rats. Whereas the levels of vasoactive prostacyclin were lower in the diabetic rats compared to control rats, suggesting a shift to a prothrombotic state.[34] The changes observed in platelet and vessel wall arachidonic acid were normalized by pancreatic islet cell transplantation to these diabetic animals (data not shown). For the first time, these studies demonstrated the differential effect of hyperglycemia on vascular and platelet prostaglandin production. In this overview, we have limited our discussions to the role of platelets in thrombosis. We have not discussed the role of coagulation pathways in this complex process.

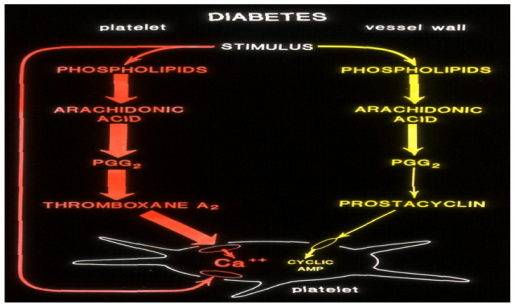


Fig. 7. *Altered platelet and vessel wall prostaglandin production in diabetes rats.*

(Courtesy: Professor John Gerrard. University of Minnesota)

Biomarkers Indicating Platelet Activation and Prothrombotic State

Circulating preactivated platelets and a prothrombotic phenotype can be detected as a marker of platelet activation.[35] Activated platelets shed P-selectin, an adhesion molecule, which is expressed on the platelet membrane.[36] Circulating platelets with p-selectin and soluble p-selectin in the blood indicate platelet activation. Activated platelets also express CD40L(CD154).[37] Activation of platelets leads to an increase in soluble CD40L(sCD40L). High-affinity fibrinogen binding sites on GPIIb/IIIa can be detected by PAC-1, a mouse monoclonal antibody.[38] Therefore, PAC-1 binding on the platelet surface is indicative of platelet activation. Similarly, even fibrinogen binding on platelets itself is indicative of activated platelets. Monitoring elevated cytosolic calcium with appropriate calcium-specific fluorophores will also indicate the activation state of blood platelets. Platelet activation also can be determined by the expression of CD62, CD63, CD41, CD42, and activated GPIIb/IIIa. Stable metabolites of thromboxane B2 in blood and urine can be used as markers of platelet activation.[39] Platelet-derived microparticles, which are strongly procoagulant, also indicate platelet activation. In addition to these markers, the international normalized ratio (INR), which measures how quickly the blood clots or prothrombin time (PT), can also be used to monitor the prothrombotic status of the blood. Readers are urged to refer to comprehensive monographs for additional information on platelet activation.[25-35]

Discussion

CVDs are the most common cause of morbidity and mortality worldwide. Despite the impressive improvements in patient diagnosis and robust risk factor management, they have been ranked the number one killer for decades and will continue to occupy this position for decades. INTERHEART study by the multicountry investigators demonstrated that modifiable risk factors, such as smoking, hypertension, blood apoproteins, diabetes, waist-hip ratio, dietary patterns, physical activity, consumption of alcohol, and psychosocial factors, account for most of the risk for myocardial infarction worldwide, and management of these risks significantly prevents premature mortality due to myocardial infarction.[40] In a similar study on stroke in 32 countries, the authors concluded, "The potentially modifiable risk factors are collectively associated with about 90% of stroke in each major region of the world, among ethnic groups, in men and women, and all ages."[41] Commenting on the results of these studies, Zeng and associates wondered whether the study might have overestimated the role of ten potentially modifiable risk factors, whereas factors such as social status, metabolic syndrome, and nutrition are important risk factors for ischemic stroke.[42]

Some authors claim the decline in mortality from CAD and stroke as the success story of the past four decades.[43] Models have shown that this remarkable decline has been fueled by rapid progress in both prevention and treatment, declines in smoking, improvements in hypertension treatment, and widespread use of statins, development, and use of thrombolytic agents and stents for acute coronary syndromes. However, recent evidence suggests that long-term decline in CVD mortality may have stagnated and even reversed in younger populations.[44] A large study from the Imperial College of London reported that although CVD mortality has declined in industrial countries, diabetes mortality has increased.[45] A multicountry study concluded, "Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease."[46] What is clear from these studies is that early diagnosis of various risk factors for CVDs and robust management of the identified risks changes in lifestyle, including healthy diet and exercise, will significantly lower premature mortality due to coronary artery disease. Despite these encouraging studies, the growing prevalence of cardiovascular risk factors and better prognosis of patients with CVDs have increased the global CVD burden.[47,48]

There is great interest in using AI and ML techniques to improve the diagnosis and treatment of vascular diseases.[49-52] These techniques have many applications in cardiovascular drug therapy, pharmacogenomics, diagnosis, and treatment planning. These approaches can be used for improving risk prediction, monitoring various clinical complications, and developing AI technology compatible with smartphones and high-tech diagnostic tools. According to British researchers, cardiology seems to be at the forefront of AI/ML applications.[53] There seems to be a great opportunity for developing accurate methods for predicting CVD outcomes, noninvasive diagnosis of CAD, detection of

malignant arrhythmias through wearables, and the development of diagnosis and treatment strategies and predictions for heart failure patients. Researchers from Australia have demonstrated that an AI-based, fully automated coronary artery calcium scoring model shows high accuracy and low analysis time.[54] CCTA has been used to predict long-term outcomes. Researchers used data from the CONFIRM study to predict 5-year all-cause mortality by combining 44 CT variables. This study included 10,000 patients with suspected coronary disease. Compared to FRS and CCTA-based risk models (segment stenosis score, segment involvement score), the model combining CCTA and clinical variables was far better in predicting 5-year all-cause mortality.[55] An editorial in *JAMA* rightly suggests that new ways to identify groups at increased risk, beyond conventional risk factors and current estimate models, are required and warrant investigation.[56]

AI, ML, software analytics, and chatGPT are growing rapidly in all fields of public health. In healthcare, where patient well-being is paramount, it is recommended to subject AI and ML analytics to clinical validation before widespread acceptance and adoption. It typically involves evaluating the performance of the technology on large and diverse populations, comparing it to existing standards or gold standards, and assessing its impact on patient outcomes. Thereby ensuring that the technology meets standards of accuracy, reliability, and safety. Clinical validation helps to verify the performance of the AI/ML model in real-world scenarios. It ensures that the results are consistent and clinically meaningful. AI/ML applications may play a significant role in improving diagnosis and opting for treatment plans. Such risk assessment tools are critical in the current approach to primary prevention of atherosclerotic CVDs.[57] A recent review by multicountry researchers covers state-of-the-art AI applications across various noninvasive imaging modalities to quantify cardiovascular risk in CAD.[58,59] A recent study published in the European Heart Journal evaluated the ability of a deep-learning-based CVD marker, Reti-CVD, to identify individuals with intermediate – and high-risk for CVD by existing risk assessment tools, including FRS.[60] Despite such findings, AI-ML-GPT-related fears have emerged with the rise of language learning models, exemplified by Open AI's GPT. The emerging technologies and their applications have left clinicians, and scientists wondering how these analytics might be used in the future and what risks these technologies pose for patients and clinicians.[61]

FRS was developed using conventional risk factors to predict the 10-year risk for developing CVDs and not for predicting acute vascular events. Researchers have used data from the CONFIRM study to predict 5-year all-cause mortality by combining 44CT variables. Coronary artery calcium is currently assessed manually. A novel AI-based model showed high levels of correlation and agreement with standard measurement. Such emerging technologies could be incorporated to develop AI and ML-based analytics for risk stratification, risk prediction, and management. What other risk scores can be included to enhance risk stratification and risk prediction? Circulating CRP seems to help to estimate the risk for cardiovascular events.[62] Researchers from Germany used CRP data to improve FRS and concluded that CRP significantly enhances global coronary risk as assessed by FRS, especially in intermediate-risk groups. Classical risk factors used to compute FRS do not account for all incident coronary events, especially those associated with acute occlusive arterial events. Such observations have led to the search and inclusion of biomarkers involved in cellular and molecular mechanisms that trigger acute vascular events. This overview briefly covered some salient mechanisms that play a significant role in platelet-dependent acute vascular events. Having said that, we must remind readers that this is only a partial story, as we have not discussed the role of coagulation pathways in these acute events. We hope future studies will include emerging risk factors that modulate the activation of platelet and coagulation pathways in computing CVD-related risk stratification and risk prediction equations.

Conclusion

Heart attacks and strokes are acute vascular events mainly caused by a blood clot that blocks and prevents the blood flow to the heart or brain. Coronary atherosclerosis is the underlying condition for these acute vascular events. Multiple risk factors are involved in the initiation, progression, and precipitation of these acute events, although the exact cause that triggers these events remains elusive. The Framingham Heart Study Group described modifiable risk factors that play a role in the development of vascular diseases. Several clinical studies have demonstrated that identifying these conventional risk factors and managing these risks significantly prevents premature mortality due to myocardial infarction. According to the experts from the Division of Preventive Cardiology, Cleveland Clinic, "90 percent of the heart disease is preventable through healthier diet, regular exercise and not smoking". Despite such good news and the encouraging results of multiple clinical studies, the global burden of CVDs has increased in incidence and prevalence. The prevalence of total CVDs nearly doubled from 271 million in 1990 to 523 million in 2019, while deaths steadily increased from 12.1 million in 1990 to 18.6 million in 2019. Metabolic diseases such as hypertension, excess weight, obesity, and T2D increase the risk of coronary artery disease. Every major clinical trial has demonstrated that management of modifiable risk factors for CVD and lifestyle changes significantly reduces premature mortality. Yet, we do not see an overall reduction in CVD incidence and prevalence worldwide. Maybe it is time to focus on reducing, reversing, or preventing metabolic diseases rather than focusing on just CVD risk management. In this overview, we have briefly discussed some salient cellular and molecular mechanisms involved in precipitating thrombotic conditions. We have speculated that including emerging risk factors in computing the risk stratification may improve risk predictability for acute vascular events.

Competing Interests

The authors declare that they have no competing interests.

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