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Review Article

Earlier Prediction of Cardiovascular Risk with Epicardial Fat Assessment

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ABSTRACT

Epicardial adipose tissue is a distinct fat depot with local and systemic effects. Distinguished from other visceral fat depots by a number of anatomical and metabolic features, this tissue exhibits increased fatty acid metabolism and a unique transcriptome enriched for genes associated with inflammation and endothelial function. As epicardial fat and the heart share an unobstructed microcirculation, it is suggested that these tissues may interact. Under normal physiological conditions, epicardial fat exhibits metabolic and thermogenic properties similar to those of brown fat, as well as mechanical properties that provide cardioprotection. However, the development of pathological conditions could cause the phenotype of epicardial fat to become detrimental to the myocardium and coronary arteries. The balance between the protective and detrimental effects of this tissue is fragile. The expression of the epicardial fat-specific transcriptome is downregulated in severe and advanced coronary artery disease. Improved local vascularisation, weight loss and targeted drugs can restore the protective physiological functions of epicardial fat. Accurate measurement of epicardial fat thickness or volume has several important clinical applications, as it correlates with visceral adiposity, coronary artery disease, metabolic syndrome, fatty liver disease, cardiac changes, arrhythmias and ventricular dysfunction. Due to the simplicity of this clinical assessment, epicardial fat is a reliable marker of cardiovascular risk and an attractive surrogate for evaluating the efficacy of drugs that modulate adipose tissue. In this article, we review the rapidly emerging evidence suggesting a specific role for epicardial adipose tissue as a marker of cardiac risk and an active player in the development of cardiac pathology, as well as a potentially modifiable therapeutic target for new drugs, even in high-risk populations.

1. Introduction

Obesity is no longer considered a cosmetic problem. The World Health Organisation (WHO) and the European Parliament, as well as many international medical and scientific societies, have recognised obesity, an excessive accumulation of adipose tissue (body fat), as a chronic, heterogeneous, progressive and frequently relapsing non-communicable disease resulting from multiple environmental and genetic factors (Table 1) [1]. Obesity is associated with increased morbidity and mortality from cardiovascular disease, type 2 diabetes, multisite cancers and premature death, requiring ongoing intervention and affecting quality of life [1–4].

Epidemiological studies have shown a link between obesity and health outcomes, with increased costs associated with caring for those affected [5]. Obesity is strongly associated with cardiovascular-metabolic (CVM) disorders including hypertension, dyslipidaemia and type 2 diabetes [2–4]. Obesity can also affect bone health and reproduction, and increases the risk of certain cancers and chronic inflammation [6,7]. A frequent myocardial disorder in obese people is heart failure with preserved ejection fraction (HFpEF) and its primary pathophysio-

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Table 1
Global obesity Burden.

In 2022, 1 in 8 people worldwide was affected by obesity.
Global adult obesity has more than doubled since 1990. Adolescent obesity has quadrupled.
In 2022, 2.5 billion adults (18 years and older) were overweight. Of these, 890 million were obese.
In 2022, 43 % of adults aged 18 and over were overweight and 16 % were obese.
In 2022, 37 million children under five were overweight.
More than 390 million children and adolescents aged 5–19 were overweight in 2022, including 160 million living with obesity.
Obesity is extremely costly in both economic and psychological terms. It requires lifelong management.
Obesity needs to be redefined and reframed to reflect both current physiological research and more evidence-based, person-centred clinical management.

logical abnormality appears to be a decrease in ventricular distensibility [8,9]. Obesity is thought to promote the development of microcirculatory abnormalities and myocardial fibrosis [8,9].

In the clinical practice, obesity is frequently assessed by a simple, easy, useful, cheap and non-invasive anthropomorphic method, originally called the *Quetelet index*, calculating the body mass index (BMI) calculated by dividing weight in kilograms by height in metres to the power of 2.0, which is only a proxy for total adiposity [10].

Current imaging techniques of adiposity such bioimpedance, dual-energy X-ray absorptiometry (DEXA), computed tomography and magnetic resonance imaging (MRI), allow a more accurate and reproducible assessment of different fat depots than anthropometric indices [3,10].

2. Adipose tissue

There are three different adipocytes: *A*) white adipocytes, which make up most of the body fat; *B*) brown adipocytes; *C*) beige adipocytes. (Fig. 1)

2.1. White adipocytes

The white adipose tissue (WAT) is composed of spherical cells called adipocytes that range in diameter from 15 to 150 μm. This enormous variability in size is due to the ability of the cell to accumulate different amounts of lipids, such as triglycerides, which form a single vacuole in the hyaloplasm. Their surface, in contact with the hyaloplasm, does not have a uniform membrane. The mitochondria are elongated and have short and randomly oriented cristae. The rough endoplasmic reticulum is organised in short cisternae, but sometimes forms stacks of variable size. The smooth endoplasmic reticulum is always clearly visible. Pinocytotic vesicles are present at the level of the plasma membrane. A distinct outer lamina is always visible on the outside of the plasma membrane [11,12].

The number of organelles, as well as their size and extent, varies according to the functional and developmental stage of the cell. The functions of WAT are important for the survival of the body and can be summarised as a source of energy, thermal insulation and mechanical cushioning. Approximately 60–85 % of the weight of white adipose tissue is lipid, of which 90–99 % is triglyceride, with small amounts of free fatty acids, diglyceride, cholesterol, phospholipids, cholesterol ester and monoglyceride. About 90 % of total lipids are made up of six fatty acids: myristic, palmitic, palmitoleic, stearic, oleic and linoleic. Varying the composition of your diet can vary the fatty acid profile in adipose tissue. The remaining weight of white adipose tissue is water (5 to 30 %) and protein (2 to 3 %). WAT is not a highly vascularised organ, but each adipocyte is in contact with at least one capillary [11,12].

2.2. Brown adipocytes

Brown adipose tissue (BAT), whose colour is due to rich vascularisation and densely packed mitochondria, is found in different locations depending on the species and/or age of the animal [11]. The mitochondria of this tissue vary in size and can be round, oval or filamentous in shape; the peculiarity of these mitochondria is a specific carrier called

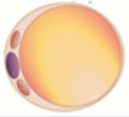
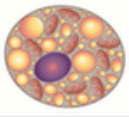
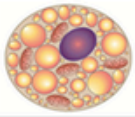
	White adipocyte	Brown adipocyte	Beige adipocyte
			
Lipid droplet	Large, unilocular	Small, multilocular	Small, multilocular
Location in adult humans	White adipose tissue depots	Supraclavicular, cervical, axillary, paravertebral, abdominal depots	Induced in fat depots by cold and adrenergic stimuli
Abundance of Mitochondria	Low	High	High
Secreted factors	Adipokines (Leptin, adiponectin, Resistin)	Batokines (interleukin-6, Fibroblast growth factor 21 (FGF21)	Batokines (interleukin-6, Fibroblast growth factor 21 (FGF21) Slit Guidance ligand-2 (SLIT-2)
Function	Energy stotage / Lipogenesis Lipolysis Glucose uptake Adipokine secretion	Thermogenesis, Lipid clearance, Glucose uptake / catabolism, Batokins secretion	Thermogenesis, Glucose uptake / catabolism,
Thermogenic capacity	None	High	Medium
Uncoupling protein 1 (UCP1) expression	Few	Abundant	Few

Fig. 1. Main differences between white adipocytes brown adipocytes and beige adipocytes.

uncoupling protein, UCP-1, which is able to transfer protons from the outside to the inside without subsequent production of ATP. BAT is important for regulating body temperature through non-shivering thermogenesis. UCP-1 in brown adipocytes is central to the uncoupling of the brown fat mitochondrial respiratory chain, the mechanism of heat production in this tissue. The cell in BAT has a more uniform diameter (60 μm) than WAT and the lipid droplet within the cell can reach 25 μm in diameter.

2.3. Beige adipocytes

Beige adipocytes are brown-like adipocytes that can induce thermogenesis. Beige adipocytes may originate as a result of transformation of a specific cohort of preadipocytes within the white adipose tissue or through direct transformation of white adipocytes triggered by environmental stimuli [11].

Beige adipocytes are molecularly different from classical brown adipocytes. Although they are capable of expressing UCP1, they can also utilise UCP1-independent thermogenic mechanisms, including creatine and Ca2+ cycling [12–15]. In humans, some conditions associated with increased adrenergic stress, such as chronic exposure to cold or burn trauma, may give rise to thermogenic adipocytes within the white adipose tissue, a phenomenon called ‘beiging’ or ‘browning [11,16,17]. Both brown and beige adipocytes have been found in human adult supraclavicular tissue [18].

3. Metabolism of adipose tissue

Lipogenesis is the process through which the adipose tissue (fat) is deposited in the cytoplasm and mitochondria of the liver. Fat energy ingested, in excess of that required, for current needs, is stored in adipose tissue [19]. In addition, dietary carbohydrate and protein can be converted to fat. Energy in the form of carbohydrate can be stored as glycogen in the liver and muscle. Carbohydrate can also be converted to triglycerides, mainly in the liver, and transferred to adipose tissue for storage. Amino acids from ingested protein are used for new protein synthesis or can be converted to carbohydrate and fat.

Fatty acids, in the form of triglycerides or free fatty acids bound to albumin, are ingested with food or synthesised by the liver. There is very little synthesis of free fatty acids in adipocytes. Triglycerides are the main source of fatty acids as this is the form in which dietary lipids are processed by the intestines and liver. Insulin, a hormone secreted by the beta cells of the pancreas, plays a major role in the lipogenic process. The net effect of insulin is to promote storage and block mobilisation and oxidation of fatty acids. Insulin exerts its effect by stimulating the production of lipoprotein lipase so that circulating triglycerides are hydrolysed and free fatty acids can enter the adipocyte.

Adipose tissue is a highly specialised organ, capable of regulating the process of energy storage and release through a complex network to meet the body's energy needs. Adipose tissue is biologically active and adapts to the metabolic needs of the individual, while diet and nutritional status influence adipose tissue metabolism, which is disturbed in the progression to obesity.

4. Adipose tissue distribution and its clinical implications: from subcutaneous to epicardial fat

Adipose tissue is a dynamic and metabolically active organ that plays a crucial role in systemic energy balance and metabolic health. Its distribution, where fat accumulates in the body, has profound implications for disease risk, particularly in obesity-related conditions such as insulin resistance, metabolic syndrome, and cardiovascular disease.

Subcutaneous Adipose Tissue: The Primary Fat Depot. The body’s first line of fat storage is subcutaneous adipose tissue (SAT), located just beneath the skin. SAT accounts for approximately 85 % of total body fat in healthy individuals and serves as a relatively benign energy reservoir. It expands primarily through adipocyte hypertrophy (cell enlargement) to accommodate excess lipid storage. Importantly, SAT has lower inflammatory activity and better-preserved insulin sensitivity compared to visceral fat, making it a metabolically safer storage site.

However, SAT has a finite capacity for expansion. When this limit is exceeded, a phenomenon termed "adipose tissue expandability failure”, the body begins diverting lipids to other depots, particularly visceral adipose tissue and ectopic sites.

Visceral Adipose Tissue: A Metabolic and Cardiovascular Risk Factor. The first sign of distress emerges when visceral fat accumulates within the abdominal organs, mesenteric fat and omental fat. Unlike SAT, visceral adipose tissue (VAT) is far more metabolically active by releasing a flood of free fatty acids directly into the liver via the portal vein, where they disrupt insulin signaling, insulin resistance and fuel systemic inflammation. The pro-inflammatory nature is due to secretion inflammatory cytokines (e.g., TNF-α, IL-6) and altered adipokines (e.g., reduced adiponectin, increased leptin *"satiety hormone"*, and resistin), while suppressing protective ones like adiponectin [20–22]. Because of these properties, the result is a perfect gale for metabolic syndrome, characterized by insulin resistance, dyslipidaemia, and elevated cardiovascular risk even in individuals who may not appear severely obese [23,24] VAT is considered a major driver of metabolic syndrome, even in individuals who are not severely obese by BMI standards.

5. Ectopic fat deposition: when fat accumulates where it shouldn’t

The most insidious phase of fat accumulation occurs when lipids spill over into organs and tissues that normally contain minimal fat, such as the liver. This ectopic fat accumulation is particularly detrimental, contributing to non-alcoholic fatty liver disease (NAFLD) and worsening systemic insulin resistance [23]. When marbled with fat, skeletal muscle loses its ability to efficiently take up glucose, thereby compounding the risk of diabetes. Most alarmingly of all, fat begins to surround and infiltrate the heart and surrounding structures, depositing in the pericardial, epicardial and even intramyocardial spaces. This has direct effects on cardiac function [21,24].

6. Epicardial adipose tissue: A unique and clinically significant fat depot

Epicardial adipose tissue (EAT) has gained significant attention due to its anatomical and functional relationship with the heart, among ectopic fat depots. In a healthy state, EAT acts as a protective cushion for the coronary arteries, supplies energy to the hard-working heart, and secretes anti-inflammatory adipokines (e.g. adiponectin) [21]. The EAT lacks any physical barriers that separate it from the underlying myocardium. There is no fascial separation and the microcirculation is shared, which facilitates crosstalk between the adipocytes and the cardiomyocytes. The EAT also comes into direct contact with the myocardium and the coronary arteries, which allows for paracrine signalling [7,8]. However, in obesity and metabolic dysfunction, this once-benign fat undergoes pathological remodelling. It becomes a hotbed of inflammation, teeming with macrophages and spewing out cytokines that promote coronary atherosclerosis [25–28]. The same tissue that once secreted protective adiponectin now floods the local environment with harmful molecules, elevated leptin and resistin, contributing to arrhythmias, myocardial dysfunction, and heart failure [29,30]. These mechanisms mean that EAT thickness, as measured by echocardiography or cardiac MRI, has emerged as an independent biomarker of cardiovascular risk, even in individuals who are not severely obese.

7. Clinical and therapeutic implications

The progression from SAT expansion to VAT accumulation and ectopic fat deposition, including EAT, helps to explain why body fat distribution is a stronger predictor of metabolic and cardiovascular risk than total adiposity alone, and why two people with the same BMI can have vastly different metabolic disease risk.

The clinical implications are profound: not all fat is equal. VAT and ectopic fat are far more harmful than SAT. Due to its proximity to the heart, EAT thickness can be measured using echocardiography, CT or cardiac MRI. This has emerged as a powerful independent predictor of cardiovascular events, offering insights beyond traditional risk factors [8,25,27].

Strategies to reduce visceral and ectopic fat (e.g., weight loss, exercise, pharmacological modulation) are therapeutic targets and may improve cardiometabolic outcomes [28–30].

8. The anatomical and physiological role of epicardial adipose tissue

Since the pivotal studies by Iacobellis et al. in the early 2000s [26,31], interest in epicardial adipose tissue (EAT) has grown rapidly among a multidisciplinary community of clinical and research cardiologists, basic scientists and internal medicine specialists. As research in cardiometabolic disease has evolved, the focus has shifted from general obesity to organ-specific adiposity and epicardial fat deposition. To date, nearly 2000 original articles have been published describing the many aspects of EAT.

Obesity and uncontrolled diabetes are major factors responsible for excessive EAT and lipotoxic effects, which lead to abnormal lipid deposition and fatty infiltration in the myocardium. In these circumstances, evidence suggests that this regional fat distribution acts as an endocrine organ, secreting hormones, inflammatory cytokines and chemokines, and playing an important role in developing an adverse metabolic and cardiovascular risk profile [22,32,33]. In an MRI-based study, Ramo et al. suggested that epicardial and pericardial adiposity were associated with incident cardiovascular diseases. However, such an association was no longer significant after adjusting for VAT. This reflects a metabolically unhealthy adiposity phenotype that is similar to abdominal visceral adiposity [34].

Much discussion surrounds the impact of EAT and pericardial adipose tissue (PAT). While it is not a matter of terminology, EAT and PAT should be considered separately for structural and clinical reasons. EAT and PAT differ in their embryological development. Unlike PAT, both EAT and intra-abdominal fat are derived from brown adipose tissue (BAT). In early life, EAT acts like BAT by providing heat and energy to the heart muscle. Anatomically, EAT and PAT are distinct. EAT is proximal to the heart, with regional atrial and coronary infiltration, whereas PAT is external. There is no muscle fascia separating the EAT from the adjacent myocardium. This proximity to the target organ is unique to EAT, as no other VAT depot has such contiguity.

The EAT and the underlying myocardium share the same microcirculation, whereas non-coronary arteries supply the PAT. This shared circulation and the absence of a barrier allow for communication via paracrine or autocrine mechanisms. EAT is a peculiar visceral lipid storage depot located between the myocardium and the visceral layer of the epicardium. It has multiple implications for contemporary cardiology research and practice, and exhibits both protective and detrimental properties [29].

The physiological role of epicardial adipose tissue (EAT) in the heart is complex and not fully understood. Its functions can be classified as follows:

1) nutritional;
2) metabolic;
3) thermogenic;
4) regulatory;
5) mechanical.

Under normal physiological conditions, EAT acts as a buffer, absorbing fatty acids and protecting the heart from high levels of them, as well as protecting against abnormal curvature of the coronary arteries. EAT is enriched in genes that encode cardioprotective adipokines, such as adiponectin and adrenomedullin, which both have potential anti-inflammatory and anti-atherogenic properties [34]. Epicardial fat is a metabolically active organ that produces a variety of bioactive molecules that, due to its proximity, may have a significant impact on coronary artery disease, arrhythmias, cardiac dysfunction and ultimately heart failure [35,30].

Epicardial adipose tissue is also clinically associated with left ventricular mass and other features of the metabolic syndrome, such as concentrations of LDL cholesterol, fasting insulin and adiponectin, and arterial blood pressure [36]. The echocardiographic assessment of epicardial fat could be a simple and practical tool for cardiovascular risk stratification in clinical practice and research [27,36–38].

9. EAT and VAT: comparative roles in cardiovascular risk

9.1. Shared pathways

Both VAT and EAT express NLRP3 inflammasomes and secrete IL-6, TNF-α, and leptin, but EAT's transcriptome is enriched for cardiac-specific genes (e.g., *ADIPOQ*, *UCP1*). While there is evidence that VAT is associated with insulin resistance and its reduction may improve cardiorespiratory fitness [39], EAT predicts the occurrence of atrial fibrillation, independent of BMI even after VAT adjustment [40] suggesting organ-specific mechanisms with direct paracrine effects on coronary arteries [41] (Table 2).

9.2. Clinical discordance

In the PROMISE trial cohort, EAT volume lost association with coronary artery disease (CAD) risk after adjusting for VAT ($p = 0.07$), yet retained predictive value for atrial fibrillation recurrence post-ablation (HR 1.8, $p < 0.01$) [42]. This dichotomy underscores EAT's role as a local amplifier of cardiac pathology. (Table 3)

Table 2
Epicardial adipose tissue.

- Epicardial adipose tissue is white adipose tissue that displays features of both brown and beige fat.
- Epicardial adipose tissue is an ectopic fat depot located between the myocardium and the visceral layer of the pericardium, and it is both anatomically and functionally contiguous with the myocardium.
- Epicardial adipose tissue is supplied by branches of the coronary arteries, whereas pericardial fat is supplied by branches of non-coronary arteries.
- Epicardial adipose tissue exhibits metabolic, thermogenic (similar to brown fat) and mechanical (cardioprotective) properties, and has the highest rates of lipogenesis and fatty acid metabolism among visceral adipose depots.
- A transcriptome unique to epicardial adipose tissue is enriched in genes associated with inflammation, endothelial function, coagulation, and the regulation of potassium channels.
- The myocardium is modulated by cytokines secreted from the epicardial fat depot.
- Epicardial adipose tissue is a marker of visceral adiposity and can be used to test the efficacy of interventions aimed at modulating adipose tissue characteristics.
- Coronary artery disease, metabolic syndrome, insulin resistance, fatty liver disease and cardiac abnormalities are all associated with increased levels of epicardial fat.

Table 3
Visceral versus epicardial adipose tissue and cardiovascular risk.

Feature	Visceral Adipose Tissue	Epicardial Adipose Tissue
Primary Association	Systemic insulin resistance	Atrial fibrillation, CAD
Inflammation	M1 macrophages dominant	Higher IL-1β, perivascular CD8 + *T* cells
Imaging	CT/MRI (waist circumference)	Echocardiography (parasternal view)

10. Methods to measure epicardial adipose tissue

The clinical application of epicardial fat is also within its measurability. Iacobellis et al. first developed an ultrasound technique to detect and quantify epicardial fat thickness using the standard transthoracic echocardiography, described in detail in Fig. 2 [26]. Echocardiography offers a convenient, cost-effective, and point-of-care method to measure EAT thickness. This technique identifies EAT as the echo-free space between the outer myocardial wall and the visceral pericardium, visualized in parasternal and short-axis views (Fig. 2).

Ultrasound measured fat thickness is not invasive and readily accessible. More importantly, epicardial fat thickness independently correlates with intrabdominal VAT, and better than waist circumference [3,43,44]. Iacobellis et al. demonstrated a linear correlation between ultrasound measured epicardial fat thickness and MRI- spectroscopy intramyocardial fat content, confirming the direct interplay between the fat and the heart. Epicardial fat thickness is also an independent predictor of CAD, AF and cardiovascular events. These features make the ultrasound assessment of epicardial fat an appealing diagnostic tool [24]. However, there are limitations due to the inter-operator variability and the mono dimensional measurement. CT and MRI certainly provide a volumetric analysis of epicardial fat and deeper assessment of anatomical locations that would be not accessible with the echocardiography. Recent studies indicated the importance of epicardial fat regionality in the development of diseases such as CAD or AF [24]. CT and MRI can detect and measure epicardial fat surrounding the coronary arteries and infiltrating the left atrium, independent players in CAD and AF, respectively. Additionally, epicardial fat density can be measured with CT and serve as marker of fat inflammation and fibrosis, with direct effects on the adjacent myocardium and coronary arteries [45]. In summary, epicardial fat imaging is an evolving tool that offers clinicians and researchers reproducible and accurate markers for assessing cardiovascular risk [45]

11. Visceral adipose tissue and clinical disorders

The basic mechanisms linking VAT with clinical disorders are only partially understood. The most recognisable adverse effects of VAT accumulation are metabolic alterations, insulin resistance, and systemic inflammation [23,46].

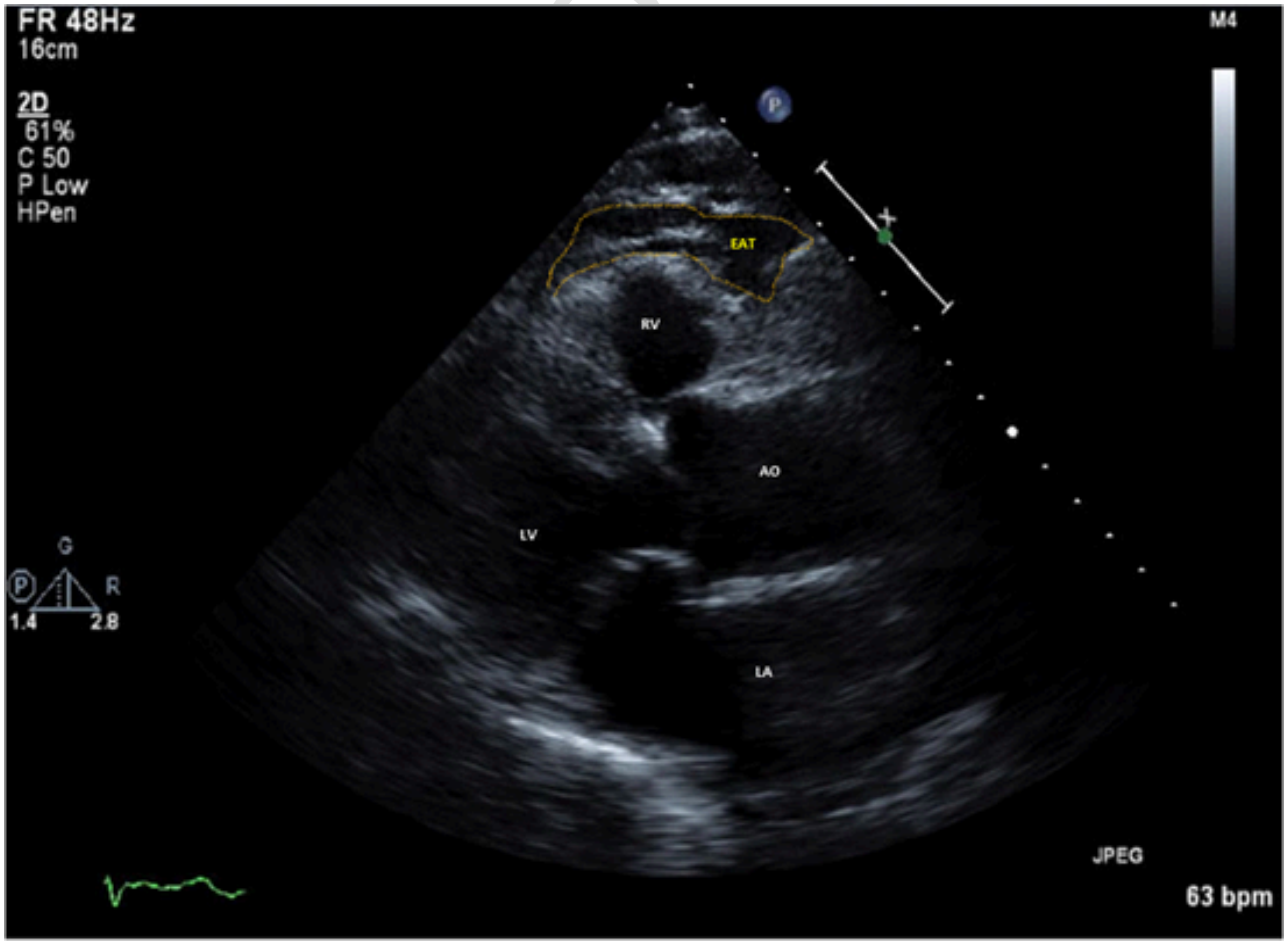


Fig. 2. Ultrasound-measured Epicardial Fat thickness. Epicardial fat can be visualized and measured using standard two-dimensional echocardiography. Parasternal long axis view of EAT thickness. EAT is the echo-free space (*within the yellow dotted line*) between the myocardial layer of the right ventricle (RV) and the visceral layer of the pericardium. EAT thickness is measured perpendicularly on the free wall of the RV at end-systole. Echocardiographic epicardial fat thickness ranges from a minimum of 1 mm to a maximum of almost 23 mm.

12. Role of epicardial adipose tissue in cardiovascular disorders

A. Coronary artery disease.

As mentioned above, EAT plays a cardioprotective role. However, in certain pathological conditions such as abdominal obesity, it is considered one of the factors that may cause and exacerbate atherosclerosis, favouring the onset of associated CAD [25,47]. A dense inflammatory infiltrate, mainly represented by macrophages, is often found in the epicardial fat of individuals with coronary artery disease.

EAT inflammation is the main feature in patients with CAD and consists mainly of dense infiltrates of macrophages, mast cells and CD8+ *T* cells. In particular, pro-inflammatory M1 macrophages are significantly more numerous and widespread than anti-inflammatory M2 macrophages. Given the proximity of the EAT to the coronary arteries; the abundant pro-inflammatory proteasome is fuelled by both increased production of inflammatory adipokines and reduced expression of adiponectin, an anti-inflammatory cytokine. The more pathologically elevated and the closer the EAT is to the coronary artery, the greater the inflammatory activity and consequently the severity of coronary atherosclerosis [48].

In patients with CAD, the EAT transcriptome is rich in genes involved in haemostasis and coagulation, including tissue plasminogen activator, which links fibrinolysis and inflammation in human adipose tissue. Epicardial adipocytes from CAD subjects significantly express cellular stress markers (such as MAP2K3 and MAP3K5 kinases) associated with coronary inflammation, as well as several proteases involved in lysosomal degradation and cell apoptosis.

EAT is also a local source of ectopic lipids [49]. Excessive secretion and release of fatty acids by epicardial adipocytes infiltrating the adventitia may contribute to lipid accumulation in the coronary arteries. Furthermore, the expression of genes encoding proteins involved in lipid metabolism, such as endothelial lipase (lipase G), neutral amino acid transporter and small subunit 1 of amino acid transporter (SLC7A5), is higher in EAT of patients with CAD and T2DM than in patients with CAD alone. In EAT, insulin-stimulated lipogenesis is greater than that measured in other visceral adipose tissue depots, while glucose uptake is extremely low [50]. Therefore, EAT may not only result in, but also contribute to, coronary insulin resistance. Furthermore, in the presence of CAD, glucose transporter type 4 (GLUT4) mRNA levels are lower in EAT than in subcutaneous adipose tissue, resulting in impaired insulin-mediated glucose uptake. Increased signalling by advanced glycation end products (AGE) and their receptors (RAGE) is observed in the EAT of patients with T2DM. In these patients, increased AGE-RAGE may contribute to oxidative stress and endothelial damage [51].

The complex molecular and cellular mechanisms involved in EAT's action in the development of coronary atherosclerosis can be applied in clinical practice to enable early diagnosis and accurate cardiovascular risk stratification. Patients with CAD have greater EAT volume and thickness than those without atherosclerosis. A higher EAT volume is associated with a coronary artery calcium (CAC) score >10, which predicts the risk of atherosclerosis with respective sensitivities and specificities of 72 % and 70 %. Furthermore, high EAT volume has been associated with the progression of coronary artery calcification, particularly in younger subjects (under 55 years old) and those with mild obesity. It has also been shown to predict the early stages of atherosclerosis in asymptomatic subjects, often independently of obesity. This can be explained by the specific phenotype of EAT and the inability to define adipose tissue distribution in the body using BMI.

The inflammatory activity of EAT also depends on its localisation. Indeed, EAT infiltration into the left atrioventricular groove is a stronger predictor of coronary atherosclerosis than total EAT volume. Therefore, assessing EAT may help predict the risk of major coronary events in individuals with asymptomatic atherosclerosis who are not obese [52].

Importantly, the distribution of epicardial adipose tissue is focally asymmetric [53,54] and thus the effect of epicardial adipose tissue in promoting atherogenesis is highly localised, with focal obstructive lesions located in coronary artery segments immediately adjacent to areas of greatest epicardial fat thickness.

The use of more sophisticated techniques to assess epicardial adipose tissue, such as CT and MRI, could therefore be introduced as a routine procedure to more effectively predict and stratify CAD itself [55,56].

13. Epicardial adipose tissue coronary artery cross-talk

The bidirectional crosstalk between epicardial adipose tissue (EAT) and coronary arteries plays a pivotal role in the pathogenesis of coronary artery disease (CAD). This dynamic interaction operates through two key pathways:

a) **Inside-to-Outside (Plaque-Derived Signals Affecting Epicardial Adipose Tissue).** Coronary atherosclerotic plaques release inflammatory mediators, such as IL-6 and TNF-α, as well as hypoxia-inducible factors, which diffuse into adjacent epicardial adipose tissue (EAT). This triggers adipocyte dysfunction and the secretion of proinflammatory adipokines [57]. This process is further amplified by extracellular vesicles (EVs) containing microRNAs (miRNAs), such as miR-133, miR-21 and miR-143, which are differentially expressed in the perivascular adipose tissue (PVAT) that surrounds atherosclerotic plaques. These EVs suppress adiponectin expression, creating a feedback loop that exacerbates coronary inflammation [58].

b) **Outside-to-Inside (Epicardial Adipose Tissue-Derived Mediators Affecting Coronary Arteries)-** EAT secretes cytokines (e.g., leptin, resistin), free fatty acids, and reactive oxygen species (ROS) that infiltrate the coronary vasculature, promoting endothelial dysfunction, macrophage polarization, and fibrous cap thinning [41]. Notably, EAT-derived SFRP5 and Wnt5a regulate vascular redox state, while pro-inflammatory adipokines like chemerin and visfatin contribute to plaque instability (Table 3) [59]. In metabolically dysfunctional EAT, impaired thermogenesis (reduced UCP1) further amplifies lipotoxicity, accelerating atherosclerosis [60].

14. Pericoronary adipose tissue (PCAT) attenuation as an imaging biomarker

Perivascular adipose tissue (PVAT) surrounding coronary arteries exhibits distinct biological properties compared to EAT located farther from the arterial wall. In 2017, Antonopoulos et al. demonstrated that the inflammatory state of coronary PVAT can be assessed using the fat attenuation index (FAI), which is a metric derived from coronary computed tomography angiography (CCTA) [57]. This index reflects adipocyte lipid content and size, serving as a non-invasive marker of perivascular inflammation [60].

15. Pathophysiological basis

PCAT attenuation (−190 to −30 Hounsfield units, HU) captures adipocyte dedifferentiation and inflammation driven by cytokine diffusion. This metric correlates with histological evidence of macrophage infiltration and has been validated against ^{18}F-FDG PET/CT [57,58].

Clinical Utility on Risk Stratification. In the CRISP-CT study, high PCAT attenuation predicted cardiac mortality (HR 5.6) independent of plaque burden [24]. Statins reduce PCAT attenuation (−5.3 HU/year), paralleling reductions in hs-CRP [61], and this is useful for therapeutic monitoring and on oncology to evaluate cardiotoxicity of chemotherapy-induced inflammation, correlated with troponin elevation and in-

creased PCAT attenuation [62] The bidirectional EAT-coronary artery crosstalk underscores EAT's dual role as both a biosensor and effector of vascular inflammation. PCAT attenuation (FAI) provides a clinically actionable biomarker for residual inflammatory risk, enabling precision therapeutic strategies [59].

B. Arrhythmias

Atrial fibrillation. Atrial fibrillation (AF) is the most common arrhythmia in obese individuals [63]. Although ventricular arrhythmias are less common, they are still associated with significant morbidity and a higher risk of mortality. AF increases exponentially with age, affecting more than 10 % of the elderly population, and can lead to long-term heart failure, stroke and, in the most severe cases, death. EAT has recently emerged as an independent risk factor for AF, not only for its pathogenesis but also for its recurrence after ablation treatment. In particular, posterior left atrial adiposity measured by CT is associated with AF burden independently of left atrial area and BMI [40].

The risk of AF may increase by as much as 65 % in individuals with a BMI >30 kg/m^2 compared with normal BMI (18.5–24.9 kg/m^2), which translates into a 4 % increased risk for each unit increase in BMI [40,63]. The mechanisms that may explain how an alteration in EAT causes or contributes to AF are diverse and include genetic factors, as well as innervation dysfunction, inflammatory and fibrotic processes, fatty infiltration, structural remodelling and atrial electrical activity. It has been hypothesised that the pathogenesis may begin during embryogenesis, with progenitor cells located in the epicardium developing into either coronary smooth muscle cells or cardiac fibroblasts, or differentiating into adipocytes, depending on the stimuli they receive. These stimuli include substances and factors (the secretome) released by atrial myocytes [40].

The periatrial EAT, which surrounds the left atrium, has a different transcriptome and secretome to that of other EAT sites. The genes it contains encode proteins involved in processes such as oxidative phosphorylation, muscle contraction and calcium signalling, all of which are involved in its potential arrhythmogenic capacity. Infiltration of free fatty acids can separate cardiomyocytes, slowing conduction due to the loss of lateral cell junctions and the disorganisation of the myocardium, as well as altering the depolarisation wavefront. The EAT also contains ganglion plexuses that are responsible for initiating and maintaining atrial fibrillation. Activation of these plexuses can result in a shortening of the action potential duration and an increase in the amplitude of the calcium transient in the atrial myocardium.

Pro-inflammatory and profibrotic cytokines (such as interleukins and TNF-alpha) and profibrotic factors (such as matrix metalloproteinases and activin A) can diffuse from the EAT into the adjacent atrial myocardium, promoting arrhythmogenic processes.

This increased propensity for AF may be explained by electrophysiological remodelling due to atrial volume expansion, conduction abnormalities, and increased expression of profibrotic mediators that contribute to the generation of a proarrhythmogenic substrate. A meta-analysis of 63 observational studies encompassing 352,275 participants reported that 1-SD increment in the volume of EAT was associated with a 2.2-fold higher risk of persistent AF compared with paroxysmal AF [40].

EAT emerged also as an independent predictor of AF recurrence following radiofrequency- and cryoballoon-based ablation [42]. EAT volume showed an association with serum CRP in those with recurrent AF suggesting inflammation as the mediator between EAT and arrhythmic risk [64]. In another study, EAT measured by echocardiography was an independent predictor of AF recurrence after cryoablation. Values of EAT >6.92 predicted AF recurrence at follow-up with a 71 % sensitivity and a 78 % specificity [65]

In addition, a reduction in arrhythmia burden has been reported up to 2 years after AF ablation; cardiometabolic risk factor management was associated with arrhythmia-free survival in 32.9 % and 87 % of patients undergoing single and multiple ablations, respectively, compared to 9.7 % and 17.8 % of patients receiving standard care [66].

Ventricular arrhythmias. The results are sometimes controversial. EAT thickness has been found to be positively correlated with ventricular ectopic burden and is predictive of QT interval prolongation (defined as >450 ms), ventricular tachycardia/fibrillation risk in heart failure and ventricular tachycardia recurrence after ablation. In contrast, others report no association between EAT volume and QTc interval, and that EAT thickness correlates better with PR interval prolongation and P wave than with QT dispersion.

However, a meta-analysis of 7197 patients showed that overweight and obese individuals had a prolonged QT interval and QT dispersion compared with normal weight, and that this was reversed by 25.77 ms and 13.47 ms with weight loss [67].

C. Heart failure

Heart failure is a complex clinical syndrome that generally results from diastolic and/or systolic dysfunction. When left ventricular filling and relaxation are impaired but the heart maintains a normal stroke volume, the condition is defined as heart failure with preserved ejection fraction (HFpEF) [68]. Heart failure is defined as heart failure with reduced ejection fraction (HFrEF) if there is an alteration in systolic performance with an ejection fraction of less than 40 %. Patients with either HFpEF or HFrEF have a poor quality of life and an increased risk of arrhythmias and premature death. Epicardial adipose tissue (EAT) may play a role in heart failure, particularly in patients with HFpEF, who have a significantly greater volume of EAT than healthy people. However, few studies have controlled for potential confounders, such as coronary artery disease (CAD) or obesity.

EAT may affect heart failure through multiple mechanisms, including increased inflammation and fibrosis via the secretion of pro-inflammatory and pro-fibrotic proteins and cytokines, autonomic dysregulation, and the adverse mechanical effects of a large fibrotic fat pad. An increased volume of EAT shows a strong correlation with worsening left ventricular diastolic relaxation and filling, resulting in reduced cardiac function [69]. Excess EAT-derived fatty acids can be taken up by cardiomyocytes and lead to ectopic lipid accumulation in the myocardium, contributing to the development of heart failure through morphological changes, contractile dysfunction and cardiomyocyte apoptosis.

EAT may also be involved through neurohormonal mechanisms, via intrinsic adrenergic and cholinergic nerves that interact with the extrinsic cardiac nervous system, both sympathetic and parasympathetic. Indeed, in patients with heart failure, norepinephrine levels in EAT are 5/6 times higher than in subcutaneous adipose tissue and 2 times higher than in plasma [70].

On the contrary, the association between EAT thickness or volume and HFrEF seems to be limited and controversial: in contrast to HFpEF patients, HFrEF patients have a smaller total EAT volume [71].

EAT represents a metabolic reserve for the myocardium and its excessive reduction could lead to cardiac cachexia, a condition that is not favourable in the presence of increased energy demands such as in heart failure. Pugliese et al. conducted an advanced study analysing the association between EAT thickness and several biomarkers and cardiorespiratory fitness, as assessed by peak oxygen consumption, in patients with HFrEF, HFpEF and controls. They found that increased EAT thickness was associated with poorer cardiorespiratory fitness, a poorer biomarker profile, RV-pulmonary artery uncoupling, and higher mortality in patients with HFpEF. Conversely, reduced EAT thickness was associated with worse LV dysfunction and mortality in patients with HFrEF [72]. This study demonstrated that the EAT has a specific pathophysiological role in the characterisation of HFrEF and HFpEF.

16. Epicardial adipose tissue and its predictive role of cardiovascular risk in adolescents

The number of overweight people tends to progressively increase in both developed and developing countries, and the proportion of obese people is around one third of the normal adolescents' population [73].

EAT thickness has been shown to be an independent predictor of insulin resistance in adolescents with obesity [74]. It has been shown that the optimal cut-off value for EAT to predict IR in adolescents with obesity was found to be >3.85 mm, with 92.5 % specificity and 68.5 % sensitivity [74]. Furthermore metformin has been shown to reduce EAT thickness in adolescents with obesity [75]. This is important considering studies showing that insulin resistance may represent a crucial marker in cardiovascular disorder development, starting as early as in childhood [76]. EAT has also been shown to be correlated with elevated blood pressure in children with obesity and metabolic syndrome [77] and also in the absence of obesity [78]. EAT has also been shown to closely correlate to carotid intima-media thickness (CIMT) in adolescents with obesity and with Metabolic syndrome [77], and it has been proposed to be an independent predictor of CIMT and thus a better marker that waist circumference as a predictor for CIMT in adolescents [79].

17. Role of EAT in obstructive sleep apnoea

EAT can contribute to the pathogenesis of obstructive sleep apnoea (OSA) [80]. OSA and epicardial fat are both associated with the development of type 2 diabetes mellitus and metabolic syndrome, and metabolic syndrome is more likely to occur in those with OSA [81]. The association of EAT with OSA has been shown to be independent of obesity, and changes in EAT may explain up to 38 % of variance in severity of OSA [82].

Recent studies demonstrating that managing VAT improves cardiorespiratory fitness and metabolic health, indirectly affecting EAT-related outcomes [83].

While prevalence of sleep apnoea tends to increase with age the clinical significance (severity) of apnoea decreases [84], thus highlighting the need for further studies in OSA in adolescents and the role of EAT in modulating the risk. Visceral fat distribution measured using MRI has been shown to be independently predictive of OSA severity in obese children [85]. Studies in children have shown that Visceral fat area was significantly elevated in moderate OSA (AHI ≥ 5), especially in boys [86]. This study also showed that release of proinflammatory cytokines by visceral adipocytes largely explains the association between central obesity and OSA in children and adolescents [86]. Increases in Inflammatory markers like CRP from childhood to adolescence have been shown to be better predictors of OSA severity, as measured by AHI (Apnoea Hypopnea Index) in later life in boys compared to other markers like waist circumference [87]. It is unclear whether dietary measures and physical activity, which have been found reduce central obesity in children, are also able to modify sleep apnoea [73].

18. Role of epicardial adipose tissue in high-risk cardiovascular disease populations: reinforcing EAT as a dynamic therapeutic target

Epicardial adipose tissue has emerged as a key factor in the pathogenesis of cardiovascular disease (CVD), particularly in high-risk populations. Its anatomical proximity to the myocardium and coronary arteries enables direct paracrine interactions that influence inflammation, fibrosis and metabolic dysfunction. Recent studies have further established the role of EAT as a dynamic therapeutic target in various at-risk groups, such as cancer survivors, HIV patients, and individuals undergoing chemotherapy. These studies have also emphasised the potential of pharmacological interventions to mitigate its adverse effects.

19. Radiotherapy and coronary inflammation

Kotanidis et al. demonstrated that radiotherapy in breast cancer patients induces coronary inflammation, with EAT acting as a potential mediator of increased cardiovascular risk in this population. The study underscores the importance of EAT assessment in cancer survivors to identify and mitigate long-term cardiovascular complications, suggesting that EAT modulation could be a preventive strategy in radiation-induced cardiotoxicity [88].

20. HIV and antiretroviral therapy

In HIV patients, chronic inflammation and metabolic disturbances contribute to accelerated atherosclerosis. Tumkosit et al. [89] found that viral suppression, while beneficial for infection control, was associated with higher EAT volume, which correlated with liver steatosis and coronary artery calcium. EAT volumes is also associated with a longer duration of antiretroviral therapy [90]. These findings suggest that EAT monitoring could enhance cardiovascular risk stratification in HIV patients on long-term antiretroviral therapy, potentially guiding early interventions to reduce atherosclerotic risk.

21. Chemotherapy-Induced cardiotoxicity

Anthracycline-based chemotherapy is known for its cardiotoxic effects, and EAT may serve as an early biomarker for such damage. Lin et al. [62] and Huang et al. [91] identified changes in EAT metabolic activity (measured via ^{18}F-FDG PET/CT) as predictive markers for anthracycline-induced cardiac toxicity in lymphoma patients. These findings support the use of EAT imaging for early detection of chemotherapy-related cardiovascular injury, enabling timely therapeutic adjustments to preserve cardiac function.

22. Lifestyle changes and pharmacologic interventions

22.1. Lifestyle modifications

The FIT-HEART trial demonstrated that a 10 % weight loss reduced EAT thickness by 18 % ($p < 0.001$) and resolved diastolic dysfunction in 62 % of patients with heart failure with preserved ejection fraction (HFpEF) [72]. Additionally, adherence to a Mediterranean diet alone decreased EAT inflammation (CRP reduction of 2.1 mg/L, $p = 0.03$) without changes in visceral adipose tissue (VAT), suggesting direct cardiac benefits.

22.2. Pharmacologic modulation of epicardial adipose tissue

Emerging evidence highlights pharmacologic agents as promising tools for reducing epicardial adipose tissue (EAT). Basdas et al. demonstrated that semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, modulates proinflammatory epicardial adipogenesis and exerts paracrine benefits on cardiomyocyte function [92], aligning with broader findings on GLP-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors, which reduce EAT volume and improve cardiometabolic outcomes [92–98].

A systematic review suggested that SGLT2 inhibitors may reduce EAT to a greater extent than GLP-1 agonists or exercise interventions in patients with type 2 diabetes mellitus or obesity [99].

Lipid-lowering therapy with atorvastatin also reduced EAT and the associated inflammation (IL-6 − 35 %, $p = 0.01$) independent of LDL changes [100].

23. Conclusions

EAT is the heart's visceral fat depot. It is anatomically and functionally linked to the myocardium. Due to its ease of measurement and the growing body of evidence supporting it, EAT is emerging as a promising biomarker for refining cardiovascular risk stratification. EAT also has the potential to be targeted by pharmacologic agents. Significant reductions in EAT and improvements in cardiometabolic profiles have been observed in obese patients following weight loss through diet, exercise, and bariatric surgery. Furthermore, the effectiveness of several pharmacological agents in reducing EAT reinforces its role as a modifiable therapeutic target.

The browning effect induced by drugs on EAT suggests potential strategies to enhance energy expenditure. Furthermore, modulating the EAT transcriptome with targeted pharmacological agents could lead to new approaches in the treatment of cardiometabolic diseases. Future research should prioritise standardised EAT assessment protocols and randomised trials to validate these interventions, ultimately improving cardiovascular outcomes in high-risk populations.

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