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Heart in Venice

From atherosclerosis to the management of coronary artery diseases

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Contents

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Heart in Venice: From Atherosclerosis to the Management of Coronary Artery Diseases

The Heart in Venice meeting brought together leading experts to address the evolving landscape of atherosclerotic cardiovascular disease (ASCVD) and its management. In recent years, ASCVD had increasingly affected younger individuals, often with a modest burden of traditional risk factors. This shift challenged the existing prevention strategies and raised the question of whether previous guidelines had remained adequate. Furthermore, significant advances in both non-invasive and invasive diagnostic tools had called for a more interdisciplinary approach to patient care, ensuring that diagnostic and therapeutic strategies were tailored to individual risk profiles. This meeting aimed to critically assess the role of past guidelines, explore novel risk prediction models, and integrate emerging diagnostic and therapeutic approaches to provide a more comprehensive and effective strategy for patient care.

Understanding the evolving nature of atherosclerosis and its direct connection to cholesterol metabolism had been fundamental to cardiovascular risk management. Large-scale epidemiological studies, including the Seven Countries Study and the Framingham Heart Study, had established a clear relationship between plasma cholesterol levels and cardiovascular risk [Catapano AL, *Eaj.* 2024; 2: 54-56]. However, recent analyses suggested that this association was not purely linear, prompting a re-evaluation of cholesterol management strategies. Insights from the Cholesterol Treatment Trialists' (CTT) Collaboration reaffirmed the substantial benefits of LDL-C reduction, with a 22-23% decrease in coronary heart disease risk per 1 mmol/L LDL-C reduction. These findings emphasized the importance of optimizing lipid management to mitigate cardiovascular risk.

Despite the well-documented role of cholesterol in cardiovascular disease, traditional cardiovascular risk prediction models, which estimated 10-year risk based on middle-aged cohort studies, had reached their limits. The need for earlier and more individualized risk assessment had become evident, considering the lifelong progression of atherosclerosis. Future models should have incorporated novel biomarkers, genetic predisposition, and advanced imaging techniques to provide a more precise, personalized risk estimation. The integration of artificial intelligence and big data analytics into risk assessment had represented a promising frontier, allowing for improved accuracy and more targeted preventive strategies [Graham IM, *Eaj.* 2024; 1: 1-3].

As risk prediction evolved, so too had the approaches to lipid lowering. Despite aggressive lipid-lowering strategies, residual cardiovascular risk had remained a challenge. The advent of next-generation lipid-lowering therapies offered new hope in addressing this gap. In addition to statins, ezetimibe, bempedoic acid, and PCSK9 inhibitors, novel approaches targeting Lp(a), CETP inhibition (Obicetrapib), and gene-editing strategies for PCSK9 modulation had emerged as promising therapies. These novel interventions had the potential to complement existing treatments, further reducing the incidence of cardiovascular events in high-risk populations [Averna M, *Eaj.* 2024; 2: 51-53].

With advances in lipid management and risk stratification, the role of imaging in assessing coronary artery disease had become increasingly crucial. SPECT and PET imaging had been essential tools in evaluating coronary artery disease (CAD), particularly in patients with intermediate-risk profiles or inconclusive initial assessments. By integrating these imaging modalities into routine clinical practice, clinicians achieved more accurate risk assessment and optimal therapeutic decision-making, ultimately improving patient outcomes [Pedretti RFE et al., *Eaj.* 2024; 1: 4-6].

The Heart in Venice meeting served as a platform to discuss cutting-edge research and innovations in ASCVD management. By re-examining existing guidelines, refining risk prediction models, and integrating novel therapies and imaging techniques, this meeting aimed to shape the future of cardiovascular care, ensuring that patients received the most effective, personalized treatments available. Through a multidisciplinary exchange of knowledge and expertise, this gathering contributed to refining best practices and advancing patient-centered approaches in cardiovascular medicine and set the stage for the activity of a group of researcher to develop independent guidance on how to approach this central issue for population and individual prevention of cardiovascular disease.

We wish to acknowledge the Menarini Fundation for organizing the meeting and for all the support received.

Alberico L. Catapano
Chair of the meeting

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Heart in Venice:

From atherosclerosis to the management of coronary artery diseases

26th-28th October 2023, Venice, Italy

Friday, 27th October 2023

Opening and Welcome - Fondazione Internazionale Menarini

Co-Presidents of the Meeting:
A.L. Catapano (Milan, IT), *F. Rigo* (Venice, IT)

SESSION I
From risk factors to atherosclerostic vascular disease

Chairpersons:
A.L. Catapano (Milan, IT), *F. Visseren* (Utrecht, NL)

When, what, why and to whom to propose a diagnostic preclinical screening to personalize the future clinical cardio-vascular risk • *I. Graham* (Dublin, IE)

What the Guidelines in cardiovascular prevention say and don't say • *F. Visseren* (Uthrecth, NL)

Atherosclerosis and cholesterol: what we should know • *A.L. Catapano* (Milan, IT)

Panel Discussion

SESSION II
Preclinical approach to vascular atherosclerosis

Chairpersons:
I. Graham (Dublin, IE), *F. Visseren* (Utrecht, NL)

Preclinical carotid atherosclerosis as an indicator of polyvascular disease? • *P. Poredos* (Ljublijana, SI)

Is cardiac ultrasound feasible in pre-clinical assessment of atherosclerosis? • *Q. Ciampi* (Naples, IT)

A novel multimodality ultrasound pre-clinical study in Venice • *F. Rigo* (Venice, IT)

Personalized approach to atherosclerotic vascular disease in 2023 • *F. Crea* (Rome, IT)

SESSION III
Preclinical approach to vascular atherosclerosis

Chairpersons:
J. Davies (London, UK), *F. Rigo* (Venice, IT)

Role of Nuclear medicine assessing patients with suspected vascular disease • *R. Pedretti* (Milan, IT)

Role of CT Scan for assessing patients with suspected artery disease: when, to whom and how? • *G. Pontone* (Milan, IT)

Role of coronary angiography and the latest technologies in weighing the burden of coronary plaque • *J. Davies* (London, UK)

Panel discussion

Saturday, 28th October 2023

Chairpersons:
A.L. Catapano (Milan, IT)

Gender and ACVD where we stand?
E. Prescott (Copenhagen, DK)

SESSION IV
From diagnosis of vessels disease to therapy

Chairpersons:
M. Arca (Rome, IT), *L. Mazzolai* (Losanna, CH)

New non-invasive approach to coronary artery disease • *Q. Ciampi* (Naples, IT)

Role of antithrombotic therapy in vascular disease • *L. Mazzolai* (Losanna, CH)

Current approaches to lipid lowering • *M. Arca* (Rome, IT)

Novel approaches to lipid lowering • *M. Averna* (Palermo, IT)

Panel Discussion

SESSION V
New approaches in CV risk assessment

Chairpersons:
A.L. Catapano (Milan, IT) *M. Ostojic* (Belgrade, RS)

Clonal hematopoiesis and CV risk • *G. Condorelli* (Milan, IT)

Proteomics in CVD prediction • *N. Nurmohamed* (Amsterdam, NL)

Integrated approaches to CV risk evaluation
B. Ference (Cambridge, UK)

Closing remarks

Co-presidents
Alberico L. Catapano, Fausto Rigo

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Marcello Arca, Maurizio Averna, Quirino Ciampi, Gianluigi Condorelli, Filippo Crea, Justin Davies, Brian Ference, Ian Graham, Lucia Mazzolai, Nick Nurmohamed, Miograd Ostojic, Roberto Pedretti, Gianluca Pontone, Pavel Poredos, Eva Prescott, Frank Visseren.

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Atherosclerosis and cholesterol: What we should know

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ABSTRACT

Epidemiological studies consistently link high low-density lipoprotein cholesterol (LDL-C) levels with an increased risk in cardiovascular disease. This correlation remains strong across various populations. LDL-C plays a key role in atherosclerosis by transporting cholesterol to arterial walls, where it induces plaque formation. Lowering LDL-C levels has proven to reduce the risk of coronary heart disease, regardless of the drug used. Although high-density lipoprotein cholesterol (HDL-C) has long been considered protective, recent studies have suggested that increasing HDL-C alone may not reduce cardiovascular risk and that the function of HDL may be relevant, rather than the HDL-C plasma level. Genetic studies, such as Mendelian randomisation, have confirmed that LDL-C is a causal factor for heart disease. Triglyceride levels, which are transported by lipoproteins, also contribute to cardiovascular risk, although lowering apolipoprotein B is considered more crucial for reducing cardiovascular events. Overall, lowering LDL-C levels remains the cornerstone of cardiovascular disease prevention and treatment.

Keywords
Cholesterol; atherosclerosis; low-density lipoprotein; lipid-lowering

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Epidemiological studies have consistently shown a strong association between elevated LDL-C levels and increased cardiovascular risk. The well-established relationship between plasma cholesterol levels and the risk of cardiovascular events is continuous, regardless of whether total cholesterol or its fractions, such as LDL-C, are considered.

When analysing plasma cholesterol levels and integrating data from several studies, including the Pooling Project, the Framingham Heart Study and the Israeli Perspective Study, a consistent association between serum cholesterol levels and coronary events was confirmed worldwide [1]. This pattern was particularly clear in the Seven Countries Study, in which the relative risks of coronary heart disease (CHD) mortality as a function of serum cholesterol levels were similar in the different cohorts studied, although the absolute risks were different [2]. The observed differences in risk between different populations are largely attributable to baseline risk values, suggesting that other factors, such as diet, may play an important role. The Framingham Heart Study has shown that its results are applicable in any country when adjusted for baseline risk, suggesting a universal pattern in the relationship between cholesterol levels and cardiovascular risk. This has led to debate because the relationship has been oversimplified and presented as linear when it is not so in absolute terms. For example, a 0.5 mmol/L (about 20 mg/dL) increase in total cholesterol correlates with a 12% relative increase in CHD mortality risk. Consistent with this observation, data from the Cholesterol Treatment Trialists' (CTT) Collaboration showed that lowering low-density lipoprotein cholesterol (LDL-C) by 1 mmol/L reduces the risk of coronary heart disease by 22-23%, which is consistent with data from clinical trials [3]. A collaborative meta-analysis of ~900,000 individuals in 61 prospective observational studies has shown that age significantly attenuates the proportional (relative) relationship between ischemic heart disease (IHD) mortality and cholesterol levels. However, cholesterol level is a strong positive risk factor for IHD mortality not only in early middle age but also in old age. Although the proportional differences in risk decrease with age, the absolute impact of cholesterol levels on annual mortality from IHD is much greater at older ages than at younger ages [4].

In summary, extensive research confirms that cholesterol is a determinant of cardiovascular risk that is consistently observed in different populations and age groups. This understanding is crucial for the development of public health strategies and individualised treatment plans.

Cholesterol is essential for cell function, as it is an essential component of all cell membranes. It co-operates with fatty acids and phospholipids to regulate membrane fluidity. Cholesterol clusters in the membranes are crucial for the localisation of receptors, including

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the LDL receptor (LDLR), in specific regions (coated pits). These areas of the cell surface are crucial for the recruitment of receptors, their ability to interact and cellular responses. Cholesterol is also crucial for the function of internal membranes, such as those of mitochondria, endosomes, and lysosomes. The body's need for cholesterol is emphasised by its ability to acquire it either from the outside, via the LDLR on hepatocytes and enterocytes, or from the inside via the mevalonate pathway. These pathways are interconnected; increased dietary cholesterol intake reduces endogenous synthesis, and vice versa. Contrary to popular belief, lowering plasma cholesterol to very low levels does not pose a biological risk, as the body can synthesise sufficient cholesterol for cell division and brain development.

When referring to plasma cholesterol, we are talking about the lipoproteins that transport cholesterol mainly in esterified form and not free cholesterol molecules. Lipoproteins carrying cholesterol, especially apoB-containing lipoproteins, are atherogenic (5). Their ability to penetrate and become trapped within the arterial wall initiates a cascade of atherosclerotic processes. Lowering LDL-C levels decreases the number of these lipoproteins and thus lowers the risk of plaque formation and progression. Remnants of lipoproteins, including very low-density lipoproteins (VLDL) and chylomicrons, also play a role in cholesterol transport and metabolism, with VLDL remnants eventually transforming into LDL.

The formation of foam cells by accumulation of excess cholesteryl esters is a key process in the initial stage of lesion development, particularly related to vascular permeability [6]. This early stage does not necessarily lead to immediate progression of the lesion. Studies conducted on young American soldiers who died in Vietnam showed numerous fatty streaks that do not always correspond to later plaque development sites. This suggests a dynamic process in the early stages, where plaques do not necessarily form at the sites of initial lipid deposition, allowing for possible damage reversal. Lowering LDL-C levels has been shown to induce plaque regression, a process in which there are significant changes in plaque composition, including a marked decrease in lipid content and an increase in the thickness of the fibrous cap (which is considered inert with respect to inflammatory activity).

LDL is a causal factor in atherosclerosis, not cholesterol itself [7]. This distinction is crucial because the role of LDL in transporting cholesterol to the arterial walls is what initiates the damage. In contrast, HDL (high-density lipoprotein), which also transports cholesterol, is not causal. Conversely, a low level of HDL-C is associated with a higher risk of cardiovascular events. However, the causal relationship between HDL-C and cardiovascular risk is more complex and less well understood than that for LDL-C. Genetic studies and clinical trials have challenged the notion that simply increasing HDL-C levels pharmacologically reduces cardiovascular risk, suggesting that HDL functionality may be more important than HDL-C levels alone [8]. Surprisingly, extremely high HDL-C levels have been associated with higher cardiovascular risk [8] casting several doubts on the antiatherogenic role of HDL and determined by the measurement of HDL cholesterol or apo A-I.

Genetic studies, including Mendelian randomisation analyses, have provided compelling evidence for the causal role of LDL-C in atherosclerosis and cardiovascular disease [7]. Individuals with genetic mutations that result in lower lifelong LDL-C levels, such as those affecting the *PCSK9* or *HMGCR* genes, have a significantly lower risk of CAD, supporting the concept that LDL-C is a causal factor in the development of atherosclerotic disease. Different genetic scores predicting a 10 mg/dL reduction in LDL-C show consistent lifelong benefits [9]. This suggests that the mechanism of LDL-C lowering, whether by statins or PCSK9 inhibitors, leads to similar outcomes. Therefore, it is the lowering of LDL-C levels that is crucial, regardless of the method used. These findings are confirmed by clinical trials of LDL-C-lowering therapies, which consistently show that reducing LDL-C levels reduces the incidence of cardiovascular events. To date, clinical trials have shown that lowering LDL-C to very low levels is associated with a further CV risk reduction with no association with excess adverse events [10].

Genetic studies, Mendelian randomisation, and clinical trials involving patients with familial hypercholesterolemia (FH) have demonstrated that cholesterol trajectories can be altered [11]. In a typical population, average cholesterol levels eventually reach a threshold where clinical disease manifests. Not surprisingly, in individuals with heterozygous FH, higher cholesterol levels from birth accelerate the progression of the disease. Early intervention to reduce LDL-C can significantly alter this trajectory, suggesting that early and sustained LDL-C reduction has a profound impact on delaying disease onset. This concept is clearly illustrated in homozygous FH, where lowering LDL-C can extend life expectancy by approximately 25 years [11]. Randomised clinical trials, observational studies, and Mendelian randomisation studies all support the notion that prolonged exposure to lower LDL-C levels accrues greater cardiovascular benefits. For instance, a lifelong LDL-C reduction of 0.3 mmol/L (10-12 mg/dL) can achieve the same cardiovascular risk reduction seen in five years of statin therapy, and this can be obtained through moderate lifestyle changes.

Triglycerides (TG) have been identified as an independent risk factor for cardiovascular disease. TG are transported by lipoproteins, mainly chylomicrons and very low-density lipoproteins (VLDL) as well as their remnants. Remnant lipoproteins are considered atherogenic, functioning similarly to LDL in terms of their pathological impact [12]. The distribution of the so-called "remnant cholesterol" is closely linked to TG levels, which makes its use as an independent marker difficult.

Mendelian randomisation studies support the causal role of remnant cholesterol in cardiovascular disease [13]. However, intervention studies specifically targeting triglycerides are limited. Lowering TG through LPL-targeted pathways, including ANGPTL3, APOC2, APOC3, and APOE, however has shown potential in observational and genetic studies. Despite numerous trials with fibrates (drugs that reduce mainly plasma TG) showing overall negative results, subgroups with high TG and low HDL-C had benefits, suggesting that targeting this subgroup may be effective. The debate on whether apoB is a more meaningful marker than TG continues. In a study that assessed the impact of genetic scores for LPL and LDL, the association of different genetic variants with apoB concentrations resulted in a log-linear relationship with the risk of coronary heart disease, establishing apoB as a reliable indicator that includes the contributions of both LDL-C and TG [9]. This suggests that the number of particles is the most accurate proxy for measuring disease causation.

This hypothesis is supported by the PROMINENT trial of pemafibrate in an ideal population (high TG, low HDL, diabetes, cardiovascular disease) [14]. Despite reductions in remnant cholesterol and TG, there was no change in apoB levels, suggesting that apoB is the primary driver of the clinical benefit. This highlights the importance of lowering apoB as opposed to simply lowering other lipid parameters. This concept is further reinforced by comparing the results of the STRENGTH and REDUCE-IT trials with omega-3 fatty acids [15, 16]. Although both trials showed a decrease in TG, only the REDUCE-IT trial showed a reduction in apoB, suggesting that the therapeutic benefit is related to apoB reduction.

In summary, apoB-containing lipoproteins fulfil the criteria for causal involvement in atherosclerosis. Lowering apoB levels is critical

even with delayed intervention, although the effects may not be fully reversible.

Conclusion

The relationship between LDL-C and cardiovascular risk is well-established and supported by a wealth of epidemiological, genetic, and clinical trial data (**Figure 1**). Elevated LDL-C is a major causal factor in the development of atherosclerosis and cardiovascular disease, and interventions that lower LDL-C levels consistently reduce the risk of cardiovascular events. While the role of HDL-C in cardiovascular risk remains less clear, lowering LDL-C levels remains a cornerstone of cardiovascular disease prevention and treatment. As research advances, further insights into cholesterol metabolism and its impact on cardiovascular health may lead to new strategies for reducing the burden of cardiovascular diseases globally.

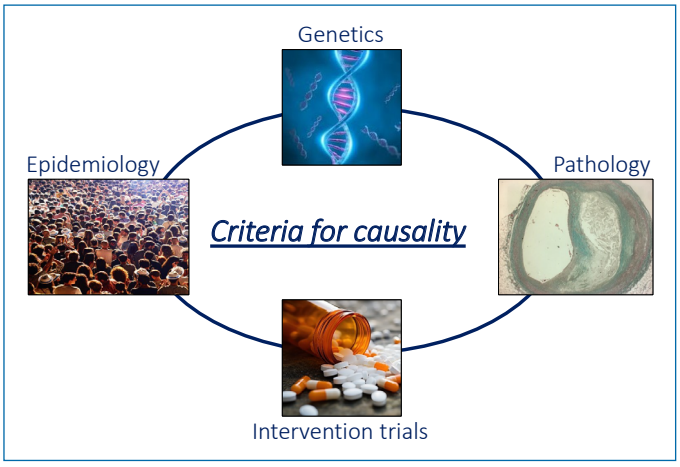

Figure 1 | LDL and atherosclerosis: Criteria for causality.

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Conflicts of interest

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Cardiovascular risk prediction- now and the future

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ABSTRACT

Current cardiovascular risk estimation systems that estimate 10-year risk based on cohort studies starting at around age 40 have probably reached their limits based on current methods.
The challenges are to develop new systems that will permit personalised risk estimation earlier in life with better estimates of true lifetime risk and likely treatment benefits. We outline approaches to address these issues.
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Terminology: It is perhaps pedantic to observe that, although the term 'cardiovascular risk prediction' has become embedded in the cardiological literature, what we in fact do is to estimate the risk to allow a prediction of the likelihood of a future clinical event. The term 'screening' strictly applies to testing to assess the likelihood of disease. 'Health risk assessment' is a wider term that includes demographics, social factors, lifestyle and assessment of risk factors.

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Keywords
Cardiovascular risk estimation; lifetime risk

Why assess cardiovascular disease (CVD) risk?

Cardiovascular risk assessment is used to guide management decisions. In general, the higher the risk, the more intense will be the preventive efforts required.

In most people, the risk of a future atherosclerotic CVD event is the product of the combined effect of a number of risk factors such as hyperlipidaemia, hypertension, smoking and diabetes. The clinical estimation of the effect of such combinations is unreliable, which is the rationale for risk scoring systems [1].

When to assess CVD risk

Current risk estimation systems are based on cohort studies that started at about age 40 and so estimate risk from then on. This misses 40 years of exposure to risk, in addition to in-utero risk. The future, discussed below, is clearly to develop systems that can estimate risk much earlier in life.

Risk evaluation may be opportunistic (when a person presents for another reason) or systematic, either population wide of in defined groups with known risk factors such as smoking or diabetes. Population wide risk assessment allows improvement in risk factors but it has been difficult to demonstrate improved outcomes [2], and hence cost-effectiveness is uncertain. Many countries prefer a combination of opportunistic evaluation and evaluation in those with known risk factors.

How to assess risk

Both the 2021 ESC Prevention Guidelines [2] and The 2019 ESC/EAS Guidelines for the management of dyslipidaemias [3] define categories of risk. In general the latter adopts a simpler approach but both agree that subjects with established CVD have declared themselves to be at very high risk and intensive and immediate risk factor advice is advised.

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In *apparently health persons,* The European Society of Cardiology 2021 Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice [2] recommend the use of SCORE2 [4] or, in persons over 70 years, SCORE2-OP [5] for risk assessment. These tools are calibrated for four risk regions of Europe and can be re-calibrated for other countries. HeartScore is a simple, interactive online calculator that facilitates the use of SCORE (www.heartscore.org)

In those at intermediate risk, screening for asymptomatic disease, for example through coronary artery calcium scoring may help to re-classify risk [2].

In America, use of the Pooled Cohort equation is recommended [6], more recently supplemented by the PREVENT calculator [7].

Limitations of current risk estimation systems

Current risk estimation systems are derived from cohorts studies, most of which started at about age 40, in other words after many years of exposure to risk. Strictly speaking, they apply only to the population from which they were derived. They may work well in other similar populations, or can be re-calibrated for others [4, 5], but the problem remains that the risk estimates apply to groups rather than individuals.

Current techniques such as Cox derive beta-coefficients that are essentially multipliers and cannot easily estimate complex interaction effects within different combinations of risk factors. Further, risk estimates are dominated by the effect of age, especially when risk is expressed over 10 years. Current estimates of lifetime risk also start too late, usually around age 40.

The impact of genetic factors has been underestimated. While polymorphisms affecting risk may have a seemingly small impact on 5-10 year risk, their impact on true lifetime risk, from birth on, may be much greater than is generally appreciated [8].

Can we see the future?

Ideally, one would like to be able to:

- allow better for the dominance of age in risk estimation
- estimate true lifetime risk from early in life
- approach more individualised estimates of risk
- make more precise estimates of treatment benefits
- explore integrating in-utero determinants of risk

Ference and others [8, 9] have pointed out that Mendelian randomisation studies suggest the impact of polymorphisms on risk has been greatly underestimated, given that they function from birth on. These effects may be direct or, probably more importantly, through their effect on determining the rate of rise of risk factors such as LDL cholesterol and blood pressure.

This has led to a suggestion to move from 10-year risk to an exposure time model in which risk is expressed as mmol/years of LDL cholesterol, mmHg/years of blood pressure or indeed years of exposure to total risk. Such an approach integrates the rate of rise of risk with time which is likely to parallel the development of atherosclerosis. Thus, given several measurements of risk over several years in younger persons, it should be possible to give a personalised estimate of risk much earlier in life than is currently possible to allow true preventive action early in life. This Mendelian Randomisation-based approach can also permit more precise and logical estimates of likely treatment benefits.

The exposure time approach may be summarised as depicted in **Figure 1**.

Vardas has commented on the transition from ancient medicine through modern medicine to what he terms metaclinical medicine [10]. The latter includes, inter alia, artificial intelligence (A-I) and decision-making models. AI is indeed necessary for the approaches summarised above and the need will grow, necessitating dialogue between medical statistics and A-I [11].

Generative A-I can be used to develop risk estimation systems. Starting with existing large data sets, A-I is used to examine patterns and interactions faster and more efficiently than can be done with conventional statistics. A subset is used for machine learning followed by deep learning such as layered neural networks and generative A-I to produce new content.

Alas, it is of course not that simple [11]. Issues include:

- Data quality. No system can allow for poor quality or non-representative data
- Conclusions based on inadequate data may be re-enforced- the 'self-fulfilling prophecy'
- Arising, results may not seem justified by expectations based on the training set- so-called A-I 'hallucination'
- Conventional statistics use clearly verifiable methods. The deeper one goes into machine learning, the more opaque the process becomes
- 'Data-set shift' [12], in which there is a mis-match between the machine-learning model's training data and the results when the model is applied. This is of course not necessarily a fault of the process if it is applied to a very different population

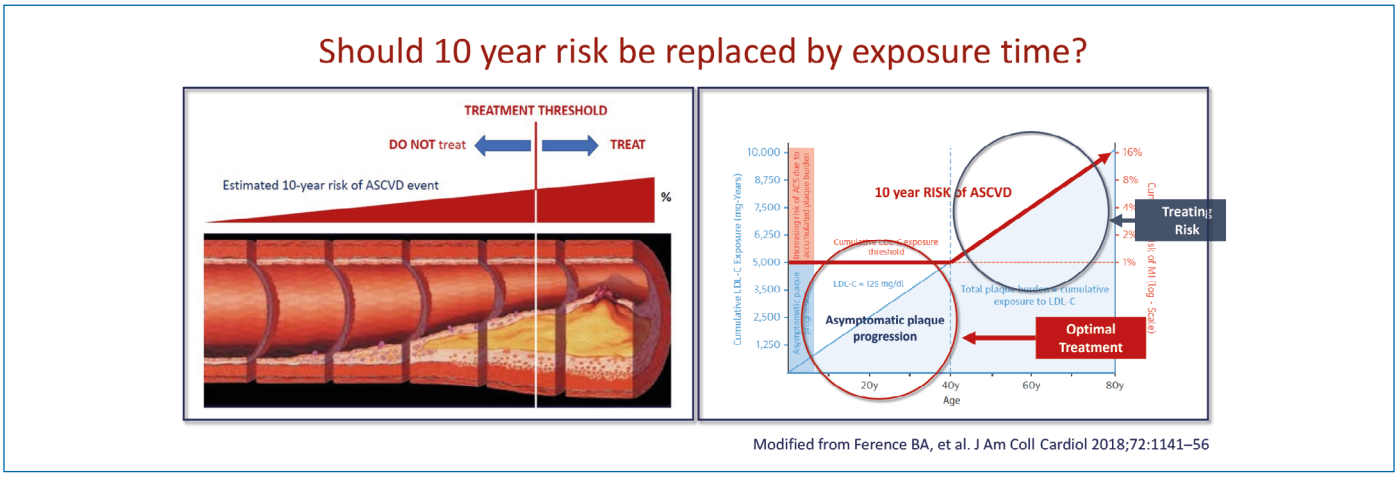

Figure 1 | The exposure time model compared with estimation 10 year risk at, say age 40 -modified from the concepts expressed in [9].

Will these advances produce better outcomes? Ference (personal communications and late-breaking session presentations at the European Society of Cardiology and American Heart Association and American conferences) provides compelling arguments. Yet it is hard to envisage how to design a randomised controlled trial to compare usual care with conventional risk estimation and with the A-I based exposure time approach. The clinician is advised to simply see if a risk estimate, based on whatever estimation process, is plausible.

A comparison of machine learning and conventional risk estimation [13] found in favour of machine learning by a modest amount but with substantial caveats-

"In this systematic review and meta-analysis, ML algorithms were found to be superior to traditional risk equations on comparison of C-statistics in the pooled meta-analysis of 11 studies.

However, findings need to be interpreted with caution as the quality of studies was sub-optimal- with all studies performed on retrospective cohorts, half of the studies providing no comparative calibration metrics, and only three with external validation. In addition, most studies were assessed to have a high risk of bias".

Finally, should determinants of risk in utero [14] be incorporated into a single approach to risk estimation? Those with low birth weight may benefit from early assessment and management of risk. A fully integrated approach to risk from conception through childhood and into adult life would seem logical.

Conclusion

Risk estimation had become rather static. We now enter an exciting new era of risk estimation based on A-I supported risk estimation, Mendelian randomization and risk expressed as exposure time that has the potential to permit personalised risk estimation early in life with better estimates of likely treatment effects.

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Novel approaches to lipid lowering

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Keywords
Lipid-lowering; oral PCSK9 inhibitors; antisense oligonucleotide; small interfering RNA; PCSK9 gene editing

ABSTRACT

Lowering cardiovascular risk by reducing apoB-containing lipoproteins (primarily low-density lipoproteins, LDL) is the key step in cardiovascular prevention. Current treatments such as high-intensity statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective, but some patients still experience cardiovascular events due to residual risks determined by factors beyond LDL-cholesterol (LDL-C) levels, including triglyceride levels and inflammation. New approaches are currently under investigation to further reduce cardiovascular risk. These include next-generation CETP inhibitors such as obicetrapib, which lowers LDL-C and increases HDL-C without the side effects of earlier drugs. Oral PCSK9 inhibitors (MK-0616 and AZD0780) show promise, potentially overcoming economic barriers. Efforts to reduce Lp(a) include antisense oligonucleotides, siRNAs and assembly inhibitors like muvalaplin, all showing significant Lp(a) reduction. PCSK9 gene editing using CRISPR-Cas9 technology has shown dramatic cholesterol-lowering effects in preclinical studies and thus offers potential for the future. These new approaches could significantly advance cardiovascular risk management.

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Introduction

This review focuses on novel and future approaches to reduce the cardiovascular (CV) residual risk by reducing the apoB-containing lipoprotein levels. We assume that in the clinical practice a combination therapy based on the use of high-intensity statins, ezetimibe, bempedoic acid, monoclonal antibodies (mAbs) targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) or inclisiran may reduce most of the cardiovascular risk associated with the apoB containing lipoproteins and may contribute to achieve the LDL-cholesterol (LDL-C) goal in the majority of individuals at high and very high risk. However, we can assume that a proportion of well-treated patients will develop new cardiovascular events. Many factors such as the genetic background, the pre-existing burden of disease and the residual risk attributable to triglycerides, inflammation, coagulation and platelets may explain this recurrence of events. We discuss some novel options to reduce the residual risk due to the two main apoB-containing lipoproteins, LDL-C and Lp(a), that are (**Figure 1**):

- the newest-generation CETP (cholesteryl ester transfer protein) inhibitor, obicetrapib;
- the oral PCSK9 inhibitors;
- the novel approaches to reduce Lp(a) plasma levels (antisense oligonucleotides-ASO; small interfering RNA-siRNA; assembly inhibition);
- the PCSK9 gene editing.

Obicetrapib

CETP is a glycoprotein which regulates the two-way exchange of cholesteryl esters and triglycerides from high-density lipoprotein (HDL) particles to low-density and very low-density lipoproteins (LDL and VLDL) and also the transfer of triglycerides from LDL and VLDL to HDL particles. The human genetic model of CETP deficiency has shown that mutation carriers have no CETP activity and very high levels of HDL-cholesterol (HDL-C). Epidemiological data demonstrated that HDL-C is inversely correlated with the cardiovascular risk. It was obvious to design trials with drugs known to increase HDL-C such as fibrates and niacin to demonstrate a reduction of cardiovascular events due to the increase in HDL-C plasma levels [1].

The early CETP inhibitors, torcetrapib, dalcetrapib and evacetrapib were tested in clinical trials but, despite a significant increase

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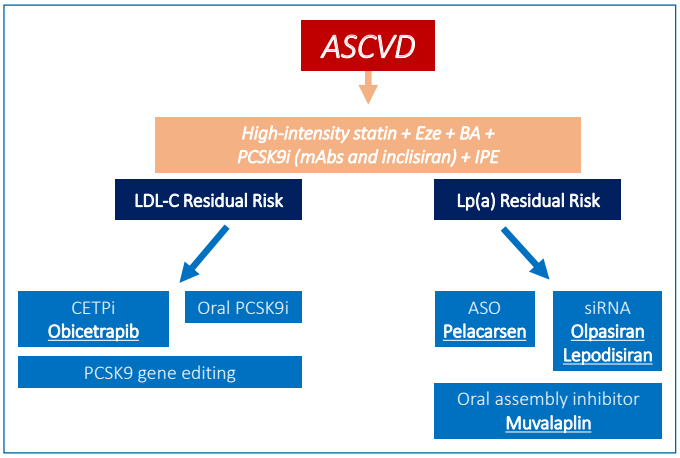

Figure 1 | Future approaches to apoB-containing lipoprotein-related residual risk. *ASCVD: atherosclerotic cardiovascular disease; Eze: ezetimibe; BA: bempedoic acid; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors; mAbs: monoclonal antibodies; IPE: icosapent ethyl; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a); CETPi: cholesteryl ester transfer protein inhibitors; ASO: antisense oligonucleotide; siRNA: small interfering ribonucleic acid.*

in HDL-C (72%, 30% and 133%, respectively), torcetrapib increased cardiovascular events mainly for an off-target effect of blood pressure and dalcetrapib and evacetrapib trials were stopped for futility [2].

Anacetrapib, a CETP inhibitor, was tested in the REVEAL trial and showed a significant reduction in cardiovascular events attributable to the reduction in apoB-containing lipoproteins rather than the increase in HDL-C. The drug development was stopped because of the long-lasting accumulation of anacetrapib in the adipose tissue, but this trial paved the way for reversing the negative feelings regarding CETP inhibition as a cardiovascular prevention strategy [3]. In addition, recently the Mendelian randomization approach has shown that reducing LDL-C by CETP inhibition produces the same cardiovascular benefits as those achieved by statins, ezetimibe and PCSC9 inhibition, and there is also evidence of the ability of CETP inhibition to reduce the risk of new-onset diabetes since glucose tolerance and insulin sensitivity are improved [4]. Obicetrapib is the last-generation CETP inhibitor in the more advanced stage of development. The phase 1 and 2 studies have shown that obicetrapib significantly lowers all apoB-containing lipoproteins, including Lp(a) and the small LDL particles, and increases the levels of mature HDL as well as pre-beta HDL. In the phase 2 clinical trial ROSE2, obicetrapib in monotherapy or combination with ezetimibe reduced LDL-C by 43% and 63%, respectively, and increased HDL by 142%. Obicetrapib has been safe and well tolerated in thousands of patients enrolled in phase 1 to 3 clinical trials. None of the off-label or pharmacokinetic effects of torcetrapib and anacetrapib respectively have been seen in the thousands of patients enrolled in obicetrapib trials. The data from the outcomes study-PREVAIL will be known in 2026 and recently the results of the BROOKLIN trial have been released showing a significant reduction (41.5%) in LDL-C obtained in a difficult-to-treat population such as patients with heterozygous familial hypercholesterolemia (HeFH). In the ongoing TANDEM trial, the efficacy and safety of fixed-dose combination (FDC) of obicetrapib plus ezetimibe in adult patients with HeFH and/or atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD are under evaluation [5]. Once approved for clinical use, obicetrapib will represent a novel LDL-receptor-independent approach to reduce LDL-C and cardiovascular risk.

Oral PCSK9 inhibition

The discovery of PCSK9 as a cause of familial hypercholesterolemia and the comprehension of its role in the LDL-receptor degradation pathway has opened a new era of LDL-C lowering pharmacology. Targeting PCSK9 by monoclonal antibodies, evolocumab and alirocumab, represents today a well-established therapeutic practice. Monoclonal antibodies to PCSK9 are safe, well tolerated and effectively reduce LDL-C up to 60%. The two outcomes trials, FOURIER and ODYSSEY Outcomes, have demonstrated significant reductions in cardiovascular events and mortality [6, 7]. In addition, the real-world data indicate a very high adherence and compliance. Recently the siRNA inclisiran, administered twice a year and targeting the PCSK9 gene expression in the liver, has been approved and entered into the clinical practice. However, some barriers are still limiting the use of PCSK9 mAbs, such as costs and prescription rules adopted in many countries. The RNA display screening technology led to the discovery of macrocyclic peptides that bind the PCSK9 with a monoclonal-like affinity. The two oral inhibitors in development are MK-0161 and AZD0780. MK-0161 has been evaluated in phase I and II trials. In the phase IIb trial, 381 adults with clinical ASCVD, intermediate/high ASCVD risk or borderline risk and LDL-C in a range between 70 mg/dL and 250 mg/dL according to the risk class were enrolled. The efficacy was dose-dependent: 41% LDL-C reduction with 6 mg daily, 56% LDL-C reduction with 12 mg daily, 59% LDL-C reduction with 18 mg daily, and 61% LDL-C reduction with 30 mg daily. The drug was safe and well tolerated. The results of the CORALreef Outcomes trial on cardiovascular benefits will be available at the end of 2029. AZD0780 is an oral small-molecule PCSK9 inhibitor; in the phase I trial the drug was administered on top of statin treatment and the efficacy results showed an LDL-C reduction of 52%. The development of oral, small molecules able to inhibit PCSK9 is promising and, if successful, would enrich our therapeutic armamentarium, potentially overcoming the economic issues and expanding the clinical settings of the PCSK9 targeting [8].

Novel approaches to reduce Lp(a)

Lp(a) was discovered 61 years ago by Kare Berg, but only in the last two decades a body of epidemiological and genetic studies have confirmed the role of Lp(a) as a cause of ASCVD and calcific aortic valve disease (CAVD). Lp(a) is the main carrier of oxidized phospholipids (oxPL) and plays a pivotal role in the residual CV risk; to date, lipid-lowering drugs are ineffective o poorly effective in reducing Lp(a) plasma levels. An ASO, a siRNA and a small molecule that interferes with the LDL-apo(a) binding are under development [9].

Antisense oligonucleotide-ASO

Pelacarsen is a N-acetylgalactosamine-conjugated oligonucleotide that was demonstrated in phase 1 and 2 studies to reduce Lp(a) plasma levels up to 80%, with up to 98% of patients achieving Lp(a) plasma levels <50 mg/dL [10]. The outcome trial, Lp(a) Horizon, was designed to measure the cardiovascular endpoints reduction in patients with myocardial infarction (MI) or ischemic stroke and clinically significant symptomatic peripheral artery disease and with entry-level of Lp(a) of 70 mg/dL. The endpoints-time to CV death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization requiring hos-

pitalization - will be evaluated in patients with baseline Lp(a) ≥70 mg/dL and ≥90 mg/dL. The results are expected in 2025 [11].

Small interfering RNA-siRNA

Olpasiran and lepodisiran are two siRNAs that potently lower Lp(a), according to the results of the phase 1 trials. Olpasiran has reduced Lp(a) levels up to 98% in individuals with entry levels >75mg/dL. The drug was well tolerated and safe. Lepodisiran reduced Lp(a) levels up to 97% in subjects with entry levels >30 mg/dL and was also safe and well tolerated. The outcome trials to establish the clinical effectiveness of reducing Lp(a) are ongoing [9]. For olpasiran the results of the OCEAN study are expected in 2026; OCEAN has enrolled 7,000 patients with very high CV risk with an entry-level of Lp(a) ≥90 mg/dL and the endpoint is a 3-point coronary heart disease MACE (cardiovascular death, myocardial infarction, and coronary revascularization) [12]. Lepodisiran outcome trial, ACCLAIM-Lp(a), will enrol 12,500 patients with ASCVD or high-risk patients including HeFH patients and an Lp(a) entry level of 80 mg/dL. The main expected outcome is the reduction of CV mortality and the results are estimated to be delivered in 2029 [13].

Assembly inhibition

Lp(a) is assembled following a noncovalent interaction between apo(a) kringle 7 and 8 domains and lysine residues of apoB100 in the hepatocyte. Muvalaplin is a small molecule that inhibits the formation of Lp(a) by blocking the formation of the covalent disulfide bond [14]. In the phase 1 trial muvalaplin reduced Lp(a) plasma levels by 65%, with up to 93% of enrolled individuals achieving Lp(a) levels <50 mg/dL. The drug was safe and well tolerated. Muvalaplin could represent a valid alternative to the other more expensive Lp(a)-lowering drugs.

PCSK9 gene editing

The study of the mechanisms of DNA repair including the discovery of the enzymes involved opened the way to the concept of gene editing. A crucial step has been the discovery of the CRISPR-CAS9 as a gene-editing tool. As a DNA-editing tool, CRISPR-Cas9 can abolish or increase the function of a given gene. The potential of this methodology will lead to the cure for many genetic diseases. Since the adenovirus cannot be used to deliver the CRISPR-CAS9 apparatus because it is too large for the vector capacity, lipid nanoparticles with N-acetylgalactosamine (GalNAc) are currently used. GalNAc is a high-affinity ligand for the asialoglycoprotein receptor which is located only on the hepatocytes and this allows selective delivery to the liver. PCSK9 gene is a good candidate for a gene editing approach: i- carriers of loss-of-function mutations in the PCSK9 gene have very low levels of LDL-C and this marked reduction from birth translates into a dramatic reduction in cardiovascular diseases; ii- the clinical use of mAbs anti-PCSK9 resulted in an effective reduction in CV events. In the mouse model targeting the PCSK9 gene by CRISPR-CAS9 gene editing produced a ~95% decrease in plasma PCSK9 and a ~40% total cholesterol levels decrease [15]. In non-human primates, the improvement of gene editing technology produced a ~90% decrease in plasma PCSK9 levels and a parallel 60% reduction in LDL-C levels [16]. The preclinical results opened the way to clinical studies and the efficacy of the PCSK9 gene editing is currently tested in heterozygous familial hypercholesterolemia patients (trial NCT05398029 by VERVE Therapeutics). The preliminary results of the VERVE-101 trial on HeFH patients with severe ASCVD are promising, as a stable reduction in LDL-C up to 55% was observed after 6 months. However, many issues remain unanswered including the ethical aspects, the long-term safety and the right target disease-population.

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Role of nuclear medicine assessing patients with suspected coronary artery disease

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ABSTRACT

Nuclear medicine is a critical component in the field of cardiology as it provides diagnostic and prognostic insights that are essential for the effective management of heart disease.

Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) play a significant role in assessing the likelihood of ischemic heart disease based on pre-test probabilities. Both SPECT and PET should be integrated into the clinical pathway according to the patient's individual risk profile, symptoms, and initial test results. The guidelines recommend using these imaging modalities to refine risk stratification, particularly in intermediate-risk patients, and to guide further invasive diagnostic or therapeutic procedures based on the imaging findings.

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Keywords
Coronary artery disease; single photon emission computed tomography; positron emission tomography; non-invasive tests

Initial evaluation of patients with suspected ischemic heart disease

According to the 2019 European Society of Cardiology (ESC) guidelines on chronic coronary syndromes, a patient with suspected ischemic heart disease, commonly referred to as coronary artery disease (CAD), is typically identified based on risk factors, clinical presentation, and initial non-invasive evaluation [1].

The presence of risk factors such as hypertension, dyslipidemia, diabetes, smoking, a family history of early coronary artery disease, and obesity increases the likelihood of coronary artery disease. Symptoms can be summarized as dyspnea, typical angina pectoris characterized by chest pain or discomfort that occurs with exertion or emotional stress and is relieved by rest or nitroglycerin, atypical angina and non-anginal chest pain when not all the criteria for typical angina are met.

A detailed initial assessment, including medical history, physical examination, and diagnostic tests like an electrocardiogram (ECG), is used to define the pre-test probability of CAD, based on age, sex, and the nature of chest symptoms.

Subsequent management can range from lifestyle modifications and medical treatment for low-risk patients to more aggressive interventions such as revascularization for those at high risk.

Noninvasive diagnostic evaluation

Non-invasive tests to assess ischemia include several techniques, such as exercise testing, stress echocardiography, myocardial perfusion imaging by nuclear imaging with Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), and cardiac magnetic resonance (CMR). These tests help to detect myocardial ischemia and evaluate the need for further invasive investigations such as coronary angiography.

Each non-invasive diagnostic test has a particular range of clinical likelihood of obstructive CAD where the usefulness of its application

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is maximal [1]. Given the clinical likelihood of obstructive CAD and the likelihood ratio of a particular test, one can assess the post-test probability of obstructive CAD after performing such a test [1]. Using this approach, one can estimate the optimal ranges of clinical likelihood for each test, in which they can reclassify patients from intermediate to either low or high post-test probability of CAD [2].

Patients can be categorized as having low, intermediate, and high pre-test probability of having ischemic heart disease and the choice of diagnostic tests is guided by these categories [1]:

- Low Pre-test Probability (<15%): For these patients, non-invasive testing might often be unnecessary, and routine testing is not recommended as it could lead to false positives and unnecessary further invasive procedures.
- Intermediate Pre-test Probability (15-85%): This group benefits the most from non-invasive imaging tests like stress echocardiography, SPECT and PET. SPECT is commonly used due to its availability and efficacy in detecting areas of reduced myocardial perfusion indicative of CAD. PET, while less commonly available, provides higher accuracy and better quantification of myocardial blood flow, and may be particularly useful in certain complex cases.
- High Pre-test Probability (>85%): In these patients, direct invasive strategies such as coronary angiography are often considered appropriate due to the high likelihood of significant coronary artery disease. However, PET can be used in specific scenarios to assess myocardial viability, especially when considering revascularization options.

Coronary Computed Tomography Angiography (CTA) is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. It detects subclinical coronary atherosclerosis but can also accurately rule out both anatomically and functionally significant CAD. It has higher accuracy values when low clinical likelihood populations are subjected to examination [3]. Trials evaluating outcomes after coronary CTA to date have mostly included patients with a low clinical likelihood [4, 5].

The non-invasive functional tests for ischemia typically have better rule-in power. In outcome trials, functional imaging tests have been associated with fewer referrals for downstream coronary angiography compared with a strategy relying on anatomical imaging [6-8].

The clinical significance of high-risk ischemic patterns

Before revascularization decisions can be made, functional evaluation of ischemia (either non-invasive or invasive) is required in most patients. Therefore, functional non-invasive testing may be preferred in patients at the higher end of the range of clinical likelihood if revascularization is likely or if the patient has previously been diagnosed with CAD.

When severe myocardial ischemia, indicative of substantial coronary artery obstruction, is identified, it represents a key determinant in the decision-making process for proceeding with interventional procedures. Patients displaying severe ischemia are often recommended for coronary angiography, which can lead to interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). These procedures aim to restore adequate blood flow to the ischemic areas, thereby improving symptoms, cardiac function, and overall prognosis [9, 10].

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial provided significant insights into the impact of the extent of myocardial ischemia on therapeutic decision-making in patients with stable CAD.

This trial explored the outcomes of patients with moderate to severe ischemia who were treated either with conservative medical therapy alone or with an initial invasive strategy involving angiography and possible revascularization [11].

The trial demonstrated that the initial invasive strategy did not significantly reduce the risk of major cardiovascular events compared to medical therapy alone in the overall cohort. However, subgroup analyses suggested that patients with more extensive ischemia might benefit more from revascularization in terms of symptom relief and quality of life improvements [11].

These findings emphasize the importance of personalized treatment strategies based on the extent of ischemia. While the results challenge the necessity of routine invasive procedures for all patients with moderate to severe ischemia, they highlight the need for a tailored approach, considering the individual patient's ischemic burden and symptomatic status.

Clinicians are required to carefully assess the extent of myocardial ischemia using non-invasive imaging techniques in stable CAD patients [1].

The ESC Guidelines summarize the definitions of high event risk for the different test modalities in patients with established chronic coronary syndromes [1, 12-14]:

- Exercise ECG: cardiovascular mortality >3% per year according to Duke Treadmill.
- Score SPECT or PET perfusion imaging: area of ischemia ≥10% of the left ventricle myocardium.
- Stress echocardiography: ≥3 of 16 segments with stress-induced hypokinesia or akinesia.
- CMR: ≥2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments.

The role of nuclear medicine in patients with suspected CAD

Nuclear medicine is a critical component in the field of cardiology, offering diagnostic and prognostic insights that are essential for the effective management of heart diseases. This branch of medicine utilizes radioactive substances, known as radiotracers, to create images of the heart and study its function and structure in detail.

Both SPECT and PET play significant roles in assessing the likelihood of ischemic heart disease based on pre-test probabilities [1]. Guidelines outline specific scenarios in which SPECT and PET are particularly valuable, emphasizing their utility in refining diagnostic accuracy and guiding clinical decision-making [1].

Myocardial perfusion imaging with SPECT has been generally regarded as the reference standard for the evaluation of myocardial perfusion [1]. SPECT imaging is a robust tool for diagnosing CAD by evaluating myocardial perfusion deficits during stress testing. It is particularly useful for assessing the severity and extent of ischemia, helping to guide decisions about the necessity for angiography or revascularization [1].

Otherwise, PET offers several advantages over SPECT, including higher spatial resolution, the ability to quantitatively assess myocardial blood flow, and reduced radiation exposure to the patient [1]. PET is highly effective in evaluating myocardial viability and differentiating between scarred and hibernating myocardium, which is crucial for planning revascularization in patients with severe ischemia or complex coronary anatomy [1].

Both SPECT and PET should be integrated into the clinical pathway according to the patient's individual risk profile, symptoms, and initial test results. The guidelines recommend using these imaging modalities to refine risk stratification, particularly in intermediate-risk

patients, and to guide further invasive diagnostic or therapeutic procedures based on imaging findings.

A patient-centric approach, using the best available diagnostic tools to inform treatment strategies, thereby optimizing care for patients with suspected or confirmed CAD, is advocated to apply the best cost-effectiveness approach to an increasing disease.

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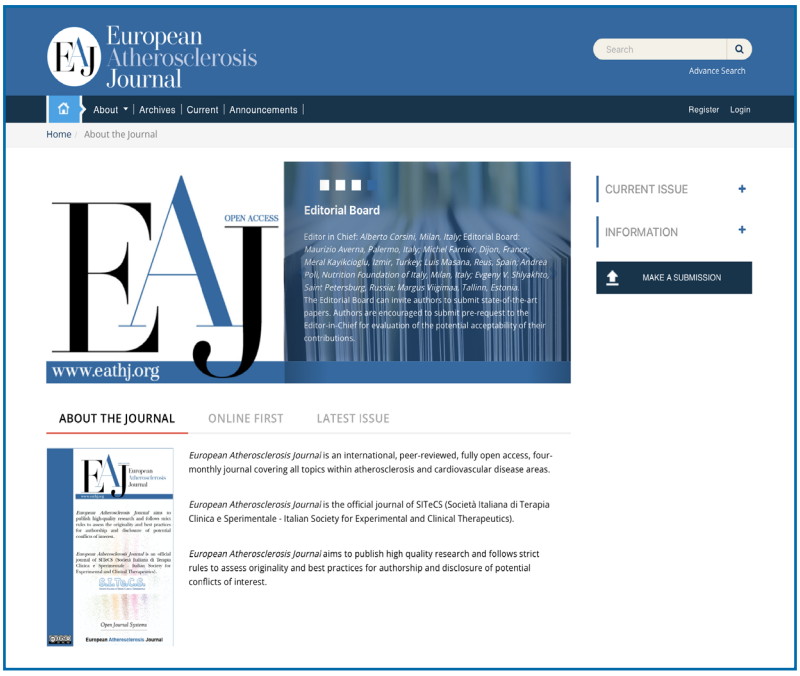

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