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The Lancet Commission on rethinking coronary artery disease: moving from ischaemia to atheroma

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Executive summary

Coronary artery disease has long been understood through the paradigm of epicardial coronary artery obstruction, causing myocardial ischaemia (a mismatch between myocardial blood supply and demand). However, this model, which focuses on diagnosing and managing coronary artery disease based on ischaemia and cardiovascular events, is flawed. By the time ischaemia manifests, it is often too late for optimal intervention, limiting the effectiveness of treatment options. Despite decades of medical advances, coronary artery disease continues to be a leading cause of morbidity and mortality globally, highlighting the inadequacy of this traditional ischaemia-centric model.

The central limitation of current approaches is the focus on the temporary solutions of restoring myocardial blood flow after obstruction, rather than tackling the underlying disease. Coronary artery disease, caused by atherosclerosis, often results in myocardial infarction through mechanisms that emerge earlier in the progression of disease. The focus of medical care has predominantly been on the recognition of symptoms and treatment of acute events, missing opportunities for early detection and prevention of disease. Billions of dollars in health-care funding continue to be spent on identifying and managing coronary ischaemia; yet, the dominant mechanisms for myocardial infarction are atherosclerotic plaque rupture or erosion and, to a lesser extent, erupted calcified nodules that can emerge at a much earlier stage of the disease.

This Commission advocates for a shift in the conceptual framework of coronary artery disease. We suggest reclassifying the condition as atherosclerotic coronary artery disease (ACAD), moving away from the traditional emphasis on ischaemia and acute cardiac events towards a more systematic understanding of atherosclerosis. This reframing will enable the identification and management of the disease much earlier in its course, potentially saving millions of lives worldwide.

Risk of ACAD develops over a lifetime, beginning in utero, progressing through childhood and adolescence, and continuing into older age. The early stages of disease, which involve the formation of atherosclerotic plaques, are often undetected. A major shift is needed from acute event-centred care to strategies focused on early diagnosis, prevention, and management of atherosclerosis. In this new framework, ACAD should be recognised across all stages, from the earliest signs of atheroma formation to the advanced stages of disease.

Our goals should not just to be to manage symptoms and events but to prevent the disease from developing in the first place and, where possible, reverse its course.

Early detection and prevention of ACAD

The prevention of ACAD must begin with early detection and modification of risk factors. If behavioural and metabolic risk factors, such as smoking, hypertension, high cholesterol, and poor diet, were eliminated or controlled early in life, the global burden of ACAD could be dramatically reduced. Eliminating these risk factors by 2050 could decrease the rate of ACAD deaths by 82·1%, potentially saving 8·7 million lives annually. Public health initiatives should emphasise lifestyle changes and the management of metabolic disorders to prevent the onset of atherosclerosis.

Early detection and effective prevention remain a challenge. The implementation of screening strategies to identify individuals at risk of developing ACAD is crucial. Targeted screening programmes, integrated into health-care systems, can detect early signs of atherosclerosis and enable timely intervention. Such interventions, if applied early, have the potential to halt, delay, or even reverse the progress of the disease, reducing the risk of cardiovascular events in later life.

Addressing the global burden of ACAD

ACAD is not a uniform problem across the globe. Disparities exist between high-income countries and low-income to middle-income countries in terms of prevention, diagnosis, and treatment. These differences contribute to variations in health outcomes. Between 2022 and 2050, mortality rates from ACAD are forecasted to increase by 19·2% in lower-middle-income countries and 4·2% in upper-middle-income countries. This global disparity underscores the importance of equitable access to prevention, diagnosis, and treatment to reduce the global burden of ACAD.

Health-care systems must be designed to prioritise prevention and early detection of ACAD rather than simply treating advanced disease. This prioritisation requires a fundamental shift in the education and training of health-care providers, with a focus on the early stages of the disease and the integration of prevention strategies into clinical practice.

A comprehensive international approach to ACAD treatment requires increased research funding, the development of novel treatments, and investment in early

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Key messages

Atherosclerotic coronary artery disease (ACAD) clinical pathways must be refocused away from ischaemia and towards atherosclerosis

- ACAD death rates are forecasted to increase by 19·2% in lower-middle-income countries and by 4·2% in upper-middle-income countries between 2022 and 2050. ACAD is projected to remain the leading cause of death, responsible for the death of 10·5 million people annually by 2050
- The focus of management of coronary artery disease needs to shift from the late stages of the disease, coronary artery obstruction and resultant ischaemia and infarction, towards strategies aimed at early prevention, regression, and cure of atherosclerosis

ACAD should be seen as a lifetime continuum from early life through to older age

- This new perspective would move the focus from diagnosis after the development of ischaemia or a cardiovascular event towards defining lifetime risk for an individual or a population at the earliest opportunity

The onset of ACAD can be prevented with early risk factor modification

- ACAD and associated cardiovascular events must be recognised as preventable. Complete elimination of known behavioural and metabolic risk factors by 2050 would reduce the rate of ACAD deaths by 82·1% and save 8·7 million lives per year globally

Effective strategies for early screening and detection of ACAD are needed

- These strategies should aim to maximise the effect of therapies to delay, halt, and revert the process of atherosclerosis by using targeted screening and detection earlier in the life course

Implementation of current approaches to ACAD needs to be improved

- Implementation of evidence-based knowledge in ACAD is poor and variable, contributing to avoidable death, disability, and waste of resources
- Stakeholders should support implementation efforts to maximise the uptake of known effective strategies for ACAD prevention and treatment globally and equitably

Local and global disparities in prevention, diagnosis, treatment, and outcomes of all people at risk of and with ACAD must be addressed

- Research in ACAD is not representative of diverse populations and might not be transferable to all settings

- Practical and pragmatic research must be promoted and conducted by stakeholders that is inclusive of routine health care using decentralised and adaptive platforms of interventions that allow a greater proportion of diverse patients to be randomised within clinical trials with lifelong follow-up

New therapies to eradicate atherosclerosis must be developed

- The eradication of atherosclerosis is possible with transformative research

A global standard of data collection and dissemination to inform population-based decision making in ACAD should be established

- A systematic international approach can generate and make data accessible for research and policy
- The necessary resources and legislation should be provided by stakeholders to embed sustainable, integrated, standardised, accessible, and accurate databases of key health indicators in ACAD within all countries, with fair and easily accessible mechanisms

The ACAD health-care workforce and research infrastructure should be aligned towards early detection and prevention

- The current workforce is focused on diagnosis and treatment of late-stage disease. This focus is variable, inequitable, and not resilient to economic, social, and environmental challenges and catastrophes
- The global workforce must be trained to redirect delivery of care to prevention, detection, and management of earlier stages of ACAD, considering the relevant national context

Research funding must reflect the global burden of ACAD

- Current research resources and investment are not commensurate to the global burden of morbidity and mortality attributable to ACAD. Without additional investment, the global incidence of acute coronary syndromes will double by 2050
- Research funding must increase to match the burden of disease and support transformational research to improve outcomes worldwide

detection methods. The development of new therapies to prevent, reverse, and eradicate atherosclerosis is crucial. Research funding must be increased to support these efforts, particularly in the development of transformative therapies and imaging technologies that can accurately assess disease progression at all stages.

Current research is insufficient and does not match the global burden of the disease. Research is not representative of diverse populations, often neglecting the specific needs of low-income and middle-income countries. More research is needed to ensure that clinical pathways for the prevention and treatment of

ACAD are adaptable and effective across all health-care settings.

The reframing of coronary artery disease as ACAD represents a crucial shift in the way we approach the disease. By recognising ACAD as a lifelong condition, from early atherosclerotic plaques to advanced disease, and shifting priority towards early detection, prevention, and treatment, the potential to save millions of lives annually is substantial. Implementing these changes will require global collaboration, increased investment, and a commitment to equitable health-care delivery. Stakeholders should work together towards the stabilisation, reversal, and ultimate elimination of ACAD, reducing the global burden of this preventable disease.

Introduction

The history of coronary artery disease and ischaemic heart disease has been intertwined with the evolution of technology, which has led to the currently used definitions, diagnostic methods, and treatments for these conditions. The earliest known description of symptoms resembling angina dates to ancient civilisations,¹ and by the 18th and 19th centuries, autopsies showed evidence of coronary arterial narrowing and occlusion in individuals who had died from heart-related symptoms.^{2,3} In 1912, James B Herrick made the groundbreaking observation that a patient who died after reporting angina had coronary artery occlusion at autopsy.⁴ Advances in diagnostic techniques gave clinicians the electrocardiogram, enabling detection of myocardial ischaemia and infarction. In the 1950s, selective coronary angiography provided a direct means to visualise coronary artery stenosis. In 1961, the first successful coronary artery bypass graft surgery was performed, and in 1977, the first coronary angioplasty took place.^{5,6} These advances heralded the rapid expansion of methods to detect ischaemia and therapeutics to relieve coronary obstruction. As a result, coronary artery disease research has largely focused on the diagnosis and treatment of coronary obstruction and ischaemia.

From the 1990s, key developments in non-invasive coronary anatomical imaging have shifted the focus towards detection of the underlying pathology of atheroma. By the time obstructive coronary artery disease is detected, prevention is no longer possible, and fewer therapeutic options are available. Although revascularisation appears to be an attractive solution, it provides only a temporary fix in a limited anatomical location that cannot halt the progression of systemic atherosclerosis.

As disease definitions change in response to scientific advances, the way cardiovascular disease is characterised, prevented, and managed continues to improve.^{7,8} Ischaemic heart disease was the term traditionally used to denote obstructive coronary artery disease, and is still used in present medical coding to denote clinically manifested coronary artery disease (chronic coronary

syndrome and acute coronary syndrome) and its associated consequences. However, ischaemia in the presence of an epicardial coronary artery stenosis refers to physiologically significant coronary artery disease and is a late manifestation of the disease. Atherosclerotic coronary artery disease (ACAD) is defined as the presence of atheroma in the wall of a coronary artery, which might be present at a very early and asymptomatic stage. We propose that the definition of coronary artery disease should be reframed away from ischaemia and the late stages of disease and focus instead towards the presence of atheroma. Directing attention instead on ACAD will lead to prioritisation of strategies for early risk factor detection and modification, as well as screening aimed at prevention, early diagnosis, regression, and cure of a systemic disease with repercussions beyond the heart.

Coronary atherosclerosis develops over time, but accumulation of plaque is not linear and can be punctuated by periods of accelerated progression or abrupt instability that either resolve spontaneously or lead to an acute clinical event. Guidelines have been developed to consider distinct entities of prevention and acute and chronic coronary syndromes.^{7–9} Although definitions of these coronary syndromes are appealing for diagnosis, their categorical nature does not reflect the biological continuum in which ACAD exists. In addition, the detection of subclinical ACAD by screening in the absence of symptoms does not fit into our current categories of acute or chronic coronary artery disease. Current definitions are limited to end-stage disease and

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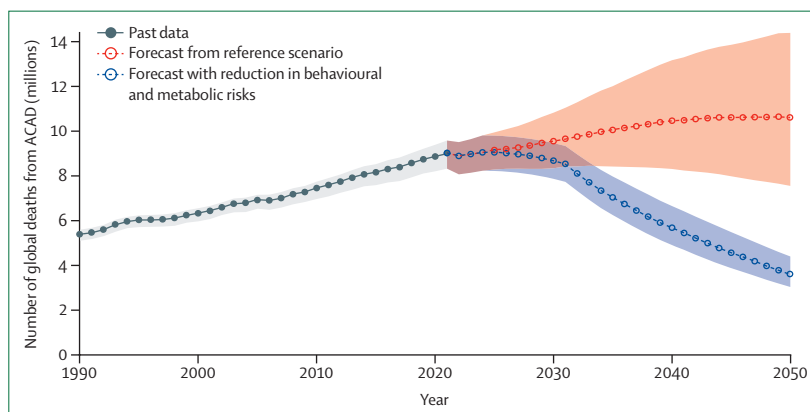


Figure 1: Number of deaths from ACAD from 1990 to 2021 and projection to 2050 with and without elimination of metabolic and behavioural risk factors

Raw data were acquired from the Institute for Health Metrics and Evaluation through the Global Burden of Disease Foresight and Results tools. Data from 1990 to 2021 are based on past observations.¹⁰ Data from 2022 to 2050 are forecasted.¹¹ The forecasted data consists of two scenarios: a reference scenario and an improved behavioural and metabolic risks scenario (with 5-year delay). In both scenarios, the risk, demographic, and environmental factors were first forecasted until 2050 and then used to regress the mortality trends. Under the improved behavioural and metabolic risks scenario, the original study assumed that: (1) metabolic risks, high adult BMI, high systolic blood pressure, high LDL-cholesterol, and high fasting plasma glucose, are linearly eliminated by 2050; (2) exposure to non-optimal diet is eliminated by 2050; (3) the number of smokers reduces linearly until reaching zero in 2050; and (4) there are no new smokers after 2022.¹¹ For each measurement, the mean value and the 95% uncertainty interval (from percentile 2.5–97.5; shown as shaded areas) were used. Data were visualised using the Matplotlib, Seaborn, and GeoPandas packages in Python programming. No imputation and alteration of the data was performed. ACAD=atherosclerotic coronary artery disease.

restrain innovation in the prevention, diagnosis, treatment, and cure of ACAD and systemic atherosclerosis. Clear delineation between symptomatic and asymptomatic people with ACAD overstates the association between symptoms and severity of disease. These definitions and guidelines need to change from dichotomous categories and towards acknowledgment of the continuous spectrum of ACAD.

Globally, health-care spending costs for cardiovascular disease in 2021 were US\$1·66 trillion dollars, and are projected to increase to \$2·59 trillion by 2050, assuming no change in current trends. If all behavioural and metabolic risk factors were controlled and eliminated, 82·1% of atherosclerotic heart disease deaths could be prevented and 8·7 million lives could be saved by 2050 (figure 1).^{10,11} Moving the current focus away from the diagnosis and treatment of the clinical consequences of coronary atherosclerosis and towards the root cause is essential to enhance the potential to reduce the global number of cardiovascular events, the personal, societal, and economic burden of the disease, and to relegate acute coronary syndrome to events that are seen as a failure of prevention rather than a consequence of the disease. Each acute coronary syndrome event should lead to an investigation of what went wrong and what can be learned for future care. In the 1980s, AIDS-defining illnesses were seen as the inevitable consequence of HIV infection. In the present day, thanks to transformative investment in scientific discovery, HIV is treated as a chronic disease that is no longer life-limiting in most patients worldwide. Imagining an analogous outcome for coronary artery disease is possible, if attention is directed towards prevention and cure rather than diagnosis and intervention at the later stages of the disease.

Scope and aims

With this Commission, we aim to shift the focus towards ACAD, to consider the risk factors and continuum of systemic atherosclerosis, and to move away from the historical attention on late sequelae of the disease in terms of obstructive epicardial coronary stenoses and ischaemia. We identify areas of need for future research with an overarching goal of reducing the global burden of ACAD and related morbidity and mortality. We will focus on the risk factors, prevention, diagnosis, and treatment of atherosclerosis, noting that ischaemic and acute coronary syndromes in the absence of atherosclerosis are beyond the scope of this Commission.

A clear and universally agreed upon definition of ACAD that identifies the distinct stages of pathology according to the severity of cardiac and extracardiac involvement, and that considers the effect of these stages on survival is urgently needed. We need to recognise that the evolution or progression of ACAD might not necessarily occur in a sequential, linear and predictable way, and understand the potential role of

therapies in disease reversal. ACAD needs to be considered along a biological spectrum and a likely manifestation of systemic atherosclerosis. Conventional terms such as primary and secondary prevention might be unhelpful and their application to individuals with subclinical atherosclerotic disease detected by non-invasive or invasive imaging is undefined. A timepoint for the end of an acute coronary syndrome and subsequent stabilised chronic coronary syndrome is arbitrary, and the utility of these distinctions is uncertain and unlikely to be helpful in reducing the global burden and impact of the disease.

We will consider this Commission to have been successful if acute coronary syndrome events are seen as a failure of upstream preventive and curative care, and become avoidable and rare because of transformative advances in care.

Mechanisms of atherosclerotic coronary artery disease

The pathogenesis of ACAD is a complex interplay of endothelial dysfunction, lipid accumulation, inflammation, and vascular smooth muscle cell proliferation. Understanding the underlying pathogenesis of ACAD is indispensable for prevention. ACAD pathogenesis can be summarised into the following stages: (1) maladaptive endothelial function and intimal thickening associated with inflammation; (2) formation of fatty streaks marked by lipid-laden macrophages termed foam cells; (3) migration and proliferation of vascular smooth muscle cells, which contribute to plaque bulk through extracellular matrix components; (4) cellular necrosis and inflammation within the core of the developing plaque; and (5) gradual encroachment upon the luminal area, or potential rupture or erosion of the plaque, stimulating thrombus formation and impaired blood flow through the vessel.¹²

Endothelial cellular dysfunction, characterised by impaired vasodilation, increased permeability, and altered expression of adhesion molecules, is a pivotal initial step in atherogenesis.^{13,14} Another key feature of incipient coronary atherosclerosis is retention of apolipoprotein B (ie, LDLs, intermediate-density lipoproteins, and VLDLs) in the vessel wall, triggering an inflammatory cascade and recruitment of leukocytes, including macrophages.¹⁵ Macrophages, via macrophage scavenger receptors, engulf oxidised LDLs, leading to the formation of foam cells—a hallmark of early coronary atherosclerosis.¹³ Oxidised lipoproteins can lead to foam cell death, resulting in necrotic debris and cholesterol clefts within the lesion. Lipoproteins, particularly when oxidised or glycated, also stimulate cytokine production by endothelial and vascular smooth muscle cells. Immune-mediated responses further affect the arterial wall, with cytokines and adhesion molecules amplifying the recruitment of immune cells and further promoting atherosclerosis.¹⁶ Leukocytes

tend to accumulate at the shoulder regions of plaques, where plaques merge with typical vessel architecture. This leukocyte clustering is thought to contribute to the increased vulnerability of the plaque region to rupture. Proliferation and migration of vascular smooth muscle cells further contribute to plaque formation and remodelling. Over time, atherosclerotic coronary artery plaques evolve into complex structures typically characterised by a fibrous cap and lipid core, often with calcification. Vascular smooth muscle cells migrate from the media into the neointima, proliferate, and produce extracellular matrix constituents, such as collagen, proteoglycans, and procollagen. The extracellular matrix proteins often compose a

substantial volume of the plaque and the fibrous cap, which might vary in thickness and stability. An interactive relationship exists between inflamed perivascular fat and plaque formation.¹⁷ Mature atherosclerotic plaque is composed of a fibrous cap consisting of smooth muscle cells and extracellular matrix proteins overlying a necrotic lipid core, which includes free cholesterol, foam cells, other leukocytes (such as T cells), and necrotic debris. Plaque factors associated with increased risk of rupture include a thin fibrous cap, a large lipid core, and an abundance of inflammatory cells concentrated at the shoulder regions of the plaque. Necrotic debris within the plaque and the presence of prothrombotic tissue factor increases the

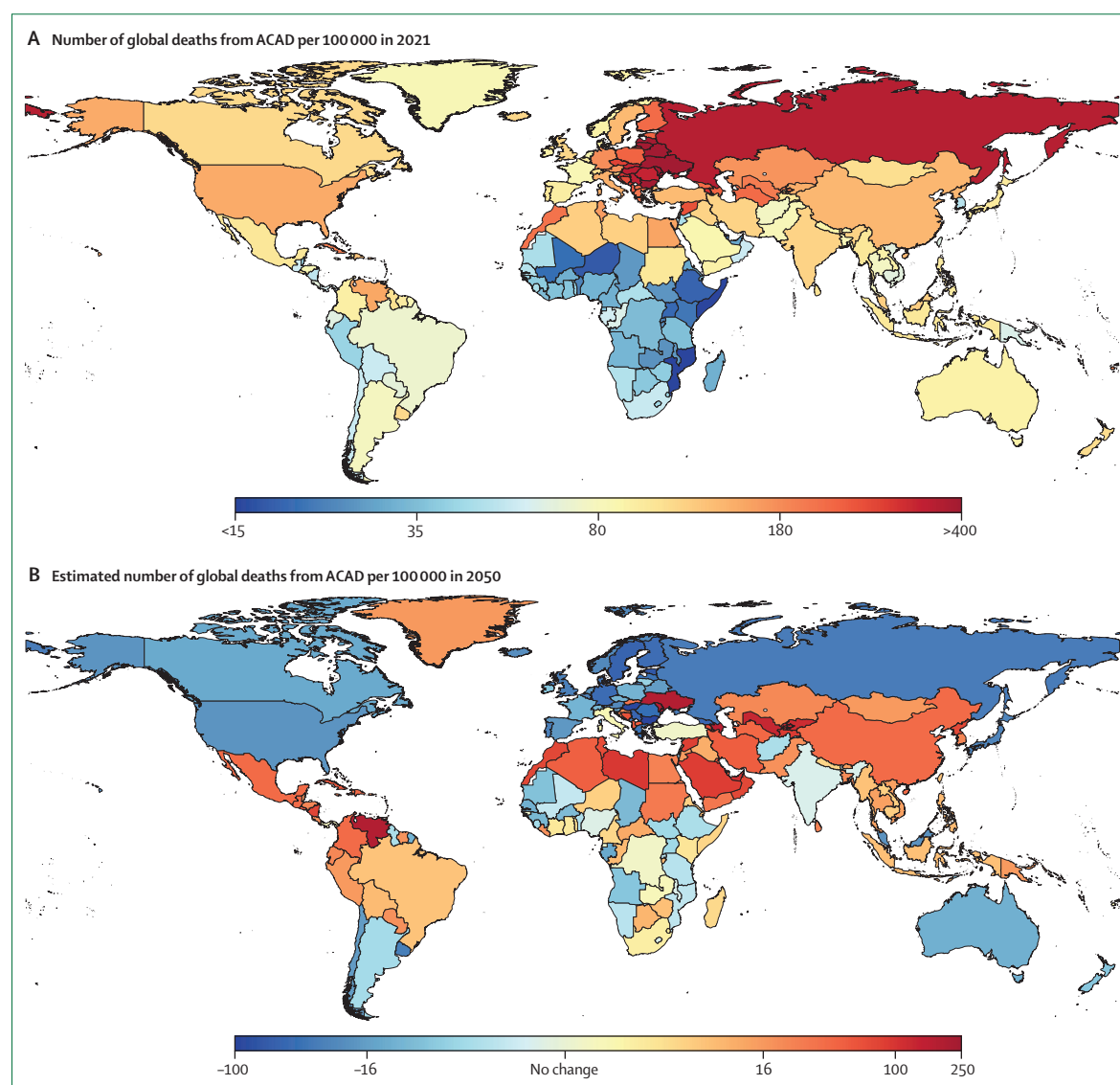


Figure 2: Projected change in number of ACAD deaths from 2021 to 2050

(A) Number of global deaths from ACAD per 100 000 population in 2021. (B) Projected change in global deaths from ACAD per 100 000 population from 2021 to 2050. Global Burden of Disease estimates for ischaemic heart disease were used to construct choropleth maps. ACAD=atherosclerotic coronary artery disease.

risk of thrombus formation and obstruction of blood flow.

Vascular remodelling involves the restructuring of cellular or non-cellular components of the wall and can occur in response to a variety of stimuli, such as hypertension. In atherosclerosis, remodelling often consists of compensatory enlargement of the vessel to preserve luminal area. The development of endothelial dysfunction, lipid accumulation, and inflammation are driven by traditional, non-traditional, and emerging risk factors. Traditional risk factors, such as dyslipidaemia and atherogenic lipoproteins, blood pressure, smoking, obesity, and diabetes, all lead to endothelial dysfunction, lipid accumulation, and inflammation.¹⁸ Non-traditional and emerging risk factors, such as hypertensive disorders of pregnancies in women, air pollution, stress, disturbed sleep, the microbiome, and related social determinants,

are also causal in atherogenesis through endothelial dysfunction and inflammation.¹⁴

Clinical manifestations of ACAD, such as angina or acute coronary syndrome, arise from narrowing of the coronary artery and any combination of plaque instability, erosion, rupture, and thrombosis, resulting in myocardial perfusion supply-demand mismatch. Once partial or complete occlusion of the coronary artery occurs, myocardial ischaemia can lead to angina or myocardial infarction. Atherosclerosis is a non-linear process, in which even mild coronary plaques can rupture, leading to acute events. The association between angina and disease severity is also not linear and more symptoms are not always associated with an increased burden of atherosclerosis. Importantly, the hallmarks of ACAD development are often observed much earlier in life than typically expected, including precursor features in children and adolescents.¹⁹ Clinical and research efforts need to shift from detection and treatment of end-stage disease to detection of risk factors and early-stage ACAD earlier in both the life course and disease course (when prevention, regression, and cure are still achievable), and on optimisation of long-term outcomes.

Global burden of atherosclerotic coronary artery disease

Current outlook

Cardiovascular disease is the leading cause of death worldwide, with ACAD being the main contributor and the focus of the modelling within this Commission (figure 2).²⁰ Data on the prevalence and incidence of ACAD are minimal. The Global Burden of Disease reports on ischaemic heart disease (of which ACAD constitutes the vast majority) and most of the available data come from high-income countries with established systems for data reporting and collection. Between 1990 and 2019, the global prevalence of ischaemic heart disease increased from 1811 per 100 000 population to 2549 per 100 000 population.^{21,22} As the disease burden from infectious diseases and malnutrition declines, shifts towards cardiovascular disease are being observed in low-income and middle-income countries (figures 3, 4).²³

In 2019, the highest rates of ischaemic heart disease were in eastern Europe (eg, Ukraine, Poland, and Russia). The next most affected countries were upper-middle-income countries and lower-middle-income countries (including northern Africa, the Middle East, and Asia), followed by high-income countries (Europe, USA, Canada, and Australia). Rates of ischaemic heart disease are rising in China.²⁴ The lowest rates of ischaemic heart disease were seen in the high-income countries of Japan and South Korea. However, differences in the prevalence of risk factors across these countries are complex. Both Japan and South Korea have diets characterised by low caloric intake, low red meat intake, and high fish consumption.²⁵ Rates of obesity, a crucial risk factor underlying both hypertension and diabetes, are low in

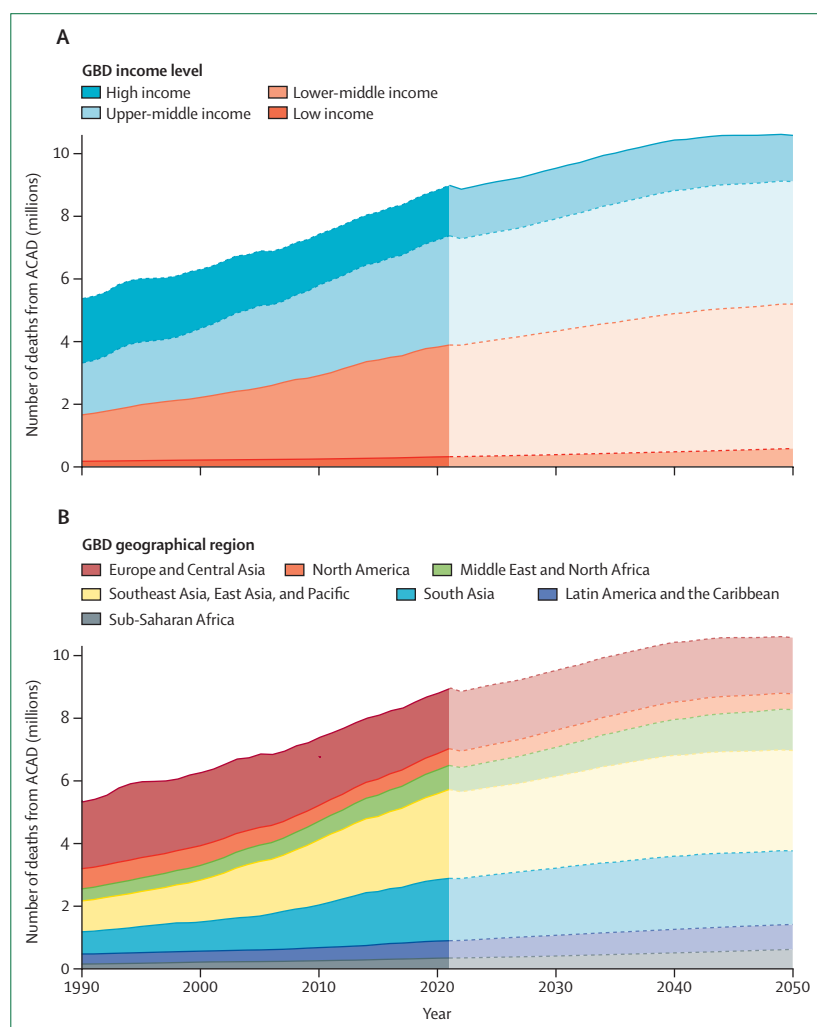


Figure 3: Absolute number of deaths from ACAD by income and geographical region, current and projected to 2050

(A) Deaths by income level. (B) Deaths by geographical region. Estimates are from the GBD model and definitions. ACAD=atherosclerotic coronary artery disease. GBD=Global Burden of Disease.

both Japan (4·5%) and South Korea (5·9%).²⁶ Conversely, tobacco use in both nations remains moderately high, at 16·7% in Japan and 20·8% in South Korea.²⁷

Understanding of the differences in the prevalence and incidence of ACAD is hindered by variations in data collection, differing availability of national resources to accurately categorise cause of death, inconsistency in primary hospitalisation discharge diagnoses, and absence of a globally representative cohort or cross-sectional studies on the prevalence of common diseases. Furthermore, existing data sources might undersample specific populations, for example, women, Indigenous people, people from rural or remote areas, and other underserved population subgroups, complicating cross-national comparisons.

Age-adjusted mortality from cardiovascular disease has progressively decreased since the 1990s globally, although prevalence has largely plateaued.²² In the past 30 years, age-standardised rates of some major risk factors, such as tobacco use, decreased substantially. However, during the same period, the prevalence of other risk factors such as obesity, dyslipidaemia, diabetes, and exposure to air pollution continued to rise, offsetting the benefits of reduction in other risk factors.^{26,28,29} Although ACAD is increasingly seen in older populations within high-income countries, individuals presenting with ACAD in low-income countries tend to be younger and many are affected by ST-elevation myocardial infarction, which is particularly noteworthy because such cardiovascular events during the most economically productive period of adulthood in low-income settings is particularly damaging to both the individual and the country.³⁰ The prevalence of suboptimal diet and low rates of physical activity are also increasing with the modernisation of societies. As a result of this shift in risk factors towards increased rates of obesity, diabetes, and sedentary behaviour, the global ACAD-related death rate is predicted to double by 2050 (figure 5).²⁸ Although these data suggest rates might not increase in sub-Saharan Africa, under-recognition and limited quantity and quality of data might underestimate both current prevalence and future incidence. When coupled with population growth and ageing, there will be an inevitable rise in the absolute numbers of people with coronary artery disease globally. All countries, particularly low-income and middle-income, are at risk of societal and economic instability and conflict that can disrupt health structures and reverse progress made against preventable diseases, with substantial disparity between urban and rural areas.

Data collection and reporting standards

Accurate monitoring of disease is essential to achieve health equity and improve population health.³¹ Globally, poor data standardisation is a major impediment to understanding and reducing the rates of ACAD. The cataloguing of accurate diagnostic information and treatment varies greatly across countries and regions, and

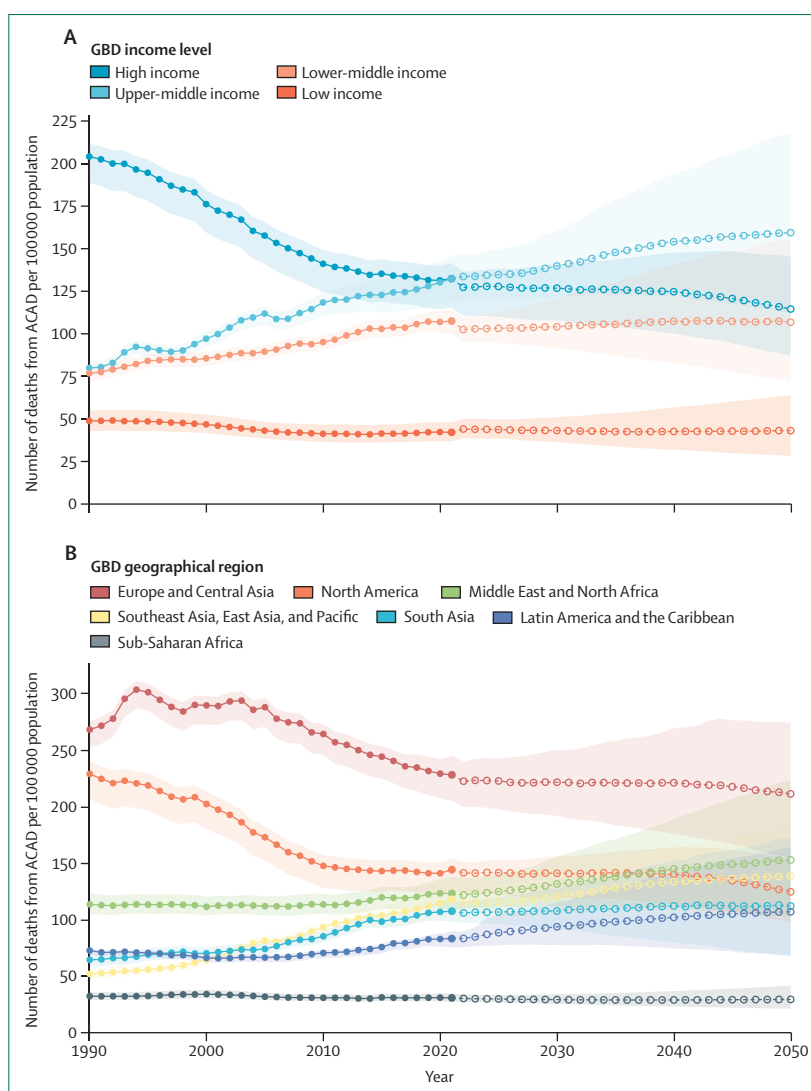


Figure 4: Number of deaths from ACAD per 100 000 population by income and geographical region, current and projected to 2050

(A) Deaths by income level. (B) Deaths by geographical region. Data are from GBD estimates. ACAD=atherosclerotic coronary artery disease. GBD=Global Burden of Disease.

certification errors in cause of death are common and occur worldwide.³²

Helping nations and communities across the economic spectrum to develop more robust data systems to monitor ACAD is crucial to reversing the current projected trends and narrowing the observed disparities in health-care outcomes. The projected growth of preventable death from ACAD globally will jeopardise gains in life expectancy and place strain on health-care systems worldwide. Standardised data points and wider use of electronic health records and clinical registries would allow comparisons and facilitate exchange of data within and between countries. Data gathering needs to be inclusive, particularly with respect to inclusion of women and

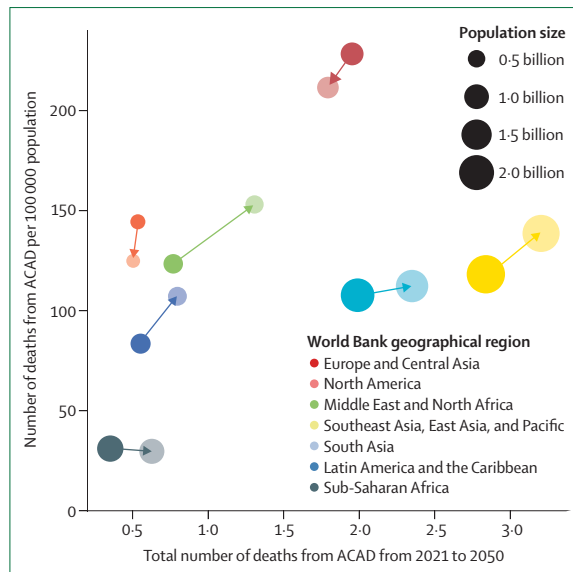


Figure 5: Projected changes in absolute numbers of deaths from ACAD by geographical regions from 2021 to 2050
Dark-coloured circles indicate number of deaths in 2021 from ACAD. Light-coloured circles indicate the projected change over time to 2050. Population size in each geographical region is represented by size of circle. Data from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease.

	ICD-11 code	Definition	Proposed update
Acute ischaemic heart disease	BA41	Acute myocardial infarction is described as ST elevation myocardial infarction (BA41.0) and non-ST elevation myocardial infarction (BA41.1)	Include mechanism of myocardial infarction in coding to distinguish between atherosclerotic and non-atherosclerotic causes
Chronic ischaemic heart disease	BA52	Coronary atherosclerosis of native arteries (BA52.0), bypass grafts (BA52.1 and BA52.2), or unspecified (BA52); subcodes for severity focused on single vessel (XS2V) versus multiple vessel (XS8U) disease; codes used to associate with angina and myocardial infarction	Recode to a new umbrella term of atherosclerotic coronary artery disease, focused on coronary artery atheroma; include codes that identify the stages of disease from early atheroma through to extensive atherosclerosis

Table 1: Current classification of ischaemic heart disease and proposed updates to promote global reporting of atherosclerotic coronary artery disease

under-represented groups, which can differ between countries.

Further work is needed to improve understanding of the global burden of ACAD. This work requires addressing the current variability of data collection, data quality, availability of national resources to accurately code cause of death, and inconsistency in primary hospitalisation and discharge diagnoses. The current accepted method of disease coding involves using WHO's ICD, which categorises diagnoses into acute ischaemic and chronic ischaemic heart disease—coding that perpetuates the focus on end-stage disease. Crucially, the condition of interest needs to be coronary atherosclerosis rather than myocardial ischaemia. The proposed ICD-11 codes offer

some improvement from ICD-10, with the inclusion of coronary atherosclerosis of native arteries, bypass grafts, or unspecified origin. However, the diagnostic codes are still limited by a focus on the reporting of ischaemic heart disease, under the assumption that the disease is predominantly due to coronary atherosclerosis. Reframing of ICD coding to mandate reporting of coronary atherosclerosis at stages that precede ischaemia and making a distinction between atherosclerotic and non-atherosclerotic causes of ischaemic heart disease would improve international reporting standards of ACAD and help to refocus direct attention towards atheroma and away from ischaemia. To facilitate this change, we propose updates to ICD-11 coding (table 1).

Risk factors

ACAD develops over the life course, with initial features of atherosclerosis evident as early as the first decade of life.¹⁹ Many factors are known to increase the risk of ACAD and can be broadly categorised as behavioural, metabolic, environmental, genetic, or related to other comorbidities (figure 6; panel 1). Although several traditional risk factors for ACAD are well recognised, the emphasis has moved towards novel, emerging, and undiscovered risk factors, which require further investigation across diverse populations and age groups.³³

The landscape of ACAD risk factors is expected to evolve considerably as demographics, ecology, lifestyle, and environment changes and technological advancements unfold. Global disparity in risk factors is a crucial public health issue that reflects the uneven distribution across different regions, populations, and socioeconomic groups. This disparity is influenced by a complex interplay of genetic, environmental, and behavioural factors, as well as factors related to health care. Understanding these differences is essential to developing targeted interventions to reduce the global burden of ACAD. The division between traditional and novel risk factors is arbitrary and dependent on the timing of discovery, rather than conveying importance or utility. Novel risk factors have, at times, been called risk enhancers, although overwhelming evidence shows that they independently increase ACAD risk.

Age

Age is a powerful risk factor for ACAD, generally considered to be non-modifiable; therefore, age tends not to be adequately studied and discussed, which means that important potential therapeutic targets might have been so far overlooked. The deleterious effects of ageing have been linked to specific maladaptive processes such as genome and epigenome instability, telomere shortening, dysregulated nutrient sensing, mitochondrial dysfunction, stem-cell exhaustion, and cellular senescence.³⁴ This dissociation of biological from chronological ageing suggests that the ageing process might be modifiable; therefore, the associated damaging processes might be

modifiable also.³⁵ Perhaps more importantly, ageing is a measure of the duration of risk factor exposure. With enormous demographic shifts predicted, such as the number of people age 65 years or older projected to reach 2.2 billion by the late 2070s—surpassing the number of children (under age 18 years)—any age-related variance in risk factor profile (eg, hypertension) or absence thereof is amplified in the therapeutic effect of interventions.³⁶ Given the growth of risk factors in the current young adult age group (age 18–24 years), the duration of their exposure to hypertension will be substantial by the time they reach age 65 years. For example, in certain regions, such as Zimbabwe, prevalence of hypertension is as high as 32% of young adults aged 18–24 years, with potential for long duration of exposure.^{37,38}

Specific regions and countries are going through marked demographic shifts that are masked within the overall global numbers. For example, the proportion of older people aged 65 years or older is predicted to double between 2024 and 2054 from 17% to 33%, particularly in the group of countries that have already peaked in size, such as China, South Korea, and Hong Kong.³⁶ This shift has considerable implications for access to health care, disease burden, and focus on preventive interventions in low-income countries. As clinical trials in ACAD have often excluded older people and have not been reflective of real-world data,³⁹ more research is needed to establish the modifiability of age-related risk.

Sex

Biological females live longer and develop ACAD later in life compared with biological males, and there is an interaction between sex and country-specific socio-economic status.^{40,41} However, these findings should not obscure the fact that ACAD is now the leading cause of death of biological females globally. ACAD risk factors specific to biological females include premature menopause, polycystic ovary syndrome, gestational diabetes, and hypertensive disorders of pregnancy.⁴¹ These factors require specific consideration and investigation of strategies for prevention and management to adequately mitigate risk of atherosclerosis.

Hormonal changes, particularly involving sex hormones, also influence the risk of ACAD. Oestrogen concentrations decline in females who are postmenopausal.⁴¹ Oestrogen has protective effects on the cardiovascular system, including vasodilation, anti-inflammatory properties, and favourable lipid profiles. Testosterone concentrations in males also have a role, with both low and excessively high concentrations being linked to increased risk of ACAD.⁴²

Family history, genetics, and genomics

Having a closely related family member with premature ACAD is associated with a higher individual risk. Part of this association is related to rare monogenic conditions, such as familial hypercholesterolaemia; however, ACAD

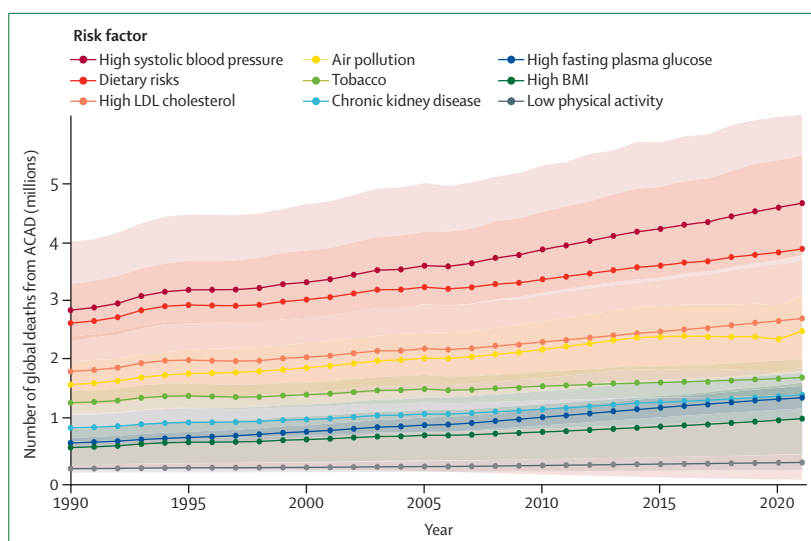


Figure 6: Contribution of leading risk factors to global ACAD deaths between 1990 and 2021

Data are from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease. Dietary risk is defined as a diet low in fruits, vegetables, legumes, whole grains, fibre, nuts and seeds, seafood omega-3 fatty acids, calcium, polyunsaturated acids, and milk, as well as a diet high in red meat, processed meat, sugar-sweetened beverages, sodium, and trans fatty acids.

Panel 1: Addressing risk factors for atherosclerotic coronary artery disease

- Obesity, sedentary behaviour, poor diet, hypertension, and diabetes constitute an epidemic of risk factors that begin in early life with risk exposure even in utero. These risk factors are particularly relevant in high-income and middle-income countries and are also becoming more prevalent in low-income countries. Screening for risk factors for atherosclerosis should therefore begin earlier in life
- Control of traditional risk factors continues to be crucial in reducing the burden of atherosclerotic coronary artery disease (ACAD). Global ACAD risk factor data do not capture important regional and intracountry and intercountry differences that require personalised approaches to mitigate individual ACAD risk
- Identification of novel ACAD risk factors, encompassing not only biological but also social and technological factors, will provide further opportunities to improve health outcomes and to reduce disparities within and between regions
- Multi-measure and multi-territory longitudinal studies are required to understand the relationship between risk factors and health outcomes from ACAD over time

is more commonly associated with polygenic clustering, and is most likely to have myriad genomic and potentially epigenomic variations. Use of such information requires adequate study in diverse populations due to regional genetic and genomic variation.⁴³ In addition, the definition of a family history of ACAD is inconsistent

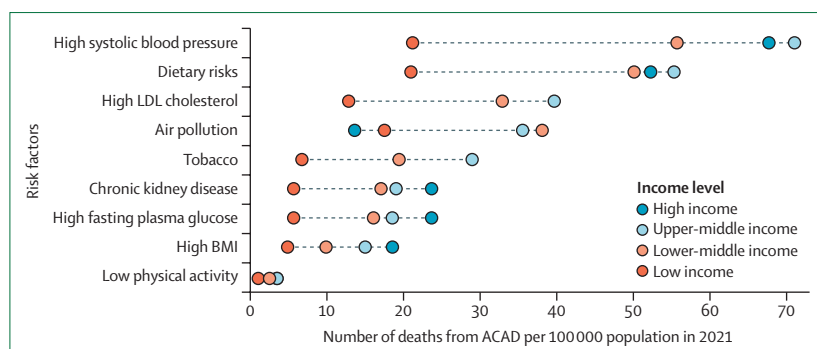


Figure 7: Leading risk factor contributions to ACAD DALYs by income level for 2021
Data are from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease. DALYs=daily-adjusted life-years.

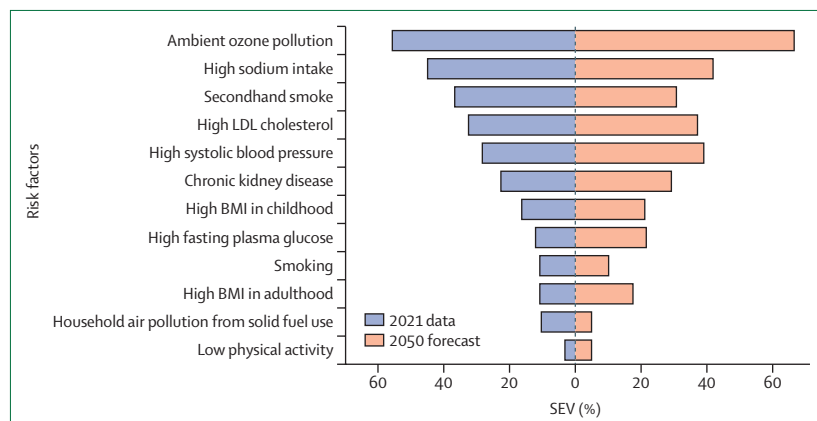


Figure 8: Global prevalence of leading risk factors contributing to all causes of death between 2021 and projected to 2050
SEV is the ratio between the weighted average of the excess risks among individuals in the global population and the maximum excess risk. Data are from Global Burden of Disease models. This metric includes both the prevalence of the exposure and the extent to which such exposure would affect the disease. SEV is 0% when everyone in the population has no excess risk and 100% when everyone is at maximum risk. For a dichotomous risk factor, SEV is equivalent to the prevalence. SEV=summary exposure value.

across studies and often inadequately reported. In the context of heterogeneous definitions, prevention guidelines highlight that family history is only incrementally predictive of ACAD risk over other risk factors.⁹ Conversely, smoking can increase risk of ACAD by more than five-times in older individuals.⁹ Emerging new approaches might be able to isolate heritable risk and improve the utility of risk estimates in clinical practice.

Smoking

Tobacco initiates and accelerates progression of ACAD and associated deaths (figure 7).^{44,45} The precise mechanisms are not fully understood but have been linked to nicotine, carbon monoxide, oxidant gases, and other potentially toxic components of tobacco smoke (including second hand smoke). These components, in turn, appear to negatively interact with established pathophysiological mechanisms known to initiate or accelerate atherosclerosis,

such as platelet activation, endothelial dysfunction, and upregulated inflammatory pathways.

Although tobacco use prevalence over the past two decades has declined globally from one-third to one-quarter of adults (with similar reductions seen in males and females, although males are five-times more likely to be smokers than females),²⁷ the effects of tobacco smoke on ACAD events will remain substantial due to the delay between exposure and events (figure 8). Tobacco use accelerates the development of ACAD and increases the risk of associated events. The risk of myocardial infarction for someone who smokes a light amount (less than 20 lifetime pack-years of smoking) returns to the same risk as someone who never smoked approximately 5 years after cessation, while it takes 15 years for those who smoked heavily (20 or more pack-years) to return to the same risk as someone who never smoked.⁴⁶

Despite population growth, absolute numbers of tobacco users have remained relatively stable at 1.3 billion people globally, with the age-standardised tobacco use prevalence declining, on average, in all WHO regions.²⁷ While overall tobacco smoking prevalence has decreased, the slowest decline is occurring in the Western Pacific, African, and Eastern Mediterranean WHO regions²⁷ with increases projected in Africa and Eastern Mediterranean regions by 2030.⁴⁷ In north Africa, smoking is the most prevalent modifiable risk factor for ACAD based on local registry studies.⁴⁸

Sex differences are narrowest in the Americas and Europe, where the male-to-female ratio is only 2 to 1, which is appreciably different from the demographic situation in the Western Pacific (where the ratio is 17 to 1).²⁷ Continued reductions in smoking prevalence are anticipated, caused by regulatory measures and the increase of alternative nicotine delivery systems.⁴⁷ However, the long-term cardiovascular effects of these alternatives, such as e-cigarettes, remain uncertain. The growth in the use of these products, which are predominantly used by adolescents (age 10–17 years) and young adults (age 18–24 years) is of particular concern given their relatively recent emergence and consequent scarcity of longitudinal outcome studies. Public health efforts must continue to focus on reducing tobacco use globally to decrease ACAD risk.

Obesity

Obesity is a spectrum of atypical or excessive fat accumulation that presents a risk to health, is relapsing and progressive in nature, and requires continuous effort to control or improve.⁴⁹ Overall, 2.5 billion adults (43%) globally in 2022 were overweight or obese. This percentage varies considerably by region, from 31% in the WHO South-East Asia and African regions to 67% in the Americas region.²⁶ Global prevalence of overweight and obesity has more than doubled in 30 years, from 16% in 1990 to 43% in 2022, with one of eight adults currently having obesity. The number of children with obesity has

quadrupled globally in the same period, with 160 million (8%) children now with obesity.²⁶ Although the increase in obesity rates is particularly problematic in high-income countries, the shift in such demographics in other areas is just as troubling. In Africa, the number of children with obesity has increased by approximately 20% since 2000.²⁶ Almost half of all children aged younger than 5 years with obesity currently live in Asia.²⁶

Obesity is strongly associated with a higher risk of ACAD prevalence and death (figure 7).⁵⁰ Previous concepts of the obesity paradox (ie, lower cardiovascular risk with higher BMI) are largely dispelled with the nuanced understanding that BMI is a suboptimal measure of obesity, which is more closely related to visceral fat content rather than weight.⁵¹ Furthermore, so-called metabolically healthy people with obesity have a higher risk of metabolic syndrome over time and of incident ACAD than metabolically healthy people without obesity.⁵²

The limitations of BMI are now well recognised,⁵¹ although familiarity, cost, resources, and measurement accuracy are reasons that BMI continues to be widely used instead of waist circumference, waist-hip ratio, waist-height ratio, bioimpedance, and dual energy x-ray absorptiometry. The most useful measure for risk assessment of ACAD and whether the associations are robust across age, sex, and ethnicity is not yet clear.

The obesity-ACAD connection is underscored by countless physiological and metabolic disturbances that derive from obesity, which collectively promote the development and progression of ACAD, largely through adverse effects on other risk modifiers, although Mendelian randomisation studies suggest there might be direct effects.⁵³ Pathophysiological mechanisms almost ubiquitous with obesity include atherogenic dyslipidaemia (such as increased triglycerides and decreased high LDL cholesterol), insulin resistance, raised blood pressure (through activation of renin-angiotensin-aldosterone and sympathetic nervous systems), and chronic inflammation (as visceral fat secretes proinflammatory and elevated atherogenic cytokines such as TNF and IL-6).⁵⁴ All of these mechanisms further contribute to enhanced endothelial dysfunction, which is directly affected by adipokines⁵⁵ and is a key early event in the development of atherosclerosis.

Given the global rise in obesity prevalence, addressing this modifiable risk factor is paramount to preventing and eliminating ACAD. Effective management will substantially mitigate the risk of ACAD initiation, progression, and events.

Raised blood pressure and hypertension

Raised blood pressure exerts both mechanical and neurohormonal stress on the coronary arterial wall to perturb endothelial homeostasis, leading to initiation and acceleration of coronary atherosclerosis.⁵⁶ Reducing blood pressure is an extremely effective method to reduce risk of ACAD. For every 10 mm Hg reduction in blood pressure, the risk of ACAD is reduced by 17%, irrespective

of starting blood pressure.⁵⁷ Raised blood pressure remains the most important risk factor for ACAD in terms of mortality and disability-adjusted life-years (figure 7).

Despite more than 70 years of randomised clinical trial evidence, proven cheap therapies, and affordable diagnostics, global hypertension control rates are abysmal.⁵⁸ Current hypertension prevalence is approximately 1·5 billion⁵⁹ and is projected to remain unchanged until 2040. However, this projection masks important regional variations, such as marked increases in hypertension in various countries such as Pakistan, Croatia, Trinidad and Tobago, Chad, Uganda, and Niger.⁶⁰

Insulin resistance, hyperglycaemia, diabetes, and metabolic steatotic liver disease

500 million people globally have diabetes, and this number is predicted to triple to 1·3 billion by 2050, when almost half of all countries will have a prevalence of 10% or higher (caused largely by obesity).²⁹ Diabetes is more prevalent in particular ethnicities and regions, such as in south Asia.²⁶ Oceania, for example, has a six-times higher age-standardised diabetes prevalence compared with east Africa.²⁹ Diabetes, insulin resistance, and hyperglycaemia lead to ACAD through distinct biochemical pathways that directly or indirectly damage the coronary vasculature and induce coronary inflammation.⁶¹ The association of hyperglycaemia with coronary atherosclerosis is continuous and has been observed well below the diagnostic thresholds for diabetes or prediabetes.⁶² Insulin resistance, diabetes, and obesity are further associated with metabolic dysfunction-associated steatotic liver disease, increasing in prevalence and risk of ACAD.

Dyslipidaemia

Dyslipidaemia is a well known risk factor for ACAD⁶³ and is caused by monogenic and polygenic risk, diet, and comorbidities (such as diabetes and obesity). Hyperlipidaemia has received intense focus as a modifiable risk factor because of increased availability of drugs that alter blood lipid concentrations and reduce risk of ACAD, ACAD-related events, and deaths. LDL cholesterol accumulates in the vascular wall, causing endothelial dysfunction and promoting leukocyte influx, whereby macrophages internalise oxidised LDLs and become proinflammatory with feed-forward effects on endothelial health and oxidation of LDLs, accumulation of more inflammatory leukocyte in the subendothelial space, and generation of atherosclerotic plaque.⁶⁴

Dyslipidaemia, characterised by elevated concentrations of LDL cholesterol and low concentrations of HDL cholesterol, will continue to be a crucial risk factor for ACAD. Elevated cholesterol has often been thought of as a problem for high-income countries eating a so-called Western diet. Rapid changes in dietary patterns that render this notion a fallacy have already happened.⁶⁵ Over the past 40 years, no change in total or non-HDL

cholesterol globally was noted. Cholesterol concentrations were highest in northern Europe in 1980; however, the concentrations are now highest in east Asia and Western Pacific regions.⁶⁶

Blood lipids other than LDL and HDL cholesterol are also important. Lipoprotein(a) consists of an LDL-like particle and a specific protein called apolipoprotein(a), which distinguishes it from other lipoproteins. Elevated concentrations of lipoprotein(a) are genetically determined and vary widely, with individuals of African descent having higher values, and concentrations increasing by approximately 25% for women after menopause.⁶⁷ This association is notable because the relationship between lipoprotein(a) and ACAD is established.⁶⁸

Chronic kidney disease

Chronic kidney disease is a major and independent risk factor for ACAD (figure 7).⁶⁹ The relationship between chronic kidney disease and ACAD is complex and multifaceted, involving a combination of traditional cardiovascular risk factors, which are over-represented in the chronic kidney disease patient population, and non-traditional risk factors unique to chronic kidney disease. This relationship is bidirectional because cardiovascular disease also contributes to the progression of chronic kidney disease. Myocardial infarction and other cardiovascular events can lead to decreased renal perfusion, further impairing kidney function—a cycle in which chronic kidney disease and ACAD exacerbate each other, leading to further adverse clinical outcomes. The progression of chronic kidney disease also exacerbates the risk of ACAD due to the interplay of metabolic, vascular, and inflammatory processes that affect the cardiovascular system. Both declining glomerular filtration rate (<60 mL/min per 1.73 m²) and increased albuminuria are independent risk factors for ACAD.^{70,71}

In individuals with chronic kidney disease, altered mineral metabolism, chronic inflammation, oxidative stress, and endothelial dysfunction are enhanced, leading to increased ACAD risk. In particular, chronic kidney disease disrupts calcium and phosphate homeostasis (via elevated parathyroid hormone and fibroblast growth factor-23) leading to coronary calcification, a key contributor to ACAD.⁶⁹ Inflammation and oxidative stress are also heightened in chronic kidney disease, contributing to endothelial dysfunction and accelerated atherosclerosis, thereby exacerbating the risk of ACAD.

The complex relationship between chronic kidney disease and ACAD highlights the need for early intervention, comprehensive management of both renal and cardiovascular health, and lifestyle modifications to reduce the burden of these inter-related conditions.

Novel risk factors: refinement and opportunities

Inflammation

Chronic inflammation has a crucial role in the pathogenesis of ACAD. Beyond the acute inflammatory responses seen in myocardial infarction, low-grade chronic inflammation is now recognised as a distinct risk factor. Elevated concentrations of high sensitivity C-reactive protein, an acute-phase reactant, have been linked to increased risk of ACAD. Similarly, IL-6 and TNF are cytokines involved in systemic inflammation and have been implicated in atherosclerosis.

Moreover, immune system dysregulation, including autoimmunity, has been garnering increased attention. Immune cells contribute to the progression and evolving vulnerability of atherosclerotic plaques.⁶⁴ Autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, are associated with higher incidences of ACAD, suggesting that autoimmune-mediated vascular inflammation might contribute to atherosclerosis. Inflammatory indices have been added to particular risk calculators (eg, QRISK-3) and some anti-inflammatory therapeutics appear to reduce ACAD outcomes in secondary prevention,⁷² although these therapies have not been tested in primary prevention. Beyond blood biomarkers, imaging of perivascular fat attenuation indices is now a well established marker of inflammation and is highly predictive of major adverse cardiovascular events.^{73,74}

Hyperhomocysteinaemia

Hyperhomocysteinaemia has been identified as a potential independent risk factor for coronary atherosclerosis, primarily due to its association with endothelial dysfunction and oxidative stress.⁷⁵ However, this link has been challenged by several high-quality randomised clinical trials and meta-analyses, which have shown that lowering homocysteine concentrations with folic acid and B vitamins does not reduce the risk of cardiovascular events in a northern European population.⁷⁶ Despite these findings, emerging evidence suggests a stronger association between hyperhomocysteinaemia and coronary artery disease in Asian and African populations, highlighting the need for further research in diverse populations.^{77,78}

Microbiome

The human gut microbiota, comprising trillions of microorganisms, has emerged as a novel factor influencing ACAD risk.^{79,80} Dysbiosis, or the imbalance of gut microbiota, can lead to the production of proatherogenic metabolites, such as trimethylamine N-oxide. Elevated trimethylamine N-oxide concentrations have been associated with increased risk of ACAD by promoting cholesterol deposition in arterial walls and enhancing inflammatory responses. Measurement of the microbiome is not straightforward or necessarily reproducible. Most studies linking microbiome to atherosclerosis have been conducted in

high-income countries with diets less relevant to other regions. Leveraging this information for ACAD benefit might require the testing of probiotics to alter microbiome taxa without the need for test–retest conditions.

Physical activity

Physical inactivity and prolonged sedentary behaviour are well recognised risk factors for ACAD.⁸¹ Minimal physical activity can lead to obesity, insulin resistance, hypertension, and dyslipidaemia, all of which contribute to ACAD. Regular physical activity has been shown to improve endothelial function, reduce inflammation, and enhance lipid profiles.⁸² Adjunctive resistance training is further associated with fewer ACAD events and can also aid in balance and offset age-related declines in activities of daily living. Physical rehabilitation after myocardial infarction is well recognised as lifesaving, although large-scale exercise studies in primary prevention of ACAD have not been conducted.

Diet

Diet and nutrition are a cornerstone of ACAD prevention, although the optimal dietary pattern for ACAD health is yet to be defined.⁹ While most guidelines recommend elements or complete versions of the Dietary Approaches to Stop Hypertension, Mediterranean, or plant-based diets, the effects on the cardiovascular system of novel diets, such as palaeolithic and ketogenic, as well as intermittent fasting, are not yet fully known. The most studied dietary modification for cardiovascular health is reduction of sodium intake, largely thought to work by lowering blood pressure, which has proven benefits on vascular mortality and in reducing rates of acute coronary syndrome.⁸³

Stress

Psychosocial factors, including chronic stress, depression, and anxiety, have been linked to ACAD.⁸⁴ Chronic stress triggers the release of stress hormones like cortisol and epinephrine, which can lead to increased heart rate, hypertension, and endothelial dysfunction. Additionally, stress can lead to unhealthy behaviours such as poor diet, smoking, and physical inactivity, further exacerbating ACAD risk.

Sleep and obstructive sleep apnoea syndrome

Short and long sleep durations have been associated with increased risk of cardiovascular disease, particularly in individuals with high risk of ACAD.⁸⁵ Obstructive sleep apnoea syndrome is increasingly recognised as a crucial independent risk factor for cardiovascular diseases, particularly hypertension, atrial fibrillation, heart failure, coronary atherosclerosis, and stroke. The intermittent hypoxia and sleep fragmentation inherent in obstructive sleep apnoea syndrome contribute to systemic inflammation, oxidative stress, and sympathetic nervous

system activation, which accelerate the development and progression of atherosclerotic lesions in coronary arteries.⁸⁶

Cancer

A previous diagnosis of cancer is associated with an increased risk of atherosclerosis. In survivors of childhood cancer (≥ 5 -year survival from a cancer that was diagnosed before age 21 years), there is evidence of an increased future risk of ACAD-related mortality.⁸⁷ The relationship between cancer and ACAD risk is complex and likely mediated by factors specific to the patient, disease, and treatment, including an increased prevalence of other modifiable risk factors for atherosclerosis and cardiotoxic effects of particular cancer treatments (eg, mediastinal radiation). Beyond this link, evidence to conclude that a previous diagnosis of cancer is an independent risk factor for ACAD is insufficient. However, given improvements in prognosis of many cancers, there are reasonable grounds for increased recognition, heightened surveillance, and early lifestyle and risk factor modification in long-term (≥ 5 years) cancer survivors. There is plausible evidence of shared mechanisms of atherogenesis and malignancy, centred mainly around atypical cell proliferation,⁸⁸ offering the intriguing possibility of therapeutic targets that could reduce the two leading causes of global mortality.

Social determinants of health

Social determinants of health pervade all known risk factors. Access to high-quality education, the quality of the neighbourhood and environment people reside in, the support from social networks and communities, availability of quality health care, and financial stability all affect an individual's ability to reduce their risk of ACAD. Low socioeconomic status is also associated with higher levels of stress and poor mental health, which contribute to ACAD. In Brazil, a prospective cross-sectional cohort study in a single region showed that higher rates of cardiovascular risk factors were present in Indigenous communities with a higher rate of urbanisation (based on geographical location, proximity and contact with cities, maintenance of traditional culture; and influence of the city on the group's dynamics) compared with those with lower urbanisation, suggesting that living in cities might have a negative effect on ACAD risk.⁸⁹

In many high-income countries, there are advanced health-care systems, comprehensive public health initiatives, and greater access to medical care. However, even within these countries, substantial disparities between different socioeconomic groups exist. For instance, in the USA, widely documented epidemiological analyses show that Black African American and Hispanic populations have higher rates of obesity, hypertension, and diabetes than other population subgroups. This association has been proposed to be, in part, due to

inadequate access to high-quality health care and societal biases. However, even within these demographic subclassifications, there is heterogeneity with respect to the prevalence of cardiovascular risk factors. For example, within the Hispanic population in the USA, analyses of the National Health Interview Survey data by country and area of origin (Mexico, Puerto Rico, central America, South America, Cuba, and Dominican Republic) showed that the prevalence of raised blood pressure and diabetes varied by country of origin. US citizens from Puerto Rico and Dominican Republic had an almost two-fold increase of raised blood pressure prevalence of 24% and 22%, respectively, than US citizens from Mexico, with 13% prevalence.⁹⁰ Research of health disparities should include representation from all Hispanic subgroups. Furthermore, the effects on health resulting from shifting immigration patterns worldwide has yet to be fully realised.

Education plays an important role in health behaviours and outcomes. Higher levels of education are associated with healthier lifestyles and better access to health care. Promoting education and health literacy can empower individuals to make informed health decisions, ultimately reducing the risk of ACAD. Investments in education and health literacy programmes are crucial for improved long-term outcomes in ACAD. In low-income countries, promotion of healthy lifestyles (eg, school programmes) is crucially absent. One of the barriers to advocacy of healthy lifestyles is the absence of belief of policy makers in their cost-effectiveness and ability to improve long-term cardiovascular outcomes.

Socioeconomic factors, access to health care, education, and digital poverty have crucial roles in cardiovascular health. Policy interventions aimed at reducing these disparities will be essential to combat ACAD in the future. These interventions include improving access to preventive care, addressing social determinants of health, and ensuring equitable distribution of health-care resources.

Over the next few decades, the integration of wearable devices (eg, smart watches), digital health platforms, and the application of artificial intelligence (AI) and machine learning could enhance our ability to monitor cardiovascular risk factors, predict future events, and personalise therapies. The application of technological advances has the potential to improve access and equity of care for patients with potential ACAD. Telemedicine gained prominence during the COVID-19 pandemic and is likely to become a mainstay in health-care delivery. This shift could improve access to cardiovascular care, especially in remote and underserved areas, potentially reducing the burden of ACAD through improved management of risk factors.

ACAD is a leading cause of life expectancy differences noted in epidemiological studies between Indigenous and non-Indigenous populations in the USA, Canada, and Australia.⁹¹ Both cardiometabolic (obesity, diabetes, dyslipidaemia, and hypertension) and lifestyle (smoking

and sedentariness) risk factors are invariably reported as being of higher prevalence in Indigenous populations than in non-Indigenous populations in Australia, New Zealand, and the USA.⁹² Most of the literature on the health of Indigenous populations is descriptive and does not propose or implement potential solutions.⁹³

Both people in south Asian countries (eg, Bangladesh, India, Pakistan, and Sri Lanka) and in the south Asian diaspora are observed to have a high prevalence of ACAD and, in particular, premature ACAD (usually defined as onset of cardiovascular events 10 years earlier than standard norms).⁹⁴ Analysis of the UK Biobank cohort suggests that this prevalence is not explainable by existing cardiovascular risk factors used to derive cohort risk equations (eg, QRISK-3 or pooled cohort equations),⁹⁵ suggesting an interplay of social determinants (eg, economic, nutritional, sociocultural, and environmental factors) and biological risk factors, including genomic and epigenomic differences. For example, for cardiovascular mortality, poor education and grip strength were observed in the global PURE epidemiological survey to have the highest population-attributable risk fraction compared with other traditional modifiable risk factors in south Asians.⁹⁶ Addressing the modifiable risk factors and improving the socioeconomic status of the population are crucial to reduce the burden of these diseases. Given the high prevalence of ACAD and related premature mortality, the conceptual move from ischaemia to atheroma as a focus for prevention and diagnosis would be predicted to make further improvements with respect to disability-adjusted life-years and other related health metrics.

How best to use information on social determinants of health to refine risk estimation or management for individuals remains unknown. However, tackling barriers to access screening and diagnosis of ACAD are key to improving clinical outcomes across diverse populations. Systematic identification and coding are also essential to improving practice.

Global disparity in cardiovascular risk factors is a crucial public health issue that reflects the uneven distribution of heart disease risk across different regions, populations, and socioeconomic groups. This disparity is influenced by a complex interplay of genetic, environmental, and behavioural factors, as well as access to health care. Understanding these differences is essential to the development of targeted interventions to reduce ACAD globally. Effective global public health policies and interventions, such as smoking cessation programmes, obesity prevention campaigns, reduced dietary salt, and efforts to reduce air pollution will be fundamental in addressing the multifaceted risk factors for ACAD. However, the implementation of such policies faces numerous challenges. Limited financial resources, competing health priorities, and political instability often hinder the development and enforcement of effective public health strategies.

Collaboration between governments, health-care providers, and communities will be key to the success of these initiatives. Additionally, public health policies must be adaptable to emerging challenges across diverse settings and informed by the latest scientific evidence. Through a combination of scientific innovation, technological advancement, and equitable health-care policies, the future burden of ACAD could be considerably mitigated.

Climate and pollution

Climate change can increase ACAD risk through extreme weather events, heat stress, the spread of infectious diseases, migration, and urbanisation. These factors can exacerbate existing cardiovascular conditions and contribute to new cases of ACAD.⁹⁷ Adaptation and mitigation strategies will be necessary to address the health effects of climate change. Public health systems must be strengthened to respond to climate-related health challenges, and global efforts to reduce greenhouse gas emissions must be intensified.

Environmental pollutant exposure (air pollutants, fine particulate matter, and heavy metals) also contributes to the development of ACAD.⁹⁸ Air pollution is a growing concern for cardiovascular health due to the magnitude of the exposed population (figure 8), and predictions of increased population at risk by 2050, particularly for ground-level ozone. Exposure to fine particulate matter (PM_{2.5}) and ground-level ozone is linked to increased ACAD risk through diverse mechanisms such as oxidative stress leading to increased inflammation; loss of bioavailable nitric oxide leading to endothelial dysfunction; enhanced sympathetic signalling leading to raised blood pressure; and increased platelet activation.⁹⁹ Microplastic and nanoplastic exposures might also be associated with increased risk of ACAD.¹⁰⁰ Industrialisation and urbanisation in low-income countries are likely to exacerbate this issue. Efforts to mitigate pollution through cleaner technologies, stricter regulations, and global cooperation will be essential. Additionally, research into the cardiovascular effects of other environmental pollutants, such as noise and light, is needed, and appropriate mitigation strategies are required.

Future research on risk factors

Interdisciplinary research that integrates genetics, epigenetics, environmental science, and social sciences will be crucial for understanding the complex interactions between various risk factors for ACAD across the life course. Collaborative research efforts that bridge these disciplines could lead to more holistic and effective prevention and treatment strategies. Funding and support for interdisciplinary research initiatives will be important for advancing the field. Longitudinal studies that track individuals over extended periods will be essential in understanding the long-term effects of novel risk factors

on ACAD. These studies can provide insights into how risk factors interact over time and inform the development of comprehensive prevention strategies. Investment in large-scale, multicentre longitudinal studies enrolling and validating across diverse populations will be crucial to advance understanding of ACAD.

Prevention

ACAD is an acquired and preventable condition. The purpose of prevention is to avoid or delay development of the disease, halt progression of existing disease, and avert acute events related to established disease (panel 2). Large-scale, multinational, case-control, and prospective cohort studies, such as the INTERHEART study, suggest that 70–80% of coronary events are attributable to a small cluster of modifiable risk factors.¹⁰¹ Preventive strategies for ACAD are impactful throughout the lifespan but might be more effective if instituted earlier.¹⁰² Preventive measures include overlapping health and education strategies, screening and diagnostic detection approaches, and diverse treatment targets. Current guidance considers the categories of primary and secondary prevention. Moving towards consideration of ACAD along the continuum of disease and early prevention at the primordial stage has the potential to deliver on the promise of earlier prevention and eradication of the disease.

Panel 2: Atherosclerotic coronary artery disease prevention targets

- Recognise and prioritise the role of primordial prevention of atherosclerotic coronary artery disease (ACAD)
- Research the effect of screening for risk factors and starting preventive strategies earlier in life to reduce lifelong risk of ACAD
- Understand the trajectory of ACAD risk factors and the initiation of preventive strategies in childhood and adolescence within populations with increased genetic and environmental risk
- Establish early detection strategies using diverse tools that measure disease activity or directly visualise atherosclerosis
- Develop tools incorporating multimodal data computed by appropriate predictive models, including using artificial intelligence, with a focus on early detection and longitudinal assessment of risk
- Further evaluate the effectiveness of long-acting therapies, vaccines, polypills, and novel therapies on cardiovascular disease risk factors, patient adherence, and ACAD outcomes
- Evaluate genetic testing and genomic-based therapies in preventing ACAD
- Repurpose proven therapeutics into different populations (eg, GLP-1 receptor agonists for prevention of ACAD beyond individuals with diabetes and obesity)

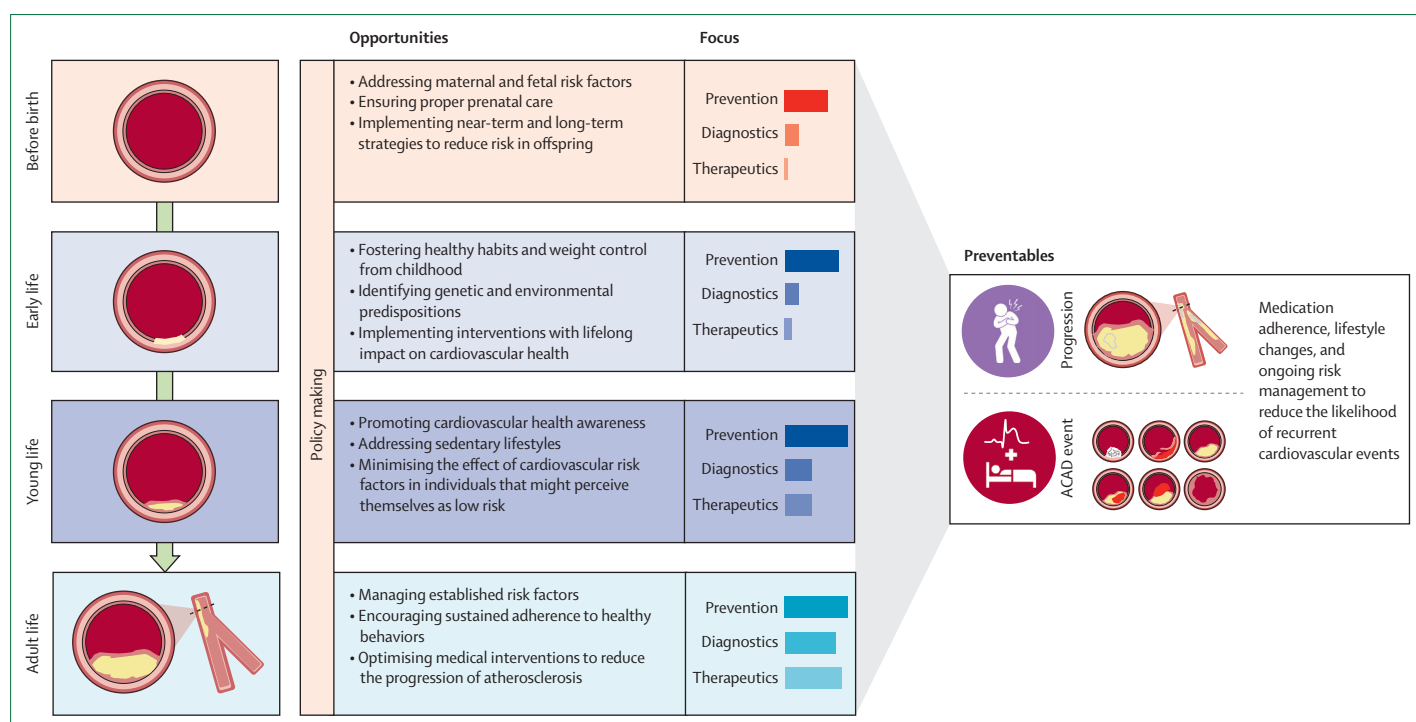


Figure 9: Opportunities and strategies to prevent atherosclerotic coronary artery disease over the life course

Early life defined as age 0–3 years. Young life defined as age 4–17 years. Adult life defined as age 18 years and older. ACAD=atherosclerotic coronary artery disease.

In addition, clearer preventive strategies throughout the life course need to be defined. Individuals at higher baseline risk of clinical events will tend to have greater absolute reductions in risk with preventive interventions. However, more upstream preventive strategies might have more lifetime cumulative effect. Proactive primordial and primary preventive strategies might render prevention in later life less necessary. Conversely, prevention at age 65 years and older, when there is more immediate risk of ACAD-related events, might improve absolute risk reduction. A pragmatic focus on near-term risk, such as with the 10-year pooled risk calculator, obscures this exchange. However, evaluating comparative preventive strategies across the lifespan is difficult to study within prospective trials.

Major advancements in genomics are expected by 2050, which will provide deeper insights into the predisposition to ACAD. Precision medicine approaches and use of genetic information could lead to targeted and effective prevention and treatment strategies. Understanding the complex interactions between genomic factors and environmental influences will be crucial to the development of personalised interventions.

Epigenetic changes, influenced by environmental factors and lifestyle, can alter gene expression and contribute to ACAD risk. Knowledge of these modifications could lead to novel interventions aimed at reversing harmful epigenetic changes. This field is still in the early stages of development, but is promising for

future ACAD management. Research into the epigenetic effects of diet, exercise, stress, and exposure to toxins will be integral to comprehensive prevention strategies.

Primordial prevention

Primordial prevention of ACAD refers to prevention of the development of risk factors (figure 9), usually achieved through lifestyle interventions. Such measures might begin at conception and continue through the lifespan. Those who reach midlife with optimal levels of all physiological risk factors and who do not smoke have very low ($\leq 8\%$) remaining lifetime risk of major ACAD-related events.¹⁰² Moreover, once a risk factor develops, even with restoration of optimal levels, cardiovascular risk remains higher than in people whose risk levels were always optimal.¹⁰² For this reason, primordial prevention is an opportunity to greatly reduce the burden of ACAD.¹⁰²

Prenatal exposures are being increasingly recognised to predispose to increased risk of ACAD in later life.¹⁰³ Gestational diabetes, hypertensive disorders, and tobacco or drug exposure are associated with development of adverse metabolic risk factors, vascular dysfunction, and worsening cardiovascular outcomes for offspring in later life.¹⁰⁴ Maternal dyslipidaemia is associated with a higher incidence of atherosclerotic lesions during the fetal period and faster progression of these lesions in childhood (age 1–13 years), even in normocholesterolemic offspring.¹⁰⁵ However, disentangling the contribution of concomitant

social determinants, environmental exposures (eg, pollution or infection), and genetic factors that also predispose to ACAD is challenging. Moreover, the most effective strategies to control risk factors during pregnancy remain poorly understood. A comprehensive baseline assessment of ACAD risk during childhood years is much needed.

Pregnancy and childhood are major opportunities for early identification and modification of future risk of ACAD and have potential for primordial prevention by introducing lifelong healthy habits. Pregnancies complicated by diabetes or hypertension have a higher prevalence in underserved populations,¹⁰⁶ which might reflect social determinants of health versus underlying genetic factors. However, high-income and middle-income countries currently report growing trends in childhood obesity and type 2 diabetes, largely caused by shifts in lifestyle and food consumption.²⁶ To date, randomised trials of early childhood interventions show only modest ability to reduce rates of metabolic syndrome, hypertension, and dyslipidaemia through education and counselling, and policy-based models identify this period as high value to reduce rates of adult death and disability.¹⁰⁷ Attention has been given to dietary factors, but the quality of contemporary research on nutrition epidemiology remains poor. The prevention and control of hypertension, obesity, diabetes, tobacco and drug use, and dyslipidaemia are high-yield targets for reducing ACAD burden. However, how to best implement these large public health interventions, evaluate their effect, and attenuate the increasing prevalence of cardiovascular risk factors is poorly understood and therefore ideally suited to hybrid studies of effectiveness and implementation.

Primary prevention

Currently, primary prevention is defined as the detection and treatment of modifiable risk factors to prevent ACAD or related complications. Primary prevention is directed at the adult population without known cardiovascular disease, but with an adverse risk factor profile that places them at moderate-to-high risk of acute atherosclerotic events in the next 5–10 years or the remainder of their lifetime. There are multiple unresolved questions regarding who should be screened for ACAD risk factors and the appropriate timing and frequency of repeated screening, given that risk levels over the lifespan are dynamic. Identifying effective primary prevention therapies is resource-intensive and clinical trials require large sample sizes and long-term follow-up. Alternative strategies aimed at detection of the course of disease progression or activity have not been defined and might provide alternative trial designs using surrogate outcomes of serial assessment.

Risk prediction tools

Assessment of ACAD risk is the foundation of primary prevention.⁹ However, the accuracy of current

cardiovascular risk prediction scores in the young, older people, women, and individuals of diverse race and ethnicity who have been under-represented in population research is unknown.^{9,41,108,109} Because age is the most important predictor of cardiovascular disease risk, many risk scores are not used in individuals aged younger than 50 years and do not estimate lifetime risk.¹⁰⁸ Many of these models were originally created and validated in small populations mostly consisting of White men aged 30–62 years from high-income countries, and therefore more research is needed to enhance accuracy across different races and ethnicities. Older predictive scores overestimate risk in contemporary populations, likely the result of better preventive therapies that are more broadly used in primary prevention populations.¹⁰⁹ In addition, traditional risk prediction scores have variable inclusion of novel or emerging risk factors, such as physical activity, inflammation, and sleep disturbance. Data-driven techniques based on AI and machine learning trained on very large datasets that capture a wide range of types of information might have promise in improving risk prediction models by incorporating increased numbers of traditional and non-traditional risk factors.¹¹⁰ The incorporation of data on novel risk factors, available biomarkers, and socioeconomic factors with use of AI might enable risk prediction models to be used at a young age and enable lifetime risk prediction. However, although machine learning algorithms have been seen to outperform traditional risk scores in ACAD risk prediction, the incremental value is modest.¹¹¹ Longitudinal studies are needed to validate such risk scores across populations and regions worldwide, and implementation research is needed to examine how AI models can be used for primary prevention. In the Mediterranean region, where several national cardiology societies are sister societies of the European Society of Cardiology, cardiovascular risk assessment was made possible by including these populations in widely used risk prediction scores, such as SCORE2 and SCORE2-Diabetes. The advent of smartphone risk calculators might improve access to cardiovascular risk assessment and prescription of preventive medications such as statins, ezetimibe, SGLT2 inhibitors, and GLP-1 receptor agonists.

The use of polygenic risk scores in risk prediction models has the potential to improve precision, with the aim of facilitating earlier and targeted preventive measures.^{112,113} Polygenic risk scores are the weighted sum of the risk conferred by multiple disease-associated single nucleotide variants across the genome. The polygenic basis of the development of cardiometabolic diseases is supported by the fact that monogenic risk variants, which are rare but confer a high risk of disease (eg, familial hypercholesterolaemia), only account for a small proportion of heritable cardiovascular disease risk in familial aggregation studies (ie, many families do not have monogenic variants and still have cardiovascular disease).^{112,113} Common genetic variations,

present in at least 1% of the population, contribute considerably to risk.¹¹⁴ The polygenic basis of cardiometabolic diseases has been confirmed by genome-wide association studies. Further study into the complementary role of polygenic risk scores in risk prediction is needed.⁹ Identification of biological processes such as clonal haematopoiesis of indeterminate potential might also yield important future personalised measures of risk.¹¹⁵

Future directions for traditional risk scores and polygenic risk scores include the concept of enhanced phenotyping using a patient's extensive medical record from birth onward, with support from large language models. Such an approach could consider risk-enhancing factors such as inflammatory conditions, pregnancy-related complications, early menopause, and social determinants. Given the availability of electronic health records (including social determinants of health, albeit with varied degrees of completeness), there is a need for research that aggregates available health data in prediction of ACAD risk.

Primary prevention strategies

The greatest missed opportunity for prevention of ACAD is effective implementation of primary prevention strategies that are known to be clinically effective. The target is to reach normal blood pressure range and blood glucose concentrations, reduce tobacco use, and treat dyslipidaemia. Several primary prevention strategies are grounded in high-level evidence from randomised controlled trials among high-risk populations, although many are not contemporary. Pooled data from randomised controlled trials on the use of antihypertensives and lipid-lowering medications provide evidence for the effect of medical therapies to reduce incident ACAD in populations at risk.^{116,117} Modelling studies suggest that from a cost perspective, treating all populations with a 10-year ACAD risk of 2.5% with a generic statin medication is cost-effective and reduces population-wide cardiovascular events.¹¹⁸ Trials evaluating aspirin have found little or no benefit in older people or people with hypertension, hyperlipidaemia, and diabetes for primary prevention and are no longer endorsed by society guidelines for this indication.⁹ This gap between trial-proven efficacy strategies and real-world implementation remains a major hurdle to control of risk factors across larger clinical population subsets.

Diet and lifestyle modifications are recommended by multiple international guidelines for prevention of cardiovascular disease based on substantial data linking poor diet with ACAD outcomes.⁹ Modelling based on data from the Global Burden of Disease study suggests that high-quality diet (ie, high intake of fruits, vegetables, nuts, legumes, wholegrains, and seafood, with low intake of red or processed meat, sugar-sweetened beverages, trans fatty acids, and sodium) has the potential to reduce

death from multiple causes, and especially from coronary artery disease.¹¹⁹ However, few randomised controlled studies of dietary interventions for prevention have been published. The dietary intervention with the most evidence of effects on ACAD is the Mediterranean diet, but associated data are limited by issues of study design and methods.^{120,121} Over the next 50 years, promoting healthy eating habits and ensuring access to nutritious foods will be crucial. Public health campaigns, policy interventions, and community-based programmes can encourage dietary changes that reduce ACAD risk. Advances in nutrition science, personalised nutrition, and food technology might also offer new opportunities for improving cardiovascular health. More randomised trials assessing diet are a high priority for research given the effect of diet on multiple cardiovascular risk factors such as obesity, diabetes, and hypertension.

The interventions that are most likely to produce substantial reductions in smoking rates are population strategies such as taxation and legislative reform. Nowadays, over 70 countries have some form of smoking restriction, and several countries plan for generational restriction on tobacco.¹²² Pharmacotherapy for smoking cessation has not been shown to substantially decrease risk of ACAD, but can be used in combination with medical care supplemented by behavioural support.¹²³ Clinical trials of lifestyle and nutritional interventions need to be rigorous in design and attempt to answer questions and hypotheses based on promising observational research.

Advances in understanding the biological pathways linking stress to ACAD could lead to better prevention and treatment strategies. However, addressing the societal changes needed to reduce stress levels, such as improving work-life balance and social support systems, is a complex and multifaceted undertaking. Urbanisation and the shift towards more sedentary jobs have reduced physical activity levels globally. High-income countries attempted to reduce this shift by providing better infrastructure for promoting physical activity, such as parks and recreational facilities, but many low-income and middle-income countries still do not have enough safe spaces for exercise. Public health measures to increase physical activity will need to be designed with local gender, culture, climate, and built environment issues at the forefront of these decisions.

The global obesity epidemic is expected to increase, posing a substantial risk to programmes in addressing ACAD (figure 8), with more than half of the global population predicted to have obesity by 2035.¹²⁴ Addressing obesity is crucial in the prevention and management of ACAD. Strategies include lifestyle modifications (eg, behavioural therapy, dietary changes, and physical activity), pharmacotherapy, and interventional procedures. Advanced pharmacotherapies and interventional procedures proven to reduce general cardiovascular risk have limited availability, even in

high-income countries. Urbanisation, sedentary jobs, and the increasing availability and normalisation of daily consumption of high-calorie, ultra-processed, low-nutrient foods contribute to rising obesity rates. Public health initiatives, policies, and education aimed at promoting physical activity and healthy eating will be crucial in combating these trends globally. Advances in behavioural interventions, weight management programmes, and increased access to pharmacological and interventional treatments might offer additional tools to address the risk of obesity-associated ACAD. Cultural and gender-related differences in attitudes to physical activity cannot be overlooked if such interventions are to work in different global settings. Studies suggest that GLP-1 receptor agonists as an obesity prevention strategy reduce cardiovascular events related to ACAD.¹²⁵ There is indirect evidence for beneficial effects of naltrexone–bupropion on cardiovascular mortality.¹²⁶ Other weight loss drugs show no evidence for effects on ACAD or have uncertain evidence for effects on risk factors other than diabetes.^{127,128} Recently developed weight loss drugs (eg, tirzepatide and retatrutide) have been proposed to decrease bodyweight by 20% or more, with multiple mechanistic avenues currently being pursued in the development of effective weight loss drugs.^{129,130} Expanded use of these medications to patients at lower risk with pre-diabetes should be a priority for future clinical trials. However, for these agents, issues remain in relation to sustainability of weight loss, cost-effectiveness, and the need for concomitant dietary changes (including increased protein intake) coupled with aerobic exercise and strength training.

Non-pharmacological obesity treatment (with or without total diet replacement or bariatric surgery) is not supported by evidence from randomised studies for effects on morbidity other than diabetes,¹²⁸ although non-randomised data suggest an increase in life expectancy after bariatric surgery in a propensity-matched control cohort.¹³¹

Advances in health-care systems are anticipated to improve hypertension management. For instance, provision of blood pressure management and salt substitution by non-medical workers has shown to reduce blood pressure and major adverse cardiovascular events, including myocardial infarction.^{83,132} Innovations in decision support systems¹³³ or use of remote monitoring could aid in better management and early detection, potentially further reducing the prevalence of hypertension-related ACAD. However, disparities in health-care access, particularly in low-income and middle-income countries, might stymie these benefits. In these countries, other issues pertaining to hypertension management include the absence of unified national screening programmes and few standardised management protocols. Access to hypertension medications is unequal between regions

and dependent on socioeconomic factors. Public policies related to salt intake restriction might help to substantially improve blood pressure control.

Appropriate management of diabetes, especially using modern therapies such as SGLT2 inhibitors, appears to have a specific effect on reducing ACAD outcomes.¹³⁴ Advances in diabetes management, such as artificial pancreas systems, continuous glucose monitors, and personalised medicine, might mitigate some of the risks. However, ensuring widespread adoption and equitable access to these technologies remains a challenge. Modifications towards healthy lifestyles have an important role in risk factor control, including programmes for aerobic exercise and strength training. Addressing social determinants of health and implementing comprehensive public health interventions will be essential in reducing the burden of diabetes-related ACAD.

Specific consideration should be given to the elevation of cardiovascular risk due to familial hypercholesterolaemia. Important questions and uncertainty remain about appropriateness, timing, and cutoffs for population-based screening as an alternative to cascade screening following case detection, which is reflected in global heterogeneity in public health approaches to familial hypercholesterolaemia. Beyond identification, equally broad questions remain about preventive strategies incorporating new technologies, including serial atherosclerotic imaging to assess plaque progression and regression. Only 3% of patients with familial hypercholesterolaemia reach target LDL cholesterol concentrations,¹³⁵ highlighting the need for innovative interventions. Passive immunotherapy using monoclonal antibodies, targeting PCSK9 for example, are known to provide robust and long-term LDL cholesterol reduction, although these treatments require frequent repeat parenteral dosing.¹³⁶ Active immunotherapy, such as vaccination, promises long-term neutralisation of disease-specific interactions (eg, PCSK9)¹³⁷ or other atherogenic moieties (eg, ANGPTL3),¹³⁸ although whether the technologies can avoid activation of the destructive autoreactive T-cell response yet maintain the breakdown of B-cell tolerance will require further preclinical work and careful evaluation in phase 1 trials.

Beyond the well established causal association between LDL cholesterol and risk of ACAD, there is growing interest in the role of other lipid metabolites as markers of risk and potential therapeutic targets.¹³⁹ For example, lipoprotein(a), concentrations of which are genetically determined, has possible proinflammatory and prothrombotic effects that increase the risk of ACAD. Traditional lipid-reducing therapies, such as statins, are not effective in reducing lipoprotein(a). However, novel treatments, including antisense oligonucleotides and RNA interference therapies, are being developed to specifically reduce lipoprotein(a) concentrations. Whether all individuals at risk of ACAD should have

	Primordial prevention		Primary prevention	Secondary prevention
	Prenatal population	Birth, childhood, and adolescence without risk factors (low risk for ACAD)	Greater than low risk for ACAD and established ACAD risk factors	Past acute event (high risk) and symptomatic stable ACAD (moderate risk)
Tobacco use	Risk of harm to fetus	Major modifiable risk	Major modifiable risk	Major modifiable risk
Raised blood pressure	Pre-eclampsia and hypertensive disorders are associated with increased risk of ACAD in offspring for several generations	Observed risk	Major modifiable risk ¹⁴³	Major modifiable risk
LDL-cholesterol	Elevated maternal LDL cholesterol during pregnancy associated with increased risk of dyslipidaemia in adult offspring ¹⁴⁴	LDL-cholesterol modification modelled to be cost-effective down to population 10-year risk of 2.5%	Major modifiable risk	Major modifiable risk
Diabetes or insulin resistance	Gestational diabetes causes macrosomia, possible accelerated metabolic risk in fetus, and long-term risk of ACAD in mother	Threshold for treatment of impaired fasting glucose to prevent ACAD remains unclear	Major modifiable risk	Major modifiable risk
Chronic kidney disease			Major modifiable risk (with some uncertainty in patients who undergo dialysis) ^{145,146}	Major modifiable risk (with some uncertainty in patients who undergo dialysis) ^{145,146}
Physical activity		Observed risk	Observed risk	Major modifiable risk (exercise-based cardiac rehabilitation reduces recurrent events)
Inflammation	Pre-term birth associated with inflammation, ACAD in the mother, and unknown fetal risk ¹⁴⁷⁻¹⁴⁹	Observational data of inflammation associated with risk of ACAD	Observational data of inflammation associated with risk of ACAD ¹⁵⁰⁻¹⁵²	Major modifiable risk (anti-inflammatory treatment reduces cardiovascular events) ¹⁵³
Infectious		Infection (eg, HIV) in childhood and adolescence associated with risk of ACAD ^{154,155}	HIV, hepatitis C, periodontitis, COVID-19, and influenza associated with risk of ACAD	Infection prevention after myocardial infarction or in coronary artery disease reduces risk of cardiovascular disease events or death (eg, influenza vaccine) ¹⁵⁶
Drug use disorders ¹⁵⁷	Risk of harm to fetus	Cocaine, amphetamine, and cannabinoids associated with risk of ACAD	Cocaine, amphetamine, cannabinoids associated with risk of ACAD	Cocaine, amphetamine, cannabinoids associated with risk of ACAD
Obesity	Maternal obesity associated with increased cardiovascular disease in offspring ¹⁵⁸	Contributes to hypertension, diabetes, and sleep apnoea	Contributes to hypertension, diabetes, and sleep apnoea	Contributes to hypertension, diabetes, and sleep apnoea
Diet		Little evidence for DASH diet ¹⁵⁹	Little evidence for Mediterranean or DASH diet ^{159,160}	Little evidence for Mediterranean diet ¹⁶¹
Low birthweight	Low birthweight independently associated with future risk of ACAD ¹⁶²	Low birthweight independently associated with future risk of ACAD ¹⁶²	NA	NA
Genetic risk (monogenetic)		Strong monogenic risk (familial hypercholesterolaemia or dyslipidaemias)	Strong monogenic risk (familial hypercholesterolaemia or dyslipidaemias)	Variable risk (benefits of target therapy vary) ¹⁶³⁻¹⁶⁸
Vaping, e-cigarettes, and nicotine replacement therapy			Observational data of increased risk of acute myocardial infarction ¹⁶⁹	Observational data of increased risk of acute myocardial infarction ¹⁶⁹
Atherogenic lipids			Observational association with ACAD	Observational association with ACAD
Mental health			Depression, anxiety, and psychosocial stressors associated with risk of ACAD ¹⁷⁰⁻¹⁷⁴	Depression, anxiety, and psychosocial stressors associated with increased cardiovascular events
Environmental		Air pollutants, fine particulates, and heavy metals associated with risk of ACAD ¹⁷⁵	Air pollutants, fine particulates, and heavy metals associated with risk of ACAD ¹⁷⁵	Unknown benefit of reduction in exposure
Autoimmune and inflammatory diseases ¹⁷⁶⁻¹⁸⁰		Unknown long-term risk when early in life	Associated with risk of ACAD but not independently of other risk factors; increased levels of inflammation seem to drive major adverse outcomes despite normal cholesterol levels (ie, the lipid paradox)	Targeted therapies have unknown benefit, especially with the lipid paradox
Sleep disorders ^{181,182}			Observational data of long sleep and short sleep duration associated with risk of ACAD ¹⁸³	Unknown risk in secondary prevention
Polycystic ovary syndrome			Associated with risk of ACAD but not independent to other risk factors ^{184,185}	Unknown benefit of treatment to prevent secondary events
Metabolic dysfunction-associated steatotic liver disease			Associated with risk of ACAD	Unknown; potential for incretin-based drugs (eg, GLP-1 receptor agonists) ¹⁸⁶
Sex hormone exposure			Associated with ACAD risk; unknown whether strategies (eg, hormone use) mitigate risk or cause harm ¹⁸⁷⁻¹⁸⁹	
Genetic risk (polygenetic)			Polygenic scores might reclassify risk; unclear therapeutic benefit	Unknown benefit of targeted therapy

Figure 10: Summary of evidence on risk factor exposure with ACAD according to primordial, primary, and secondary prevention interventions

Green=modifiable risk factors with multiple studies showing that intervention on this risk factor leads to improved cardiovascular outcomes. Yellow=risk factors with some data, but the efficacy of an intervention on cardiovascular outcomes has not been established. Red=minimal or no supporting data. ACAD=atherosclerotic coronary artery disease. DASH=Dietary Approaches to Stop Hypertension. NA=not applicable.

lipoprotein(a) measured at least once in their lifetime for risk refinement is debated and could further contribute to health-care inequities if not managed.

The emerging importance of lipoprotein(a) highlights the need for a sophisticated approach to the evaluation of lipid profiles beyond the existing reliance on total cholesterol, LDL and HDL cholesterol, triglycerides to identify markers of risk and, where causation is identified, the potential for novel therapeutic targets.

The advent of genome-altering technology holds promise for people with genetically driven ACAD risk. CRISPR-based technology allows targeted gene base editing of disease-specific mutations in vivo and in the organ of interest, with the potential to achieve complete or near-complete prevention of disease. Natural experiments in patients with loss of function mutations in PCSK9 suggest that moderate lifelong reduction of LDL cholesterol is associated with a considerably reduced risk of ACAD.¹⁴⁰ So-called one-and-done treatment with a liver-directed PCSK9-targeted mRNA-derived base editor to selectively edit the PCSK9 gene to a non-functional form can reduce LDL cholesterol in non-human primates by 70% after a single infusion at 15 months of follow-up.¹⁴¹ First-in-human studies are underway, but how long-term safety data for off-target effects can be evaluated and extrapolated for lifelong genetic editing, potentially for people at extreme longitudinal risk from early age, is ethically and scientifically complex to contemplate. Furthermore, whether there is patient acceptance of genetic manipulation or whether these types of technologies will finally obviate the adherence gap is still to be ascertained.

Secondary prevention

Patients with established ACAD have a high risk of subsequent events, including myocardial infarction, stroke, peripheral vascular disease, and death.^{6,142} Patients with current symptoms of ACAD, those who have had acute coronary syndrome, and those who have undergone coronary revascularisation qualify for prevention. Secondary prevention is defined as strategies aimed at preventing or delaying the onset of clinical manifestations of ACAD or reducing recurrent events in individuals with established ACAD. However, if acute coronary syndrome starts to be considered as a so-called never event and a failure of intervention, this terminology will become redundant and a misnomer. Programmes that focus on early risk stratification with advanced imaging or other laboratory markers and initiation of treatment to stop the progression of disease process are highly recommended for all. Secondary prevention interventions have well established benefits in improving survival, restoring quality of life, maintaining or improving functional capacity, and preventing further acute manifestations of ACAD.

Evidence-based interventions such as lifestyle modification, smoking cessation, control of lipid and glucose concentrations, control of blood pressure, and

antiplatelet agents are of proven benefit to improve outcomes, with varying degrees of evidence for each intervention (figure 10).^{7–9,142}

Women and men are believed to derive similar benefits from secondary prevention therapies. However, when ACAD is diagnosed, women are less likely to receive risk-reducing recommendations,^{33,41,190,191} and have been under-represented in prevention and revascularisation trials, which restricts the generalisability of results in practice.^{8,41} Therefore, the perceived absence of evidence perpetuates the underuse of established therapies.³⁹ This perception is compounded in cross-sectional studies of ethnic diversity and sex; for example, national mortality database statistics in Australia show that Aboriginal and Torres Strait Islander women have approximately double the rate of ACAD-related death than non-Indigenous Australian women.¹⁹²

Improved understanding of the biological, societal, and behavioural differences driving these observations could provide insights on risk factor reduction that could improve care for both men and women. People who are transgender and gender diverse are at increased risk of ACAD events compared with people who are cisgender.¹⁹³ This difference is likely multifactorial in origin and strategies to mitigate this risk, as well as clarification of contribution to risk by gender-affirming hormone use, are needed.

Implementation of preventive measures

Implementation of prevention measures known to reduce morbidity and mortality from ACAD is limited by long-term patient adherence,⁹ which ranges from 50% for primary prevention to 66% for secondary prevention.¹⁹⁴ Poor medication adherence accounts for an estimated 9% of people with ACAD in Europe.¹⁹⁵ Research on the use of polypills (ie, single solid dose formulations containing two or more medications targeting different pathophysiological mechanisms) and long-acting preventive therapies for ACAD risk factors (eg, injectables, depot injection, and antihypertensive or lipid-lowering therapies) could change the current situation for ACAD treatment and offer a more durable implementation of therapies.¹⁹⁶ Strategies that enhance implementation across the lifespan are needed. Mobile phone-delivered interventions or wearable devices for medication adherence have yielded inconsistent results.¹⁹⁷ The low quality of these studies creates uncertainty regarding the effectiveness and safety of such interventions, highlighting the need for further research.¹⁹⁸ Likewise, in some low-income countries (eg, in the north African region), due to shortages in qualified medical staff, therapeutic education after acute coronary syndrome is often dispensed by the practising cardiologist or the intensivist in the cardiac care unit.

Cardiac rehabilitation is a comprehensive and multidisciplinary intervention that encompasses exercise training, counselling, education, risk factor modification,

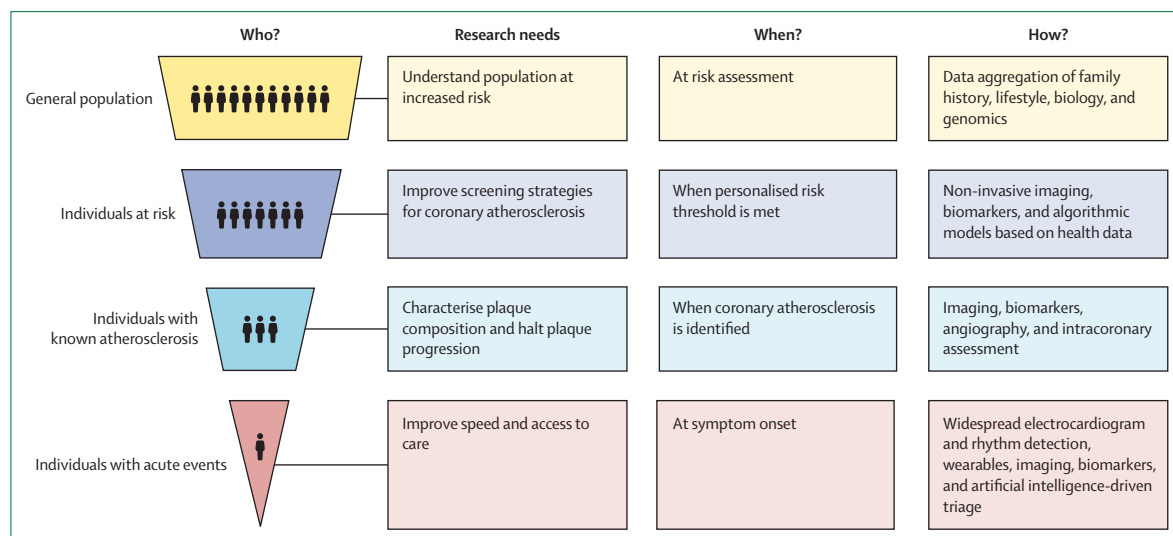


Figure 11: Guidance on screening and investigation of atherosclerotic coronary artery disease

Panel 3: Screening strategies for atherosclerotic coronary artery disease (ACAD)

- Develop and test strategies for early atherosclerotic coronary artery disease (ACAD) detection through screening asymptomatic individuals
- Focus on imaging to detect plaque burden and morphology, with consideration of cost-effectiveness and safety (ie, minimising radiation exposure)
- Conduct research assessing long-term outcomes of early ACAD detection strategies and strengthen evidence for surrogate endpoints, such as the halting or regressing of atherosclerosis

nutritional guidance, and vocational and psychosocial support.⁹ Prevention and rehabilitation programmes have been shown to reduce cardiovascular hospitalisations, myocardial infarction, cardiovascular mortality, and all-cause mortality after an ACAD event or myocardial revascularisation,¹⁹⁹ and are cost-effective.²⁰⁰ Despite the proven benefits, rates of referral, participation, and implementation remain low, especially among women, and are not often available in low-income countries.²⁰¹ Cost, intrapersonal, interpersonal, clinical, logistical, health system, and cardiac rehabilitation-related barriers have all been associated with non-participation and dropout from such programmes.²⁰² Therefore, designing and evaluating programmes that address these factors to increase uptake is essential. A text message-based prevention programme that delivered semi-personalised text messages four times per week with advice, motivation, and information to improve diet, increase physical activity, and encourage smoking cessation (if applicable) resulted in modest improvements in LDL cholesterol

concentrations and improvement in other cardiovascular disease risk factors compared with usual care.²⁰³ Mobile health delivery using smartphones for cardiac rehabilitation and heart failure management is feasible, with high rates of engagement, acceptance, usage, and adherence. This strategy was as effective as traditional centre-based cardiac rehabilitation programmes, with statistically significant improvements in quality of life.²⁰⁴ More research is needed to explore the widespread uptake of delivery of care via smartphones and novel wearable devices to remote and rural areas and to those with minimal financial means and cognitive impairment.

Research focused on developing vaccines to mitigate the progression of atherosclerosis and its risk factors or even curing ACAD is an optimistic approach but one that should be prioritised and not regarded as unrealistic.²⁰⁵

Early ACAD detection: screening strategies

A refocus from risk prediction to early detection of coronary atherosclerosis might improve our ability to individualise treatment and prevent cardiovascular events based on the key questions of who, when, and how to screen for ACAD (figure 11; panel 3).

For primary prevention, screening currently relies on risk prediction, measuring traditional risk factors integrated into a risk score upon which treatment decisions are made.⁹ Existing risk prediction scores are mostly derived from outdated cohorts and might not be applicable in contemporary populations, resulting in large and diverse populations that are poorly risk stratified.²⁰⁶ There is a need to reassess the potential value of screening with a strategy to detect ACAD. Screening strategies would ideally identify the disease early in the disease course and target individuals earlier in life, given the rising prevalence of cardiovascular disease risk

factors among adults aged 18–24 years. Detection of ACAD could lead to early treatment and implementation of lifestyle-modifying behaviours to avoid progression of coronary atheroma.

The range of permutations of who, when, and how to screen for ACAD is broad, and failure of a single approach does not mean that the concept cannot succeed. In people with undiagnosed coronary atherosclerosis, diagnostic tools that detect disease at an early stage, or even precursor features before an acute coronary syndrome event, are necessary. Research using this diagnostic approach will be limited by potentially low diagnostic yield and prevalence of outcomes. For screening, defining improved outcomes at earlier ACAD stages might require adaptations from our traditional clinical endpoints to include atherosclerosis-related endpoints to measure halting of disease progression or inducing regression. Alternatively, long follow-up periods would be required to show reductions in major adverse cardiovascular outcomes. Importantly, the potential benefits of early ACAD detection must be balanced against cost and safety issues, particularly as screening is rolled out to asymptomatic individuals.

CT imaging for screening and detection of ACAD

CT imaging, including CT coronary artery calcium (CAC) scoring, has been well studied as a tool to screen for ACAD in asymptomatic individuals.²⁰⁷ Studies have shown^{208–210} that CAC scoring can enhance risk stratification, and the presence of coronary calcification has been associated with a higher risk of myocardial infarction, stroke, and cardiac death. Programmes providing CAC scoring at low or no cost to patients have been shown to increase access for women and men of diverse backgrounds and incomes.²¹¹ Moreover, incorporation of CAC scoring has improved risk factor control compared with standard risk factor assessment alone.²¹² However, larger randomised trial data have failed to show the efficacy of CAC scoring in reducing cardiovascular events or improving survival. One screening trial using CT CAC scoring of Danish men aged 65–74 years did not reduce all-cause death when CAC and ankle brachial index testing were combined with risk factor assessment and compared with a control group.²¹³ Detection of early ACAD would ideally focus on non-calcified plaque or lipid pools; therefore, CAC might not be the ideal tool for early detection, with poor utility in individuals aged younger than 40 years.

Coronary CT angiography (CCTA) provides a more comprehensive assessment of the burden of both calcified and non-calcified plaque, along with measurement of vascular fat inflammation.^{73,214} 10-year follow-up from the SCOT-HEART trial showed that CCTA-guided care improved death rates from coronary heart disease and non-fatal myocardial infarction when compared with standard care in patients with stable angina.²¹⁵ This finding did not appear to be related to further revascularisation,

with similar rates of invasive angiography and coronary revascularisation in the CCTA group and standard care group. More preventive therapies (ie, statins and aspirin) were initiated in patients in the CCTA group, which persisted for over 10 years. Such a strategy in asymptomatic individuals might be useful for the detection of atherosclerosis, guide appropriate preventive therapies, and potentially increase patient motivation to implement healthy lifestyle changes. By contrast, individuals without atherosclerosis could have preventive medicines deferred, with due consideration to their lifetime or genetic ACAD risk. Given our limited knowledge regarding the onset of atherosclerosis and details of progressive disease patterns, cautiously supporting concepts of reducing risk remains important. However, deferred treatment might be a consideration, with near-term re-evaluation of risk.

Technological advances in CCTA have the potential to increase its utility and value in the management of coronary atheroma. Integration of the assessment of novel imaging biomarkers, such as perivascular fat, might enhance cardiac risk prediction and restratification to personalise the application of preventive strategies.⁷⁴ The additional benefit of integration of imaging-derived physiology is debatable and requires further study.²¹⁶

Widespread global utilisation of CCTA must be built around an approach focused on technological advancements, cost containment, low radiation exposure, repeatability of imaging measures, and accuracy across diverse populations. Although CCTA is available in some low-income countries where it is commonly used as a non-invasive tool to rule out ACAD in tertiary care centres (eg, Morocco, Algeria, and Tunisia), CCTA is not readily available in other regions, such as sub-Saharan Africa. Although the use of CCTA has grown tremendously worldwide, the implementation of high-quality imaging, which is a requirement for accurate plaque measurement and low-dose radiation practices, remains unknown. Alternative low-cost imaging approaches (eg, ultrasound) also require good image quality with high spatial resolution across varied body habitus.

Future directions in ACAD imaging: incorporation of data from routine imaging

Widespread collection of CAC could be achieved using measurements from imaging performed for other indications, such as AI-based image segmentation of routine chest CTs performed for lung screening or other indications; however, this approach would capture a high-risk population and might not ideally focus on early ACAD detection.²¹⁷ Breast calcification has also been reported to correlate with CAC and provides prognostic information,²¹⁸ yet is uncommonly reported on final mammography reports. Quantifying the catchment of individuals at risk based on new technology would support understanding of the potential benefits of identifying unique patient populations. For individuals identified by novel technology, systems should be in place for collection

and reporting of these data and providing care guidance for preventive therapy and lifestyle changes.

Diagnosis of ACAD in symptomatic individuals

Across the ACAD continuum, we define an optimal diagnostic strategy as one that links detectable abnormalities to a comprehensive preventive and treatment strategy, which includes lifestyle changes and preventive therapies that aim to slow progression of atherosclerosis and prevent acute coronary syndrome. Across clinical settings, core diagnostic strategies for ACAD will need to adjust according to the clinical scenario, local and regional practices, and diverse populations (panel 4). In people with acute coronary syndrome, particularly myocardial infarction with coronary occlusion, early diagnosis is essential to facilitate reperfusion and reduce mortality. Prehospital and hospital health-care systems vary widely across countries, with considerable disparities observed even within the same country. Rapid advances in diagnostic methods have the potential to exacerbate health inequities and the importance of developing cost-effective and translatable approaches is paramount. AI and digital health to allow virtual emergency and electrocardiogram review might assist quicker access to reperfusion therapies.²¹⁹ Given the wide variability in prehospital care worldwide and rapidly evolving technologies, we envision that wearables, mobile phone technology, telemedicine, and other approaches might help to diagnose acute coronary syndrome promptly and accurately to foster more timely care. Point-of-care testing of cardiac biomarkers²²⁰ has the potential to be performed by a much wider group of health-care providers to facilitate early diagnosis, rapid transfer, and care, and might be useful in resource-limited settings. These technologies would ideally reduce disparities by increasing access, delivery, and cost-effectiveness of acute cardiovascular care. However, research is needed to specifically target rural and remote areas with fewer health-care resources to reduce disparities in access, cost, and adverse outcomes.^{220,221}

In the assessment of symptomatic patients with suspected or established ACAD, stress testing remains a dominant means of assessing for ischaemia. Yet the goal

of diagnosing demand ischaemia focuses again on end-stage ACAD (ie, angina, left ventricular dysfunction, and myocardial ischaemia) rather than in the detection of ACAD itself.²²² Widespread use of stress testing to diagnose coronary disease has, in turn, been reinforced by traditional diagnostic pathways that lead to invasive coronary angiography, resulting in the lumen being imaged with a focus on stenosis severity, not coronary atheroma burden. Despite a long-standing diagnostic focus on obstructive disease, landmark trials have not shown survival benefit with revascularisation in stable coronary artery disease,^{223,224} and have shown that the total burden of coronary atheroma is associated with adverse events, rather than the presence of obstructive lesions.^{225,226} Furthermore, the historic focus on stress testing, ischaemia, and epicardial stenoses means that the broader population with early atherosclerosis is usually missed.²²⁷ A crucial step forward will be linked to detection of atheroma itself, as well as understanding the underlying dynamic biological states of atherosclerosis and atherothrombosis. Further understanding can be achieved through diagnostic strategies that include CCTA and invasive imaging methods (eg intravascular ultrasound and optical coherence tomography) to diagnose atheroma presence, burden, and high-risk features (eg, thin cap fibroatheroma and inflammation) that correlate with adverse events.^{228–231} By linking diagnostic tools to the biology of plaque stability, there is potential to move beyond diagnosis to monitoring and guiding the management of people with coronary atheroma. However, such diagnostic approaches will have to overcome challenges, such as balancing imaging quality with reductions in radiation exposure, reducing the time for offline computational analyses, and the inherent risk of complications with invasive diagnostic pathways.

In addition to a shift in the diagnostic focus towards atheroma, future diagnostic strategies could incorporate other patient characteristics, such as genetic susceptibility²³² and use of AI-based algorithms to estimate acute coronary syndrome probability for specific features.²³³ These data could be integrated with temporal information across the life course, including characterisation of symptoms and other health status measures, to reveal patterns of instability and features that lead to acute events. Once the diagnostic focus changes to detection of coronary atheroma, the overarching challenge then becomes understanding how the extent and type of ACAD can lead to better management strategies.

Panel 4: Steps to improve diagnosis of atherosclerotic coronary artery disease

- Develop strategies to foster broader access to effective diagnostic strategies for atherosclerotic coronary artery disease in resource-limited settings, including access to timely care for acute and high-risk coronary artery disease
- Develop accurate diagnostic tools to detect biological processes and mechanisms (eg, plaque burden and morphology or inflammation) to predict future risk, with consideration of cost-effectiveness and safety

Therapeutics for ACAD

Key therapeutic targets

Historically, therapeutics for ACAD have had two major objectives: first, to reduce the risk of future events and improve survival, and second, to reduce symptoms and improve quality of life. The most successful therapies to increase lifespan in ACAD have been small-molecule drugs targeting the molecular substrates of atherosclerosis and its risk factors. In the coming

decades, approaches using robotics, digital interventions, biological, genetic, and cell-based therapeutics have the potential to enter and transform clinical practice.

We believe that future progress in therapeutics should have three aims. First, to improve the universal implementation of underused therapies that are known to be effective. Second, to develop more intensive targeted treatment of coronary atheroma. Third, to ensure that these strategies are globally applicable. These pathways offer the hope of eradication of ACAD in our lifetime (panel 5).

Pharmacological interventions

Lipid-lowering agents

Overwhelming evidence¹³⁹ supports a causative role of LDL cholesterol in ACAD. Reduction of LDL cholesterol with high-potency statin treatment is effective in prevention of complications of ACAD.¹¹⁷ Although all drugs have possible side-effects, most muscular adverse effects with statins are nocebo in nature—a fact not well known by the public and many health-care professionals.^{234,235} Key unresolved research topics include how statins can be provided to all who would benefit, how to reduce public mistrust and hesitancy, side-effects, and nocebo effects, and how to improve long-term adherence.²³⁶

Newer mechanisms to reduce LDL cholesterol and earlier interventions could potentially eradicate ACAD. Further reduction of LDL cholesterol to concentrations not achievable with statins alone through monoclonal antibodies or RNA-based oligonucleotide therapeutics targeting PCSK9 has additional benefits,^{237,238} with evidence of changes in plaques into a more quiescent phenotype.²³⁹ Because LDL-lowering follows targets set by guidelines (with different guidelines recommending different target concentrations),^{6,8,142} research is needed to ascertain whether LDL-lowering should be refocused towards so-called the lower the better or the earlier the better approaches, either universally or for particular groups.

Antihypertensive drugs

Blood pressure reduction is associated with a reduction in the risk of major cardiovascular events by approximately 10% per 5 mm Hg achieved, irrespective of baseline blood pressure.²⁴⁰ However, many knowledge and implementation gaps in this area remain. For example, although early potent lipid-lowering after myocardial infarction reduces risk, similar studies of blood pressure lowering soon after myocardial infarction have not been performed. Concerns of a possible J-shaped risk curve (with excess blood pressure-lowering associated with higher risk) need to be resolved to understand whether optimum blood pressure targets can be identified or if risk reduction lies on a continuum and the lower-the-better approach is appropriate.

Even more important than finding the optimal treatment threshold is identifying people with high blood pressure in the first place. Blood pressure

Panel 5: Targeting atheroma before the end phenotype of ischaemia is established

- Examine whether, and how, some people benefit more from existing and new treatments and the efficacy of personalisation
- Develop new treatments that could reverse, cure, or eradicate atherosclerosis
- Identify broadly applicable and locally effective strategies to increase uptake of, and adherence to, proven treatments
- Reassess benefits of established treatments to identify obsolete therapies and adapt therapies to new indications

measurement is variable, heterogeneous, or absent across patient groups and geographical locations, often driven by significant clinical inequalities and treatment inertia.²⁴¹ The burden of hypertension in young adults is large, and risk for women with past hypertensive disorders of pregnancy and their children is particularly high.³⁸ Social determinants of health factors integrated within an electronic medical record across the lifespan could be used to target young individuals at risk. Further research is needed to identify the best strategies to find individuals with high blood pressure at both an individual and population level, and on how to assess and define who benefits most from treatment, and how to increase implementation of, and adherence to, treatment.

Antiplatelet and antithrombotic drugs

Many acute coronary syndrome events are ultimately triggered by platelet activation and aggregation (triggered by ruptured plaque). In primary prevention, a net benefit with aspirin has not been seen.^{9,242} The benefits of aspirin and P2Y12 inhibitors are well evidenced among people with established ACAD,^{6,8,142} with further research needed to define ideal treatment duration and combination that reduces ischaemic risk without being offset by increased bleeding events. The addition of novel anticoagulants such as factor XI inhibitors to conventional antiplatelet therapy is currently being studied.²⁴³

A definitive answer to the question of whether additional antiplatelet or anticoagulant treatment is superior in specific contexts requires head-to-head comparisons.^{244,245} Development of more nuanced strategies to identify both high thrombotic risk and high bleeding risk is also needed to individualise strategies. Although aspirin has been the mainstay of antiplatelet treatment, whether it should remain so warrants further evaluation; nevertheless, definitive trials might never be performed.²⁴⁶ Furthermore, with expanded use of CCTA, there is a melding of features deemed sufficient for coronary artery disease diagnosis, including a focus on both atherosclerotic plaque and obstructive stenosis that

results in confusion on strategies for primary antiplatelet prevention, as universal treatment does not appear to be effective.²⁴⁷ These evolutions in diagnosis mean that targeting residual risk through antiplatelet and anticoagulant agents in ACAD will require new trials with large effect sizes and substantial costs to be clinically meaningful and cost-effective.

Glucose-lowering agents

GLP-1 receptor agonists and SGLT2 inhibitors have shown remarkable cross-profile cardiovascular risk reduction. GLP-1 receptor agonists reduce rates of cardiovascular death, non-fatal myocardial infarction, and stroke in people who have obesity or overweight with pre-existing cardiovascular disease.¹²⁵ SGLT2 inhibitors

improve cardiovascular outcomes in patients with heart failure, type 2 diabetes at high cardiovascular risk, and chronic kidney disease, but have not been shown to have benefit in patients early after acute myocardial infarction.²⁴⁸ The rising prevalence of obesity and diabetes makes research on the most effective ways to treat these conditions, and the benefits of such treatment, a high priority. However, long-term adherence, durable weight loss, and effectiveness of bariatric surgery compared with (or in addition to) these new drugs remain unclear.

Anti-inflammatory drugs

Inflammation is central to development of atherosclerosis.^{249,250} The presence of C-reactive protein is a marker of increased ACAD risk.²⁵¹ Strategies to target

	Specific drugs	Challenges	Future research goals
Lipid-lowering agents	Statins, ezetimibe, bempedoic acid, and PCSK9 inhibitors (eg, evolocumab, alirocumab, inclisiran)	Poor implementation or up-titration in eligible people; public mistrust and suspicion regarding benefits and side-effects; low adherence rates; unclear optimal timing, duration, or indications for deprescribing	Investigate the ideal therapeutic goals according to risk groups; develop strategies to build public trust and understanding; develop strategies to reduce nocebo and side-effects
Blood-pressure lowering agents	ACE-I, ARB, calcium-channel blockers, β blockers, diuretics	Large proportion of population globally at risk with undiagnosed or untreated hypertension; little evidence investigating low blood pressure targets in acute coronary syndrome	Establish treatment targets for blood pressure in the early phase after acute coronary syndrome; define strategies to improve detection of hypertension on a broad scale
Antianginals	Nitrates (short-acting for acute angina or long-acting for angina prophylaxis), β blockers; calcium-channel blockers (non-dihydropyridine agents such as verapamil or diltiazem), dihydropyridine agents (eg, long-acting nifedipine and amlodipine), ivabradine; nicorandil, ranolazine, trimetazidine	Previous evidence of efficacy often based on surrogate and non-patient centred outcomes; variable treatment response; clinically significant side-effects; unclear efficacy of single therapy versus combined therapy; scarce evidence on strategies to personalise treatment	Develop new approaches to targeted antianginal medication and strategies based on endotype of disease and patient characteristics
Antiplatelets and antithrombotics	Antiplatelets and antithrombotics (administered for pretreatment, peri-interventional, postinterventional, and maintenance treatment); low-dose aspirin, oral and intravenous P2Y ₁₂ inhibitors (eg, Ticagrelor, prasugrel and cangrelor), glycoprotein IIb/IIIa antagonists (eg abixicimab and tirofiban), direct oral anticoagulants (eg, rivaroxaban), factor Xla inhibitors	High risk of bleeding; variation in treatment response for some agents; uncertainty around which patient groups benefit most from which treatment combination or duration	Individualise choice and duration of dual vs single antiplatelet therapy according to ischaemic and bleeding risk; individualise platelet function and genetic polymorphisms; role of using antithrombin (eg, factor Xla inhibitor) in addition to antiplatelet therapy after acute coronary syndrome
β blockers	Cardio-selective β blockers (eg, carvedilol, bisoprolol, and extended-release metoprolol), non-selective (eg, propranolol)	Contemporary trials show limited benefit in patient groups without impaired LVEF; side-effect profile (eg, fatigue, bradycardia, hypotension, and worsening heart failure when decompensated)	Ascertain improvement in quality of life, exercise, and angina in stable patients with ACAD; identify which subgroups benefit after myocardial infarction or stable ACAD, with preserved LVEF; identify ways to reduce side-effects
RAAS inhibitors	ACE-I, ARB, sacubitril-valsartan	ACE-I and ARB commonly used after myocardial infarction and in coronary artery disease management; limited data in context of evolving contemporary medical therapy; minimal outcome data in preserved LVEF after myocardial infarction; no additional improvement in cardiovascular outcomes with new agents (sacubitril-valsartan) vs ACE-I	Investigate whether RAAS blockers reduce cardiovascular events in patients with coronary artery disease and typical left ventricular function; investigate benefit in context of contemporary coronary artery disease therapy
Glucose-lowering agents	SGLT2 inhibitors, GLP-1 receptor agonists	Polypharmacy with associated challenges in adherence	Identify further indications for use in different groups
Anti-inflammatory agents	Colchicine, allopurinol IL-6 inhibitors, monoclonal antibody IL-1 β (canakinumab)	Minimal data on risk reduction; side-effect profile and infection risk	Measure outcome data; quantify frequency and define side-effect profile

ACAD=atherosclerotic coronary artery disease. ACE-I=angiotensin converting enzyme inhibitor. ARB=angiotensin II receptor blockers. LVEF=left ventricular ejection fraction. RAAS=renin-angiotensin-aldosterone system.

Table 2: Current pharmacological treatments, challenges, and research needs for atherosclerotic coronary artery disease

inflammatory mechanisms upstream of C-reactive protein, such as IL-1 β , through use of monoclonal antibodies or colchicine (which has several anti-inflammatory actions), or via anti-IL-6 mechanisms, have shown incremental benefit on ACAD outcomes.^{72,252,253} However, not all anti-inflammatory strategies show benefit,^{254,255} and hampering inflammatory responses is likely to increase the risk of infection.⁷² Further research on the role of anti-inflammatories, possibly targeted to aspects of plaque, perivascular fat characteristics, or patient endotype (ie, subcategorisation of patients with ACAD by demographic, clinical, genomic, proteomic, metabolomic, or imaging markers) is warranted. Novel imaging applications to target inflammatory fat depots, such as in the pericoronary adipose tissue,⁷³ might prove useful for targeted anti-inflammatory treatment in selected patients.

Antianginal medications

The use of many antianginal medications is supported by placebo-controlled evidence.^{256,257} However, most evidence on antianginal drugs is old, usually derived from small numbers in non-diverse participants, and using endpoints that might not reflect health measures that are meaningful to patients (such as time to ST depression on exercise). Whether adding a second antianginal drug alone or in combination with a first-line medication is superior in improving symptoms and quality of life in people with symptomatic ACAD remains unclear.

The effect of therapies intended to reduce symptoms and improve quality of life should be tested on the endpoints that are meaningful to contemporary patients. Inclusion of patient-reported outcome measures and digital technologies able to frequently and longitudinally capture quality-of-life metrics alongside other meaningful aspects of health (such as physical activity) in clinical studies and routine health care could improve ability to understand the benefits of these therapies. Efforts to better personalise therapies to identify those likely to benefit could provide greater clinical benefit and reduce the need for more expensive and high-risk revascularisation. Current pharmacological approaches for the management of ACAD, alongside challenges and potential research needs, are summarised in table 2.

Surgical and device interventions

Whether revascularisation reduces future risk and improves prognosis, and in which subgroups, remains intensely debated. Although outdated registries suggested a survival benefit of coronary artery bypass graft surgery (CABG) over medical therapy alone in patients with multivessel disease,²⁵⁸ left main coronary artery lesions,^{259,260} and left ventricular dysfunction,²⁶¹ most of this evidence preceded contemporary, intensive secondary prevention and current optimal medical treatment, making benefits in the current era uncertain. Since 2007, randomised controlled trials have shown that

revascularisation with percutaneous coronary intervention (PCI) does not reduce mortality or other major adverse cardiovascular events when compared to optimal medical therapy alone in patients with stable coronary artery disease with preserved left ventricular ejection fraction and without left main coronary artery disease.^{222,223,262–264} These findings were consistent across subgroups including those with diabetes, multivessel disease, moderate-to-severe ischaemia, or when PCI was guided by fractional flow reserve. Data on outcomes from surgical registries are quasi-absent and many practitioners prefer PCI over CABG in patients with diabetes or with severe left ventricular dysfunction because CABG is associated with greater procedural risk and morbidity.²⁶⁵

Revascularisation has an undisputed central role in improving outcomes and mortality in acute coronary syndrome. In non-ST elevation myocardial infarction, a routine invasive approach reduces the composite endpoints of death, recurrent myocardial infarction, and rehospitalisation for ischaemia.²⁶⁶ In ST-elevation myocardial infarction, primary PCI reduces mortality, myocardial infarction, stroke, and bleeding when compared with thrombolysis.²⁶⁷ Complete revascularisation with multivessel PCI reduces cardiovascular death or reinfarction in acute coronary syndrome without cardiogenic shock;²⁶⁸ however, the anatomical or physiological definition of complete revascularisation itself is unclear. The role and optimal timing of PCI in different groups (such as cardiogenic shock, out-of-hospital arrest, or bleeding) remains incompletely defined. Recognising that optimal therapies might vary between regions and health-care systems, there is still a need to establish the best possible strategies, such as pharmacoinvasive strategies with thrombolytics and immediate primary PCI in regions where rapid primary PCI is not available.²⁶⁹

Crucial gaps in evidence exist for specific populations at high risk of ACAD and require focused research (table 3). Advances in invasive and non-invasive imaging and molecular approaches to measure genomic, proteomic, metabolomic, and other plaque or clinical features might allow a better understanding of when revascularisation is appropriate to reduce future risk.

Symptoms and quality of life

Data on the effect of revascularisation on symptoms and quality of life comes largely from unblinded clinical trials and clinical experience.^{270,271} However, the overall effect of therapy on a subjective endpoint, such as symptoms, is composed of both the true physical effect and the placebo component.²⁷² Interventional procedures increase the placebo effect²⁷³ resulting in unblinded effect sizes that are often far larger than in blinded studies.²⁷⁴ The first placebo-controlled blinded trial found the efficacy of PCI for improving symptoms was far smaller than expected.^{275,276}

	Challenges	Future research goals
Patients with diabetes	Diffuse and extensive coronary artery disease; high mortality and repeat revascularisation rates	Ascertain the possible synergy between drugs and medical devices in diabetes
Older patients	Comorbidities; increased risk of bleeding complications and periprocedural events (for both surgical and percutaneous revascularisation); complex lesions (eg, bifurcations, calcifications, and tortuosity)	Perform more studies of revascularisation specifically recruiting older people and inclusive of patients who are frail and at high risk, with multiple comorbidities
Patients with chronic kidney disease	High rates of complex and calcified plaques; increased risk of acute kidney injury and bleeding	Perform research on acute kidney injury minimisation strategies; improved tools for management of calcified plaques; increase recruitment of people with kidney disease into clinical trials
Patients with left ventricular dysfunction	Role of percutaneous coronary intervention remains uncertain; uncertainties exist regarding the most suitable method to assess myocardial viability and whether myocardial viability can predict outcomes with revascularisation	Perform randomised studies with standardised viability assessment and quantification; develop new tools to assess viability; perform studies assessing the role of percutaneous coronary intervention with physiology and imaging guidance, studies defining the optimal role of ventricular support devices during revascularisation, and studies defining the prognostic importance of complete anatomical or functional revascularisation

Table 3: Challenges and opportunities for future research in revascularisation for specific subgroups

There is a paucity of data on the benefit of CABG for symptom relief. Data from the unblinded ISCHEMIA trial showed angina reduction with CABG or PCI when compared with a conservative approach.²²⁴ In the absence of a clear reduction in mortality and myocardial infarction rates with PCI, guidelines recommend PCI primarily for symptom relief.²⁷⁷ Importantly, many patients remain symptomatic when taking at least two antianginal medications. However, the placebo-controlled ORBITA-2 trial showed that PCI was most effective as an antianginal monotherapy.²⁷⁸ There is a possibility that guidelines suggesting that PCI is only offered to those with symptoms refractory to optimal antianginal medication select those with the least to gain. Many patients remain symptomatic after PCI, therefore more research is needed on how to target revascularisation to those who are most likely to benefit and to investigate causes and treatments for patients with post-PCI angina. Importantly, symptom characteristics themselves might help to stratify who is most likely to benefit from PCI.^{279,280}

Cardiac symptoms can be difficult to evaluate, especially because they are assessed in various health-care settings by numerous health-care professionals. Each time a patient is asked to report their symptoms, the nature of questioning can influence their answers. Symptom reporting is highly dependent on multiple factors including culture, language, physical functioning, socioeconomic status, and environment. There are substantial limitations in the tools used to evaluate symptoms in clinical practice and clinical research. Interpatient and inpatient variability, as well as recall and reporting bias, are some of the major limitations of the current patient-reported outcome measures used to evaluate symptoms.^{281–283} Novel tools for the evaluation of angina might address some of these confines.²⁸⁴ Data are needed to investigate and improve these tools because the efficacy of an antianginal therapy can only be adequately

evaluated when the best methods to predictably and reproducibly study symptoms are understood.

Other therapies are being evaluated to reduce angina and improve quality of life. In addition to ongoing studies of drug-eluting stents, drug-coated balloons, and bioresorbable scaffolds,^{285,286} devices to reduce coronary sinus blood flow^{287,288} have shown promise in placebo-controlled angina improvement. Enhanced external counter pulsation,²⁸⁹ extracorporeal shockwave myocardial revascularisation,²⁹⁰ transmyocardial laser revascularisation,²⁹¹ and cell therapies^{292,293} have all been tested for the treatment of angina, but the benefits are uncertain, and there are challenges such as poor availability, time investment, costs, and logistical difficulties. These therapies must be evaluated rigorously with placebo-control to test angina relief before widely entering clinical practice.

Failure of ischaemia-guided approaches

Ischaemia-guided approaches are inadequate, with no clear role established for revascularisation in improving prognosis in stable coronary artery disease. This should lead to a change in the framework of how such invasive and costly procedures, with associated procedural short-term and long-term risk, are used. Similarly true for non-invasive stress testing for detection of ischaemia, the benefit of revascularisation in acute coronary syndrome, but not stable disease, shows that plaque phenotype rather than anatomy and degree of stenosis can identify groups that benefit, and the substrate of the culprit plaque (eg, rupture vs erosion) might be related to prognosis with potential therapeutic implications.^{294,295}

Targeted therapeutics for atherosclerotic plaque

Coronary atheroma burden is a stronger predictor of adverse cardiovascular outcomes than the presence of

ischaemic coronary stenoses.^{225,226} Non-obstructive atherosclerotic lesions can destabilise and lead to acute coronary syndrome despite optimal medical therapy or revascularisation of culprit and non-culprit clinically significant lesions.^{228,229,296,297} Thus, therapeutic interventions targeted at obstructive ischaemia-producing lesions, rather than the overall atherosclerotic burden, can leave vulnerable and biologically active plaque untreated. Advancements in non-invasive and intravascular imaging have allowed the identification of high-risk plaque features, such as a thin fibrous cap and a bulky necrotic core, which are associated with increased rates of acute coronary syndrome despite being functionally insignificant.²³⁰ Patients undergoing CCTA are decidedly at a lower risk than patients undergoing invasive coronary angiography and this lower risk might hinder the ability of CCTA to predict future acute coronary syndromes.^{231,233} Furthermore, CT imaging of atherosclerotic plaque might be difficult in secondary prevention, such as in patients with previous revascularisation in which coronary metallic stents can impede plaque quantification using CCTA.²²⁶ Moreover, current understanding of the mechanisms of atherosclerosis progression, including variable timing across patient populations of varied risk levels, remains poor and must be improved to halt or regress ACAD.

The evaluation of high-risk plaque might be most important in patients with multivessel coronary artery disease presenting with an acute coronary syndrome. In this population, the PROSPECT study using intravascular ultrasound showed that major adverse cardiovascular events at follow-up could occur in both infarct-related and non-infarct-related arteries.²⁹⁶ High-risk characteristics, such as a plaque burden of 70% or more, minimal lumen area 4.0 mm² or less, or thin-cap fibroatheroma, were predictors of potential plaque destabilisation. Similarly, the CLIMA study (using optical coherence tomography)²⁹⁷ and the PROSPECT II study (using a combination of intravascular ultrasound and near-infrared spectroscopy)²⁹⁸ substantiated the value of these techniques in identifying high-risk plaques. These studies underscore the predictive value of imaging features such as lipid-rich plaques and large plaque burden in assessing future risk. Therapies such as high-intensity statins, PCSK9 inhibitors, and anti-inflammatory agents can reduce plaque burden and stabilise high-risk plaques, offering a chance for intensive plaque-centric management strategies, rather than ischaemia-centric.²⁹⁹ Theoretically, PCI might seal and stabilise vulnerable plaques, potentially reducing the risk of acute coronary events. PCI also offers advantages such as no systemic side-effects (beyond dual antiplatelet therapy-related bleeding), reduced procedure duration, and concentrated costs rather than prolonged expenditure over time. However, the effect of PCI remains confined to the treated lesion, and there is a risk of stent-related complications. Preventive PCI has been studied and

centres around the criteria used to diagnose and treat vulnerable plaque.³⁰⁰ Future work is needed to establish a clinical outcome benefit that outweighs the risks of an invasive procedure, and further studies should aim to identify the optimal intervention technique among drug-eluting stents, drug-eluting balloons, and bioresorbable vascular scaffold.³⁰¹ Although intravascular imaging can identify high-risk features with a very high negative predictive value (96–100%) for adverse events up to 5 years, only a small percentage (4–25%) of these high-risk plaques results in acute events,³⁰² restricting the usefulness of imaging-guided interventions for such lesions. Additionally, this approach requires three-vessel invasive intravascular imaging for screening of high-risk atherosclerotic segments and does not capture the dynamic natural history of ACAD or the changes in activity and quiescence of atherosclerosis over the lifespan. Such an approach would need to ideally combine plaque characteristics with patient characteristics to identify at-risk lesions in patients who are also at heightened risk.

Implementation of therapeutics

Available treatments for coronary artery disease are more numerous than many health-care systems can afford, and this fact will inevitably affect most, if not all, nations as more new treatments are added. Identifying both broadly applicable and locally effective strategies to increase uptake of, and adherence to, new treatments is necessary. Decades of successful discovery mean the focus should shift towards implementing what is already known to be effective and maximising efficient use of existing therapies. The greatest immediate value will be gained by understanding how to better implement treatments that are known to be effective by identification of implementation strategies that increase use of proven therapies for ACAD, and designing better trials to test our ability to increase the healthy lifespan of people with ACAD. Attention should be targeted in parallel to new drug and device discovery.

Strategies to increase the use of and adherence to treatment that could work across different regions would be of much value. Geographically relevant implementation research, including active patient engagement, should be prioritised alongside matched governmental and health-care system policies co-formulated at the same scale and pace. For high-income countries, these strategies might be a matter of prioritisation. For low-income and middle-income countries, considerable additional investment and the influence of non-governmental organisations (eg, WHO) might be required to enact change.

Clinical trials must include diverse participants from different groups and countries. The use of existing treatments consumes a huge amount of health-care resources; yet, the available data, particularly in acute coronary syndrome treatment, comes predominantly from White males of an average age of 62 years, with

under-representation of the elderly, females, and non-White participants.³⁹ As a result, whether such treatments are equally effective for these other groups remains unclear.³⁹ These historically understudied groups tend to have more comorbidities and associated symptoms, are diagnosed later, and have suboptimal patterns of medical therapy use.^{29,190,191,303} Under-representation in revascularisation and therapeutics trials of these groups must be addressed to ensure that therapies are used in the most effective way in groups that are proven to benefit.

Patients with ACAD have been recruited to randomised controlled trials in low-income and middle-income countries; however, hindrances to conducting such trials include reduced access to guideline-directed pharmacological and invasive therapies, minimal personnel (including academic staff to conduct research), ill-equipped facilities, or insufficient willingness of patients to participate in medical research. As a result, most randomised controlled trials are conducted in high-income countries and yield results that are not always generalisable. Geographical differences in treatment effects should be considered during the decision-making process and be a subject of dedicated research.

Examining whether and how some people benefit more from existing and new treatments is also of paramount importance. Decades of progress have led to a wide range of pharmacological and interventional options to address the symptomatic and prognostic effects of ACAD. Such therapeutics have necessarily been applied to broad populations both in clinical studies and routine practice. The success of such approaches is clear, but less evidence exists to guide more precise targeting of existing (or new) therapeutics to those who are most likely to benefit and those who are least likely to have negative consequences. Together, advances in imaging, omics, data science, and AI might allow for the identification of different disease endotypes.

Future interventions

The innovations with the greatest potential to reverse, cure, or eradicate ACAD might not have been discovered yet. The rapid growth of basic science and technological advancements in recent decades is astounding, could not have been predicted, and allows us to ask the question: which new discovery will change the way we prevent, treat, and cure ACAD?

With increasing technological efficiency in resourced settings, the possibility of biologically or individually targeted therapies to reverse or prevent ACAD is becoming realistic. Opportunities include detailed phenotypic characterisation of developing disease, providing information that might be harnessed to personalise therapy with a goal of deflecting the disease course. Characterisation of individual cellular, subcellular, or extracellular characteristics might also assist in determining optimised or personalised

treatment (including polypill) combinations. Opportunities exist for development of proteomic-determined and genomic-determined therapies; therapies that use gene therapy or editing; RNA technologies; and cell-based therapies for the prevention, reversal, and cure of ACAD. Regenerative and nanotechnologies to include cell, tissue, and organoid engineering, as well as development and application of novel extracellular matrices, might be applied in the future as both preventive and reparative therapies. Importantly, implementation of novel therapies should be considered at different life stages, from prenatal to late-life interventions. All therapies must be accompanied by attendant emphasis on ethical considerations, short-term and long-term safety, and outcomes.

Additionally, innovative digital interventions, therapeutics, and strategies to influence individual behaviours to reduce the risk of ACAD require ongoing research. Developments in robotics might extend care delivery and improve clinical outcomes. Innovative transformational discovery research requires sizeable financial and human resource investment from sectors such as governmental, philanthropic, or industry. Translation of basic observations to translational therapies is possible when researchers, funders, and stakeholders align.

Drug re-evaluation and repurposing

More therapeutic options exist now than at any time in history, and more expensive strategies are in development. This constant innovation raises the question of when the therapeutic effect of existing therapies should be re-examined, in what trial design (eg, routine registries, randomised controlled trials, or pragmatic studies), and of how to disinvest in treatments that are no longer appropriate. For example, β blockers have been widely used after myocardial infarction and for angina for 50 years; however, their benefit is uncertain in the era of reperfusion without left ventricular dysfunction and is being re-evaluated in several randomised controlled trials (eg, NCT03278509, NCT03646357, NCT03778554, NCT03596385, and NCT03498066).

There are substantial barriers to such re-evaluation of existing therapies, particularly the cost and the ethical challenge of conducting a study in which some groups do not receive a therapy considered beneficial. A framework is needed to establish the circumstances in which re-evaluation of an existing treatment is warranted. This framework should consider aspects such as strength of previous evidence, previous size of benefit, size of population affected, cost of existing treatment, and scientific rationale for why previous benefits can no longer be assumed.

We hope in the coming decades that this Commission will encourage research to better understand how to provide therapies reliably so that the event reductions from trials can be replicated in clinical practice across all

regions and populations. We also seek to build on advances in the identification of mechanistic pathways, ultimately leading to prenatal and primordial strategies that could prevent, reverse, and potentially eradicate ACAD. We are fortunate as patients, clinicians, and researchers to live in an era that follows more than five decades of high-quality and high-volume cardiovascular therapeutic innovation and trials. When effective risk reduction strategies are implemented in a rigorous randomised controlled trial setting, residual major adverse event risk after myocardial infarction can be reduced to an astonishingly low residual risk of approximately 3% per annum, and mortality to 1% per annum.²³⁸ However, that progress raises the bar for new preventive therapies. In a value-based framework, new therapies are judged based on incremental absolute magnitude of benefit relative to cost. Because absolute risk after myocardial infarction is already low, additional relative reduction in risk of new prevention interventions will have to be increasingly high in trials to produce absolute reductions in risk that are large enough to have favourable benefit–cost ratios and improve outcomes.³⁰⁴

Additionally, despite low adverse event rates after myocardial infarction in trials, both short-term and medium-term risk of recurrent ischaemic events remains high in real-world practice.³⁰⁵ This discrepancy further highlights the need for development and validation strategies to implement what is established in a trial setting as effective. This type of research, focused on inclusive implementation strategies, can coexist with other types of investigation, translating the identification of new cardiometabolic and lipid targets into validated upstream preventive strategies that could improve on optimised, well delivered current therapies. This combination of investigative approaches would allow both short-term improvement in outcomes to trial mortality and recurrent event estimates while pursuing the attainable goal of eradicating ACAD.

Precision medicine strategies

The value of precision medicine stems from the existence of heterogeneity in treatment effects (ie, patient-by-treatment interactions, meaning that some people respond to treatment better than others) of a magnitude that justifies personalisation of care.³⁰⁶ Some monogenic traits provide a clear case for genetic approaches to precision medicine. For ACAD, a relevant example is familial hypercholesterolaemia, for which genetic testing to guide therapeutic choices is recommended by expert panels. For example, PCSK9 inhibition may be targeted to patients with gain-of-function mutations who have the most to gain from the therapy.³⁰⁷

For complex chronic traits, as are most risk factors for ACAD, the situation is quite different. Establishing heterogeneity of treatment effect typically requires separating interperson from intraperson variance in treatment response in the outcome, which necessitates

study designs that can separate treatment effects from time-period effects, and continuous outcome variables that can be measured repeatedly. Proper trial designs to identify the potential of precision medicine in treating complex traits have very rarely been used.

Hypertension would provide an optimal scenario for precision medicine, with several different first-line drug classes having similar preventive effect on a group level, but with unknown heterogeneity of treatment effect. This question was addressed using a novel randomised, double-blind, repeated crossover trial design,³⁰⁸ which is uniquely suited to explore heterogeneity of treatment effect because it allows both adequate determination of intraperson variance in the outcome and can separate treatment effects from time-period effects. Substantial heterogeneity of treatment effect was observed, indicating a potential for personalised monotherapy for hypertension,³⁰⁸ raising hopes of further use of this trial design.

If patient-by-treatment interactions cannot be studied, some information can be gained from studies of subgroup-by-treatment interactions. The most useful interaction analyses are usually those with subgroups based on absolute risk of the outcome, and such interactions will always be present on either the multiplicative scale, additive scale, or both.¹¹⁶ With similar effects of preventive drugs across different levels of absolute risk, the most important predictor of absolute treatment benefit will be absolute risk (as shown for blood pressure-lowering and lipid-lowering treatment)¹¹⁶ and risk-based preventive treatment—hence a key precision medicine strategy.

To substantially impact ACAD, more research is needed to find the right uses for precision medicine. A genetic test that can motivate adoption of a specific (new and costly) drug is often more popular than a genetic test that discourages use of a specific (old and cheap) drug. Even for clear cases, such as the well known actionable pharmacogenetic interactions for clopidogrel (CYP2C19; poor or intermediate metabolisers have reduced clopidogrel effect)³⁰⁹ or statins (SLCO1B1; poor function leads to increased risk of statin-induced myopathy),³¹⁰ the enthusiasm for genetic testing is minimal. Steering precision medicine research to the most essential applications from a population-effect perspective is key.

Research and implementation

Research challenges and targets

Shifting care from late stages towards earlier stages of ACAD will require strategic alterations in core elements of effective research programmes to attain the ultimate goal of reducing the worldwide burden of disease. Evidence is unfolding regarding overlapping mechanisms involved in ACAD and related diseases, such that the emerging cadre of researchers will need to be varied and include those unaccustomed to the new focus on early ACAD detection and treatment. Medical training across research disciplines (eg, nephrology, neurology, and endocrinology) will be

essential to facilitate understanding of the effect of age and comorbidity on progression of ACAD.

Research approaches

Comprehensive ACAD research strategies should incorporate not only randomised controlled trials but also document real-world implementation. Major hurdles, such as ensuring site capacity for diverse recruitment and full adherence to study protocols, will need to be overcome as the focus shifts towards early ACAD strategies. Use of standardised data points for ACAD research across clinical trials and registries will facilitate validation of major findings and potential pooling of data to define the heterogeneity of treatment effects.

Elements of pragmatism across ACAD research might improve clinical applicability and reduce research inefficiency. Countries such as Sweden, Denmark, and Norway have achieved notable success with national cardiovascular registries.^{33,311} By seamlessly linking patient data across health-care sectors, these registries enable efficient monitoring and systematic follow-up over extended periods, supporting research that improves patient care, making them a model of effective and sustainable research.

A focus on intervention for younger individuals (eg, age 18–39 years) will necessitate long-term follow-up from randomised trials or registries to enhance linkage to major adverse cardiac outcomes over time, as well as progression of atherosclerosis. Similarly, after imaging of ACAD, long-term follow-up will be necessary to study prognostic patterns of major adverse cardiac events. In a strategy of early ACAD detection, radiologists and other cardiovascular imaging professionals might be required to formulate a pathway of imaging-guided care. Varied ACAD mechanisms exist that might be targeted, and each unique or combined diagnostic and therapeutic approach will necessitate not only comprehensive and tailored protocols, but also follow-up designed to formulate precise links to the long-term consequences of ACAD. Safety assessments will be a crucial component of early intervention focusing on avoidance of inappropriate follow-up testing and intervention, as well as procedural complications outside of guideline-directed care.

ACAD research should aid in the development of individualised care and formulate comprehensive and lifelong strategies of care to optimise patient health throughout stages of atherosclerosis. Such approaches require reducing the inefficient silos of health care, which are detrimental to the optimisation of patient health and wellbeing. New diagnostic approaches will require seamless integration within a management strategy, enhancing adherence and surveillance of progressive ACAD and systemic atherosclerotic conditions and complications. Research strategies must not only focus on near-term changes in management but also devise adherence strategies to optimise long-term effectiveness.

Endpoint criteria and safety endpoints

Detecting early ACAD requires varied trial designs with substantially long-term follow-up or incorporation of surrogate (or intermediate) endpoints. Increased trial duration is required to establish links with major adverse cardiac events. Although the use of combined endpoints can reduce the required sample size, component endpoints should be chosen carefully to target progressive mechanistic states of ACAD and safety issues that are failures within the strategy of care.

Additionally, therapies exerting effects across ACAD mechanisms might require incorporation of various blood or imaging biomarkers to target adiposity, inflammatory measures, or plaque subgroups (notably non-calcified plaque burden), and can be used for surveillance. Tracking surrogate endpoints, such as cholesterol concentrations or blood pressure levels, are already established to show risk factor control. Atherosclerosis is a progressive disease for which novel interventions focused on halting or regressing ACAD could be supported by serial imaging techniques. Any surrogate endpoint must have an established causal relationship with future major adverse cardiac events.

Safety endpoints should be thoroughly integrated and statistically powered within trials. Many novel therapies have considerable side-effects that detract from long-term adherence. Drug development should focus on clinical care approaches to offset negative side-effects. Research studies should include sufficient resources for tracking of any safety related endpoint.

Global uptake of evidence-based therapies for ACAD is inadequate, and long-term medication adherence is worse. Suboptimal adherence is responsible for approximately 10% of major adverse cardiovascular events.^{194,195} Patients with ACAD are anticipated to require extended or lifelong treatment, which can be undesirable to the patient and therefore contribute to low long-term adherence. Strategies must be developed to augment adherence, especially over an extended duration of treatment.

Democratisation and inclusion

A foundational principle to reducing the population burden of ACAD is diverse representation across key subsets of women and men, inclusive of demographic or socioeconomic factors, within research. Deliberate efforts to remove barriers to clinical trial enrolment are needed to improve diversity (panel 6). Any therapeutic or diagnostic test should ensure enrolment of a racially and ethnically diverse population that is representative of clinical and population cohorts. Therapeutic trials targeting a specific or varied ACAD mechanisms might improve enrolment by enriching eligibility criteria with high-risk blood or imaging biomarkers.

Effective implementation strategies

Given the transformative approach proposed for early ACAD detection and treatment, implementation strategies will be a key aspect of research. Optimisation of

low-cost established strategies must be compared with any proposed novel and generally more expensive health-care options. Locally relevant implementation research should be prioritised—what works in one country or area might not work in another. Alongside this geographical consideration, coordinated governmental and health-care system policies guided by quality evidence and population needs must be coformulated for action on a large scale and in a timely way (figure 12).

Optimising low-cost care, resource efficiency, and cost-effectiveness

Numerous preventive therapies are under development or have been approved within the past 5 years with sizable costs that are unaffordable to many patient populations and across low-income and middle-income countries. Any novel therapy or diagnostic tool must have a proven value linked to improve population health that is balanced by any heightened cost and must also be evaluated in relation to low-cost options and show an acceptable value–cost ratio. Alternative low-cost strategies should be the comparator in resource-constricted settings. Further development of polypill strategies might improve outcomes¹⁹⁹ and should continue to be validated across diverse settings.

Artificial intelligence

Many recent clinical advances in automated diagnoses, electronic health record phenotyping, symptom evaluation and tracking, and focused operational efficiencies are based on AI technology. Additional machine learning and AI tools might be able to improve cardiovascular workforce efficiency by offloading administrative tasks related to scheduling, clinical documentation, and billing. Within the field of screening and diagnosis, tools might be developed for earlier detection and triage of ACAD, from subclinical to catastrophic acute events. There are many other promising areas where AI might prove useful, such as in image quantification, which might allow for combined cancer and ACAD screening. Deep learning algorithms for image quantification might also allow for measurement of surrounding tissues (ie, adipose depots) or use novel radiomic signals for tissue phenotyping.

A wide range of potential machine learning or AI solutions might improve the reliability and diagnostic accuracy of current clinician-based interpretation and decision making. Performance of machine learning or other AI predictive models will need to be inclusive of diverse risk markers and require extensive external validation. Model performance using machine learning algorithms has not been reported to improve performance relative to traditional statistical methods.³¹² Importantly, the safety of AI-based solutions that triage, automate, or integrate ACAD parameters must be rigorously tested with ongoing surveillance and reporting of poor performance that might place patients at heightened

Panel 6: Improving diversity of participants in clinical trials

Barriers to representation

- Difficulty in accessing study sites
- Familial or caregiver responsibilities
- Cultural or language barriers, screen failure, and not being considered for screening
- Socioeconomic barriers
- Participant concerns about safety
- Limited inclusion criteria
- Poor data collection on relevant non-cardiac history

Strategies to improve representation

- Establish research sites in locations where potential participants already receive health care; provide language assistance for individuals with limited language proficiency; make reasonable modifications for persons with disabilities; and use remote (telephone or online) recruitment processes and study designs
- Reduce burdens due to trial and study participation (eg, number or frequency of study-related procedures or visits, use of local laboratory and imaging, and telehealth)
- Develop a diverse pool of investigators and staff, sustained community engagement, and screening protocols that promote unbiased screening; and promote communication adjusted to patient needs, enhancing transparency and trust
- Improve access by providing assistance with issues such as transportation
- Ensure prevalence-adjusted representation of individuals in cardiovascular clinical trials across relevant age or other categories
- Consider important previous factors from early life (eg, pre-eclampsia, endometriosis, or polycystic ovary syndrome)

risk. Public dissemination of AI tools using large language models for deep learning algorithms that can interact and provide reasonable answers to a vast array of questions are key to dissemination of effective ACAD detection and treatment strategies.

AI development should focus on providing low-cost solutions for efficient and effective care of patients at risk of ACAD. For example, tracking of outcomes might be achieved with minimal expense through smartphones (which are affordable in many low-income countries) and also wearable devices to enhance the efficiency of ACAD research.^{313,314} In some cases, implementation of AI technology might be easier than anticipated across resource-constricted settings, and benefit from technology or corporate partnership. Although AI has transformative potential in ACAD, many important unresolved questions remain in terms of accuracy in external validation, cost, and transparency, especially with regards to missing elements within predictive models. Human involvement should form a key

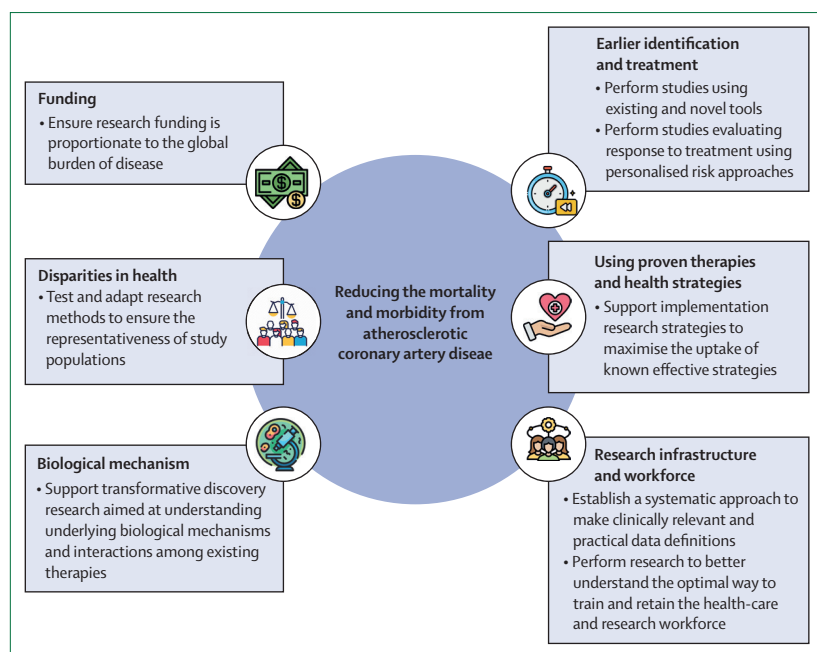


Figure 12: Recommended actions to lower mortality and morbidity from atherosclerotic coronary artery disease

Panel 7: Key targets for research

- Health services research in atherosclerotic coronary artery disease (ACAD) is required to improve health outcomes by increasing the delivery of existing clinically effective therapies
- The cost-effectiveness of clinical interventions needs to be identified to inform real-world prices and encourage appropriate allocation of scarce resources
- Collection methods of population health data should be applied to health-care systems to allow modelling for resilience testing
- Research into strategies and policies should be funded to increase the numbers of women and under-represented ethnic and racial groups in the ACAD workforce

component of any research strategy employing AI-based techniques.

Funding

Any new method of early ACAD intervention must be accompanied with sufficient financial support that ensures success and optimised population risk reduction. Research funding for cardiovascular disease does not match the worldwide burden of disease, and funding from governmental organisations tends to be insufficient and unduly difficult to access. The projected and increasing prevalence of risk factors³¹⁵ and concomitant ACAD event risk will require nimble responses from funding organisations that are appropriate to meet the needs of patient populations at risk. We hope that this

Commission will be foundational in supporting a new generation of research targeting early ACAD detection and treatment. Treating later stage ACAD has not altered the patient cohort at risk. An interventional pathway for early ACAD allows the envision of care that will have greater effect in reducing the burden of future acute coronary syndrome, heart failure, sudden cardiac death, or the need for symptom-based medical or surgical intervention. Funding should be allocated to meet the potential for sudden transformation of the burden of ACAD and improving the health and wellbeing of populations at risk around the world.

Health-care systems

For this Commission to meet its aim of reducing the global burden of ACAD, attention should be turned to the systems by which health care is delivered. Health-care services research is focused on improving the delivery and receipt of evidence-based care (panel 7). Training and provision of health care is biased towards the diagnosis and treatment of the end-stages of the disease, rather than prevention and early detection. Failures to implement effective therapy for atherosclerosis are well described in high-income countries, such as the USA, where approximately one-third of patients recommended for lipid-lowering therapy do not receive it; this inequity of access to treatment is even greater in patients from poorer backgrounds.³¹⁶ In New Zealand, less than one-third of patients admitted to hospitals with acute coronary syndrome receive echocardiography.³¹⁷ In Australia, fewer than four of five survivors of acute coronary syndrome receive 75% or more of recommended secondary prevention medications, with disparities between male and female patients.³¹⁸ Even when these medications are prescribed, discontinuation rates are unacceptably high.^{319,320} Poor adherence to recommended therapies and process measures mean that disparities are even greater within countries where fewer clinical trials are performed.

Although differences in outcomes are often linked to socioeconomic factors, in some instances, wealthy populations have worse ACAD outcomes.³²¹ For example, 30-day mortality after acute myocardial infarction is roughly 50% higher in the USA than in Canada.³²² These discrepancies have many causes but are also partly related to systems of health-care delivery. Recognition of these variations, coupled with focused efforts by health-care services to increase implementation of evidence-based, clinically effective interventions for ACAD in health-care systems and care delivery has the potential to drastically improve outcomes and reduce disparities among populations.

Key problems and targets for health-care delivery

There is tremendous potential to improve ACAD health outcomes by simply improving the delivery of existing clinically effective therapies. The use of quality indicators

helps to improve health-care delivery.³²³ Traditional physician office-based care is inferior to both community-based care and remote methods of managing hypertension and hyperlipidaemia in patients for primary and secondary prevention.³²⁴ Despite the proven efficacy of hypertension, hyperlipidaemia, and antiplatelet therapy for people with ACAD, substantial evidence shows that current health-care systems are inadequate to deliver ACAD treatments effectively. Equitable access, advances to address variability of image quality, and diagnostic accuracy of ACAD imaging will be of crucial importance, with increased emphasis on earlier detection of coronary atheroma. Financial investment to improve access and technological advances in imaging to enhance accuracy and efficiency will be needed to ensure that imaging-guided care and early intervention is a realistic global prospect.

In most cases, implementation of a novel approach to improve ACAD outcomes at a population level meets the definition of complex interventions according to multiple criteria.³²⁵ Investment into complex intervention research in the field of ACAD is urgently required to broaden the perspective beyond the unbiased estimates derived from randomised controlled trials of clinical efficacy. Methods to assess whether an intervention is implementable, cost-effective, and adaptable to be upscaled and applied in different contexts will need to be incorporated (panel 8). Emerging methods of implementation science that have appropriate theoretical frameworks can importantly identify barriers and enablers to efficacy, scalability, and sustainability.^{326–328} Although randomised controlled trials might be required, important information regarding implementation can be derived from a broader range of study designs including observational, quasi-experimental, and hybrid designs simultaneously incorporating measures of both implementation and clinical efficacy.³²⁹

Care delivery in resource-limited settings

All health-care service delivery operates in a setting of constrained resources and no single society has the capacity to cater to all the health-care needs of every individual. This difficulty is increasing due to a growing and ageing population with increased comorbidity and high expectations of health care, coupled with rapid resource-intensive technological advances in diagnostics and therapeutics. Variable governmental investments in healthcare (often a reduction in funding) are also frequently observed and result in inadequacies across populations at risk of ACAD.

In that context, health-care services aligning to maximise value and deliver the best outcome in return for each unit of investment is imperative. More than 20% of health-care service delivery is estimated to be wasteful, returning no improvement in outcome, or even causing harm.³³⁰ Within a constrained system, every individual service provided has an opportunity cost. Prices and real-world effectiveness of drugs and devices likely differ in

Panel 8: Evaluation of health-care delivery for atherosclerotic coronary artery disease

Gaps in delivery of health care for atherosclerotic coronary artery disease (ACAD)

- Worse ACAD outcomes of unclear cause
- Low adherence to performance metrics
- Scarce resources misallocated to low value therapies
- Treatments misallocated to patients at low risk
- Primary prevention risk scores not correctly indicating risk in different populations
- Health-care workforce insufficiently prepared to address care gaps, such as control of ACAD risk factors
- Overdependence on traditional care models
- Minimal ACAD workforce at the primary care level
- Poor allocation of health-care workers in diverse settings

Suggested research methods to address gaps

- Inductive qualitative methods
- Pragmatic trials of health-care delivery mechanisms (eg, nudges) to increase adherence; and pragmatic trials of alternative health-care delivery mechanisms as alternatives to traditional care (eg, home hospital, blood pressure checks in barbershops, and electronic consults)
- Decision analysis and cost-effectiveness simulations that use both effect estimates and costs that apply to local settings, including low-income and middle-income countries
- Observational comparative effectiveness research using large observational datasets adequately powered for heterogeneous treatment effects
- Trials of educational interventions to serve vulnerable populations
- Inclusive transnational clinical registries that reflect a full range of diverse populations in different countries, including low-income and middle-income countries

different countries; therefore, cost-effectiveness analyses developed in some countries might not apply in other settings.

Measurement of the value of interventions through carefully conducted health economic evaluations is an important step in prioritisation of health-care services. Rather than an effort to reduce costs, appreciation of value stimulates innovation and facilitates research investment to promote the use of novel effective interventions, which is of particular importance for ACAD (for which the clinical benefits of some interventions are uncertain, clinical equipoise persists, and the benefits and harms of any treatment or diagnostic test are multiplied at scale due to the large burden of disease). Applying an entirely utilitarian approach to the provision of health-care interventions is unlikely to be possible because that would require knowing the cost-effectiveness of each individual intervention. Nevertheless, health economic evaluation

is of particular importance when the clinical benefits of an intervention are uncertain and clinical equipoise persists.

Outcomes that facilitate health economic evaluation (eg, validated measures of health-related quality of life) should be routinely incorporated into clinical trials. Recognising that cost, health priorities, and conventional measures of value (such as willingness-to-pay thresholds) vary between communities is crucial. Economic models being published in a way that facilitates translation to other health-care settings through transparent presentation of results and provision of access to shared repositories of patient-level data is imperative. Failure to include these outcomes or present results in this manner is a considerable waste of research efforts.

Patient-reported quality-of-life measures are susceptible to bias in open-label trials, which is a problem in studies of novel procedures and devices or established therapies with perceived efficacy. Although placebo-controlled studies with blinding are challenging, they have the potential to provide important data, especially where clinical equipoise persists.

The role of clinical practice guidelines in reframing ACAD

Clinical practice guidelines from authoritative organisations (eg, the American College of Cardiology, the American Heart Association, the European Society of Cardiology and various national associations and governments) summarise available evidence to support clinical decision making and wider policy. Such guidelines are powerful instruments to initiate change, and the groups devising them will be essential to reach the target of a shift in focus from ischaemia to atherosclerosis.

Although clinical guidelines often limit their scope to individual clinician–patient decisions without consideration of the broader health-care service, the guidelines have the capacity to systematically lead clinicians away from low-value treatments. The move towards including health economic evaluation into clinical guidelines should be encouraged more broadly.³³¹ Guidelines summarise which diagnostic and therapeutic approaches are known to be effective; however, given the importance of implementation science, guidelines should also explain how best to increase uptake of existing effective strategies for atherosclerosis. We recommend that all guidelines emphasise that prevention, reversal, or cure should be the aim of the treatment of atherosclerosis.

A shift from ischaemia to prevention of atherosclerosis requires not only changes in individual management but also changes in health-care systems. The provision of early invasive treatment of both non-ST elevation myocardial infarction and ST elevation myocardial infarction is an example of how both individual clinicians and health-care systems are able to change in response to overwhelming

necessity.³³² In North America and western Europe, ST-elevation myocardial infarction mortality is as low as 2% of patients.³³³ Primary PCI utilisation for ST-elevation myocardial infarction reperfusion in Sweden is among the highest worldwide (>90% of patients).³³ Such successful implementation of treatment to different models of care could be used as a template for underperforming regions or health-care providers.³³⁴ Despite the undeniable success of the network of specialist centres delivering high-quality invasive care for late-stage atherosclerosis, willingness to embrace further transition towards better prevention and ultimately reduced need for such invasive approaches will be essential for success. To reduce the burden of and events from atherosclerosis, many of the essential interventions will be delivered in outpatient settings. As such, understanding how to improve uptake and adherence to outpatient medications will be crucial to risk factor control.

Workforce

Effective workforce delivery

ACAD care requires intensive involvement of health-care personnel. Bias towards management of late-stage ACAD has promoted investment in these services, such as coronary care units and acute coronary syndrome and cardiogenic shock networks. These services remain essential and require greater investment to address regional and global inequalities. However, a greater focus on prevention, early detection, reducing progression of ACAD, and occurrence of ACAD events will require more balanced investment within community and ambulatory care.

Although evaluation of new therapies follows well tested and regulated processes, predictable workforce changes are often implemented too late and without evidence or subsequent evaluation. Furthermore, global economic pressures and a health-care sector weakened by the COVID-19 pandemic are causing unrest and fractious relationships between health-care professionals and their employers. Thus, the future cardiovascular medicine workforce faces huge challenges. With a shift to focus on ACAD, delivering effective prediction and prevention early in the life course, while also expanding capacity to provide complex care to an ageing population with comorbidities, is necessary. This change necessitates an increased workforce in primary prevention, able to deliver interventions and prevention at large scale, and to accommodate new therapeutic options and pathways—all within budgetary constraints across varying economic environments. The growth in the global burden of modifiable risk factors for ACAD mandate that existing office-based medical care models of risk factor management need to be disrupted for benefits to be appreciated across large populations.

We define the coronary artery disease workforce as all health-care providers whose role includes predicting, preventing, diagnosing, or treating ACAD.

Comprehensive data on the numbers and types of health-care providers in the coronary artery disease workforce are challenging to find. Some professional bodies publish data on the number of cardiologists, but these data only include a proportion of the coronary artery disease workforce. Separating data on primary care physicians, nurses, allied health clinicians, radiographers, and other health-care providers into those who contribute to coronary artery disease care and those who do not, is impossible. What is clear from the little data available is that there are wide geographical variations in health-care providers delivering current coronary artery disease care.³³⁵ To research effectiveness of different workforce models, data on care delivery and patient outcomes must be collected, as well as on job satisfaction, job retainment, and the cost of different models of care. Such data are the necessary first step to future research that can support understanding of how to optimise the ACAD workforce across different settings.

Most health-care systems (especially in high-income countries) need patients to attend health-care facilities in person. This attendance requires large numbers of people to travel to a vast health-care structure, which creates substantial environmental impacts and disadvantages for some groups of people, including those who are older, from low-income backgrounds, and from rural areas. Health care must ideally be provided closer to patients, which requires upskilling and resourcing of community-based teams and evaluation of new ways of delivering care. Involvement of other health-care and non-health-care professionals, non-telemedicine digital health delivery, chatbots, and other approaches is essential.³²⁴ The WHO HEARTS global programme outlined directives for team-based care, with identification of tasks that could be shared or shifted to non-physician health-care providers, and is important to the provision of care in all levels of resource settings.³³⁶ Research that specifically tests new ways of delivering care to improve clinical and patient-reported outcomes and their effectiveness in diverse settings is required. For example, the HOPE-4 randomised controlled trial tested a model of care using non-physician health-care workers alongside primary care physicians and family within 30 communities in Colombia and Malaysia.³³⁷ The intervention resulted in reduced cardiovascular risk, absolute reductions in systolic blood pressure and LDL cholesterol, and exemplified the type of workforce-delivered care that can be tested through different research methods in diverse economic settings.

Although better community care is urgently needed, expansion of specialty care is increasing due to innovation in genetics, pharmacotherapy, medical devices, and imaging technologies. Traditional physician-delivered care limits the number of patients a single clinician can manage. Given that no single health professional can support all elements of coronary artery disease care, ACAD teams that provide integrated community and

specialist care are required. New ways of training the coronary artery disease workforce on assistive technologies offer promise of improved efficiencies in delivery and cost. Virtual simulators, remote proctoring, and robotics might allow for more efficient skill development while reducing the proportion of routine care delivered by non-specialists. The effect of assistive technologies on patient outcomes and workforce efficiency requires study. The COVID-19 pandemic forced a rapid transition to hybrid delivery of education and training, which future research might focus on for the long-term training of the coronary artery disease workforce.

Workforce diversity

A diverse workforce with representative proportions of gender, socioeconomic class, and racial and ethnic groups leads to improved organisational performance, patient satisfaction, and patient outcomes.^{338,339} Despite these facts, cardiology has the lowest percentage of female staff of any medical specialty.^{340,341} Although under-representation of females in cardiology has been extensively documented, there are minimal global data reported on racial, ethnic, and cultural diversity. In the USA, self-reported data of ethnicity and race from numerous professional medical organisations shows low representation of diverse subgroups and Indigenous people.³⁴¹ Barriers to workforce diversity include inflexible training or compensatory measures for parental or career responsibilities, conscious and unconscious bias, and gender-based or race-based discrimination.^{340,342,343} A non-diverse cardiology workforce perpetuates the under-representation of particular groups in clinical trials and health disparities seen in women and some racial and ethnic groups, thus narrowing trial generalisability. Addressing workforce diversity is essential in improving the overall quality of cardiovascular care. Strategies and policies designed to increase cardiology workforce diversity should be implemented and tested with transparent availability of data.

The ACAD workforce in high-income settings frequently attracts health-care professionals originally from, and often trained in, low-income settings. This migration of a skilled workforce calls for root-cause evaluation and context-specific approaches to job retention. Without further research, addressing the inequalities of care will be challenging.

Health policy and public education

Population-wide health policy and education have been modelled as high-value interventions to prevent and reduce ACAD burden on a large scale, with the potential to influence lifestyle behaviours such as diet, physical activity, and tobacco use.^{107,344} These longitudinal interventions are important in managing ACAD as a preventable chronic illness and reducing resultant morbidity and mortality. The combination of policy

implementation alongside educational campaigns has been highly effective. Much can be learned, and potentially reproduced, from the substantial decline in tobacco use that followed the introduction of impactful policies (eg, smoke-free laws, health warnings on packaging, restricting youth access, and taxation policies) combined with mass media anti-smoking education campaigns.³⁴⁵ Similar policies and public education strategies should be expanded to other ACAD risk factors (panel 9). For example, better city planning policy to promote bike and walking paths could align with widespread public health messaging targeting sedentary behaviours.

In nearly all countries and regions, there is a documented epidemic of obesity, hypertension, and diabetes¹⁰ largely related to poor diet, inactivity, and an obesogenic environment. Metabolic risk begins early in life, with overweight and obesity affecting 390 million children and adolescents worldwide, and with numbers increasing in low-income and middle-income countries where malnutrition and underweight often coexist.²⁶ For example, in east, south, and southeast Asia, the increase in obesity has accelerated in children, overtaking the adult trajectory.³⁴⁶ In India, where severe underweight remains prevalent, approximately 20% of children have overweight or obesity.³⁴⁷ Once overweight and obesity has been established in early life, consequent changes in behaviour and biology are difficult to overcome. Governments in low-income and middle-income countries where malnutrition has been the focus now need to shift priorities to also combat obesity in childhood. Government policies must have a key role in combating an obesogenic environment by limiting the availability, affordability, and promotion of unhealthy foods and drinks. For example, taxation can be placed on sugar-sweetened beverages to reduce their consumption³⁴⁸ and the income used to reduce the cost of fruits and vegetables. Governments should prioritise nutritional policy that reduces overweight, obesity, and subsequent health outcomes, despite lobbying from major food and beverage corporations. Conflicts of interest for all involved parties should be declared so that policy can be brought forward despite the influence of industry.

Sustained action is needed to further reduce smoking on a global scale. Concurrently, a rapidly evolving area in

need of public education and more restrictive policy is e-cigarette use (or vaping), the use of which is expanding and overtaking rates of cigarette smoking, particularly in adolescents.³⁴⁹ Health policies are needed to restrict importation of e-cigarettes and inhaled nicotine, which often serves as a gateway to smoking tobacco, particularly for adolescents and young adults.

Public education has been integral to improving awareness and recognition of the early warning symptoms of acute coronary syndrome and the need to seek urgent care. However, as acute coronary syndrome is a sign of end-stage ACAD, public education in the contemporary era needs to focus on increasing population awareness of cardiovascular risk factors and the capacity for screening and diagnosis of early atherosclerosis. It is also necessary to improve awareness of stakeholders (eg, employers, community groups, or governments) on additional ways to prevent coronary artery disease through improved care pathways, air pollution levels, and city planning. Education campaigns can shift attitudes and build support for large-scale changes in the environment and policies on tobacco use and diet.³⁵⁰

Ascertaining which formats of public education are efficacious, cost-effective, scalable, and sustainable, as well as overcoming barriers to an individual's understanding of ACAD, is important. Digital technologies and online platforms could be used to engage a wide range of people in diverse economies. Sex and gender, race, ethnicity, education, and health literacy all affect awareness, while cultural beliefs or mistrust of organisations affect response to public education.^{351–353} Other socioeconomic factors such as basic access to health care, economic and social stability, and geographical location, particularly in low-income and middle-income countries, can present barriers to adequate public health information. Public education campaigns should incorporate different cultures and languages to ensure diversity and cultural representation, necessitating involvement of consumers to create effective and relatable messaging about ACAD.

Public education campaigns around ACAD have been disrupted by misinformation, leading to confusion and misunderstanding. Media sensationalism about common cardiovascular medications (eg, statins) undermines public health advice. Public education campaigns must recognise and respond to misinformation, adapting to the platforms that spread it. For example, public education has been limited by use of older media such as print, television, and radio, which have fewer effects on informing and changing behaviours of the children and adolescents, individuals of low education and socioeconomic status, or inhabitants of rural locations.^{354,355} As mass media evolves and new technology emerges, future ACAD public education campaigns need to adapt, using evolving online platforms to reach a wider audience. Education that uses social

Panel 9: Health policy and public education goals

- Public education needs to target the prevention of atherosclerotic coronary artery disease (ACAD) from during pregnancy, childhood, adolescence, and throughout the life course
- Governments should prioritise funding of public health strategies for ACAD and a healthy built environment
- Policy is needed to combat the global epidemic of obesity, diabetes, hypertension, and poor diet

media, videos, and gamification of information might appeal more to children and adolescents.³⁵⁶ Given that traditional ACAD risk factors begin in childhood and adolescence, public education campaigns need to start as early as possible and continue throughout the life course.

Health policy and public education strategies are often presumed to be efficacious and cost-effective due to their ability to reach large populations; however, these strategies have not been tested in the same way as other interventions. With the shift to an atheroma-centric view of ACAD, we believe that researchers should now begin to scientifically test the effect of the nature, frequency, content, and mode of delivery of health policy and public education programmes. Although current research in coronary artery disease education campaigns has relied on cross-sectional before and after self-reported awareness or behaviour change, future research methods could use big data and large-scale pragmatic cluster randomised controlled trials to look at changes in risk factor prevalence, major health outcomes, and economic benefits.³⁵⁶ Isolating the effects of health policy on risk factor prevalence and clinical outcomes is a challenge and an opportunity. One example is the improvement in hypertension control and antihypertensive prescribing noted in Canada from 1999 to 2006, which occurred after initiation of the Canadian Hypertension Education Program.³⁵⁷ Although not all improvements can be directly ascribed to the programme, improvements in hypertension diagnosis, management, control, and mortality rates were documented. Successful partnership of stakeholders such as governmental bodies, cardiovascular societies, and global organisations (eg, WHO) is necessary to enable improved reach and engagement on a global scale. Cardiovascular societies and advocacy organisations (eg, heart foundations) should use their public education campaigns to pressure governments to partner with communities, researchers, and organisations to enact and measure the effect of policy change.

Finding ways to encourage more people to participate in population-based research is a priority for inclusivity of those at risk of ACAD (panel 10). Future strategies could incorporate AI and machine learning algorithms to personalise public education based on available individual data, including imaging data showing preclinical ACAD. This approach aims to provide tailored recommendations for lifestyle modification, screening, and preventive measures. Coupled with measuring behaviour changes, these developing methods could purposefully encompass increased proportions of the population and aid in the applicability of ACAD health policy and public health interventions.

Conclusion

Refocusing and reframing the definition and discussion of coronary artery disease from late-stage ischaemia and acute coronary events to early detection of coronary artery

Panel 10: Key targets for research in health policy and public education

- Rigorously test new health policies to evaluate efficacy in reducing risk factors, burden of atherosclerotic coronary artery disease (ACAD), and improving ACAD outcomes, including a focus on cost-effectiveness
- Establish the most effective methods using digital technologies and online platforms to engage a wide range of people in diverse economies
- Find optimal ways to engage more people, particularly of diverse representation, to participate in population-based research

atheroma and prevention of advanced ACAD has the potential to save 8·7 million lives globally every year. Acute coronary syndrome events must be recognised as a failure of upstream care, missed opportunities for early intervention, and should be seen as avoidable consequences of a preventable disease.

The current definition and ICD codes for ischaemic heart disease constrain the ability to devise clinical pathways for early diagnosis, effective prevention, and cure of the disease. We argue that it is necessary to measure and define coronary atherosclerosis at a much earlier stage, when the opportunity to make an impact is greatest. By the time ischaemia and obstruction develop, prevention is no longer possible, and the effectiveness of interventions on morbidity and mortality are greatly reduced.

Coronary artery disease must be recognised across all stages of atherosclerosis, from the onset of atheroma through to end-stage disease. Throughout this Commission, we have aimed to redefine the conceptual framework of coronary artery disease—from the traditional model centred on ischaemia to a continuous disease with multiple stages throughout the life course. The disease begins with precursor features even in utero, which can develop through to childhood and adolescence, progressing as individuals age. Only after redefining coronary artery disease as ACAD can data based on this new definition be collected and used to inform future advances in health care.

Strategies must be developed to prevent the onset of atherosclerosis, diagnose the disease early, and improve the implementation of known effective strategies for those who have already developed the disease. Achieving these goals, and ensuring the delivery of global and equitable care, will require investment, training, and development of a workforce focused on early risk factor modification, diagnosis, and prevention of atherosclerosis rather than diagnosis and treatment of cardiovascular events and end-stage disease.

Research funding must be increased to match the global burden of disease, and investment must be made in the development of novel therapies that can prevent,

revert, and eradicate the disease, along with imaging methods that accurately capture low-risk to high-risk disease states.

We hope that this Commission will reach patients and the public, policy makers, international societies, research funders, researchers, and health-care providers to advocate for the stabilisation, reversal, and future elimination of ACAD as a realistic and attainable goal. Together, these stakeholders can implement the actions that will take the goals of this Commission to the next step of reducing the global burden of this disease. The allocation of funding, resources, and workforce to the research highlighted in this Commission is urgently needed to combat the consequences of this preventable disease.

Contributors

All authors contributed to the conceptualisation, design, analysis, and writing of the Commission. The Commission was prepared under the lead of RKA-L. All authors had full access to all data in the study and take responsibility for the decision to submit for publication.

Declaration of interests

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