The changing spectrum of cardiovascular diseases

Nathalie Conrad[1,2], Prof. Kazem Rahimi[2], Prof. John J. V. McMurray[3], Prof. Barbara Casadei[4]

1 Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

2 Deep Medicine, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom

3 School of Cardiovascular and Metabolic Health, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom

4 National Heart and Lung Institute, British Heart Foundation Cardiovascular Research Centre, Imperial College, London, United Kingdom

Correspondence to: Dr. Nathalie Conrad, Nathalie.conrad@kuleuven.be, +44 74 70 421 005.

Advances in cardiovascular disease prevention are often hailed as one of the major public health accomplishments of the past half-century. The progress achieved is rooted in efforts challenging the inevitability of vascular events, which led to the discovery of modifiable risk factors and systematic approaches to prevent population exposure. These prevention efforts have led to steep reductions in premature vascular mortality and morbidity in many parts of the world since the 1960s.[1–3] In recent years however, this downward trend seems to have reached a plateau or even reversed in several high-income countries.[3–6] This also appears to be true for cardiovascular morbidity, with little change in the number of individuals newly diagnosed with cardiovascular disease since the mid-2000s even when accounting for population ageing.[7] A rise in the prevalence of obesity, diabetes, and chronic kidney disease is thought to underpin these unfavourable trends.[5]

A more rarely discussed perspective on this question, is how changes in the types of cardiovascular disease presentations might impact the overall population burden and affect our approach to cardiovascular disease prevention.

A series of recent large-scale studies have brought new insights into this question by investigating long-term trends across different cardiovascular conditions.[7–14] These new studies show that overall stable trends in cardiovascular morbidity mask a changing case mix of cardiovascular disease presentations. Sustained reductions in rates of acute coronary syndromes and strokes are evident,[14–17] and contrast with either stable or rising rates of non-atherosclerotic conditions, including cardiac arrhythmias, valve diseases, and venous thromboembolism.[7–12] As a result of these new and varying trends, conditions traditionally considered the most common cardiovascular diseases, such as coronary heart disease and stroke, now account for less than half of total cardiovascular morbidity (**Figure**). By contrast, other conditions have become comparatively more common. For example, atrial fibrillation or flutter is now the most common cardiovascular problem, and venous thromboembolism and heart block now have incidence rates broadly comparable to stroke or acute coronary syndromes.[7,9,14,16,18]

The increasing rates of some of these conditions are likely due to a combination of biological and practice-related factors, the latter including improved detection with more sensitive diagnostic tests, increased awareness, correction for historic underdiagnosis, and changing definitions, as well as improved survival after atherosclerotic events resulting in patients developing additional cardiovascular conditions during their extra years of life. Regardless of the exact explanation for the observed shift, the identification of increasing numbers of individuals with these problems has important implications for health services and the overall burden of disease in the population.

What can be done now? We must reflect on current prevention strategies in the context of the changing contribution of different cardiovascular conditions. For many cardiovascular conditions, such as non-rheumatic valvular diseases or atrial fibrillation, current medical practice remains largely focused on the management of symptoms and the prevention of disease-related complications.[19,20] The latest cardiovascular disease prevention guidelines, both from American and European societies, remain largely focused on atherosclerotic diseases, and so do the risk scores used to identify high-risk individuals in clinical practice.[21,22]

More comprehensive strategies for the primary prevention of cardiovascular diseases and their consequences may need to begin with increased research efforts to investigate the mechanisms and

potentially modifiable risk factors of non-atherosclerotic heart diseases and to identify effective interventions to modify these.

The study of harmful exposures and potential mechanisms across the spectrum of cardiovascular presentations, will likely encompass well-established cardiovascular markers as well as new ones. Many of the modifiable risk factors for atherosclerotic heart disease - including blood pressure, smoking, or physical inactivity - are also implicated in a range of other cardiovascular conditions, yet their exact role, effect size, and interactions between them, are less well established.[23–25] Differential effects have also been reported, including for example inverse risk associations between cholesterol and atrial fibrillation, blood pressure and venous thromboembolism, or between diabetes and aortic aneurysm.[25–27] These inverse associations deserve to be investigated in more detail, and, if confirmed, their implications more fully understood.

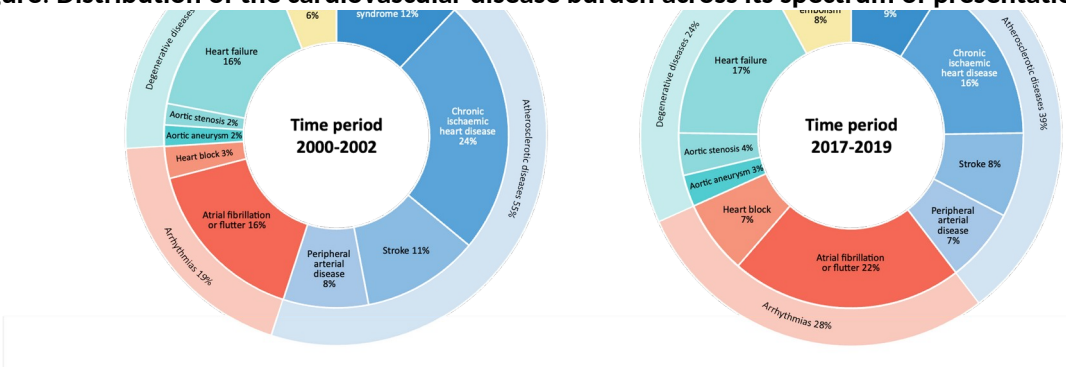
In addition to well-recognised risk factors for vascular disease, more recently discovered ones (including inflammation, immune-mediated conditions, cell senescence, or cancer therapies) have also been shown to contribute to a broad range of cardiovascular outcomes beyond atherosclerosis.[28–30] So far, the design of effective interventions targeting these novel risk factors has lagged behind those for conventional risk factors and deserves dedicated research and implementation efforts.

Several pharmacological interventions have also shown promising advances towards that aim, with both existing and new drug therapies showing potential in the prevention of non-atherosclerotic heart disease in recent years. For example, approaches to prevent or slow the progression of aortic stenosis are under investigation, with novel biomarkers and/or therapeutic targets, such as lipoprotein(a), vitamin K, or phosphate, showing potential and trials ongoing.[31] Similarly, atrial fibrillation may not be an inevitable consequence of ageing and primary prevention may be possible through treatments such as renin-angiotensin or aldosterone inhibition.[32,33] Likewise, existing therapies such as lipid- or blood-pressure-lowering therapies, have a role in reducing the development of conditions such as heart failure, and aortic aneurysms.[34,35] And novel agents such as SGLT2 inhibitors and GLP-1 receptor agonists have shown pleiotropic effects that may contribute to the prevention of heart failure, arrhythmias or valve disease, although the mechanisms by which this may be achieved are still under investigation.[36,37]

Broadening our approach to cardiovascular disease prevention will likely encompass a shift in perspective in many other ways too – including personalised and longer-term risk prognostication to capture a wider spectrum of events with an earlier start of targeted prevention. Future risk equations will likely, dynamically and precisely, assess an individual's risk of developing individual cardiovascular outcomes and recommend the most appropriate preventive treatment regimen. Risk collaboratives from European and American heart societies have already started considering a broader range of risk factors and outcomes, in a variety of populations,[38,39] and more initiatives will likely follow.

Recognition of the evolving spectrum of cardiovascular disease will hopefully provide impetus for increased research efforts in the prevention of non-atherosclerotic diseases, the development of risk scores considering and balancing risks across a series of cardiovascular outcomes, clinical trials to test novel interventions or explore broader indications of existing ones, and, ultimately, evidence-based prevention guidelines covering the full range of conditions increasingly contributing to the contemporary societal burden of cardiovascular disease.

Figure: Distribution of the cardiovascular disease burden across its spectrum of presentations



The proportion of newly diagnosed cardiovascular disease in the UK, by individual condition, in the years 2000-2002 and over the years 2017-2019. Proportions were calculated by dividing the age-sex-standardized incidence rate for the condition of interest by the sum of the age-sex-standardized incidence rates across all 10 conditions. Incidence rates, by condition and time period, were extracted from Conrad et al, BMJ, 2024. Conditions were categorized to reflect their most common aetiology, even though some may present different subtypes or result from a combination of causes. Peripheral artery disease diagnoses include presentations with ischemic or unspecified aetiologies. Stroke includes ischemic, haemorrhagic, and unspecified stroke. Heart block refers to second and third-degree heart block. Venous thromboembolism refers to deep vein thrombosis and pulmonary embolism.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Contributions

All authors - NC, KR, JJV, and BC - contributed to interpreting the data and literature, drafting the manuscript and the revisions. All authors gave final approval of the version to be published and accept responsibility to submit the manuscript for publication.

Declarations of interest

NC is funded by KU Leuven, a Wellcome Trust Career Development Award (318034/Z/24/Z), and the Research Foundation Flanders (12ZU922N).

KR is funded by grants from the National Institute for Health Research (NIHR304997), the Medical Research Council (MR/Y030419/1), the British Heart Foundation (FS/PhD/22/29321, FS/PhD/21/29110, FS/PhD/25/29632), the European Union (101080430), Roche (R94776/CN002), and Novo Nordisk Oxford Big Data Partnership; declares personal royalties or licenses from Lucem Health, personal speaker honoraria from Radcliffe Cardiology, personal honoraria for his role as Editor-in-Chief of Heart, as well as payments made to his institution for his participation on a Data Safety Monitoring Board or Advisory Board of the Medtronic Advisory Board for Renal Denervation.

JJVM is supported by grants or contracts paid to his institution from the British Heart Foundation, the National Institute for Health – National Heart Lung and Blood Institute (NIH-NHLBI), Alnylam Pharmaceuticals, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, and Roche; declares personal consulting fees from Alnylam Pharmaceuticals, AnaCardio, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, River BioMedics, Biohaven Pharmaceuticals, Chugai Pharmaceuticals, Protherics Medicine Developments Ltd., and DalCor Pharmaceuticals; Personal lecture fees from Medical and Surgical Knowledge, Centrix Healthcare, Emcure Pharmaceuticals, Eris Lifesciences, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals, Lupin Pharmaceuticals, Medscape/Heart.Org., ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, Translational Medicine Academy, Regeneron, MCI India, Hilton Pharmaceuticals, IMEDIC Pharmaceuticals Micro Labs Ltd., At the Limits Ltd., ARMGO Pharmaceuticals; as well as personal payments for his participation on a Data Safety Monitoring Board or Advisory Board of WCG Clinical Services and his role as Director of Global Clinical Trial Partners.

BC is funded by a British Heart Foundation Chair (CH/SV/22/280022) and Programme Grant (RG/18/6/33576) and by the Oxford NIHR Biomedical Research Centre. She has been supported in kind from iRhythm (ECG monitors) for a mail-based randomised controlled trial of remote AF screening in England (AMALFI).

The views expressed are those of the authors and not necessarily those of the funders.

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