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Rising to the challenge of cardio-renal-metabolic disease in the 21st century: Translating evidence into best clinical practice to prevent and manage atherosclerosis

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A B S T R A C T

Rising rates of obesity-associated cardiometabolic disorders allied to ageing populations are driving increases in cardiovascular morbidity and mortality. These adverse trends present challenges for healthcare systems that are struggling to prevent and manage the burgeoning cardiometabolic nexus of multiple long-term conditions. While potent new medications and non-pharmacological interventions have ushered in a promising new therapeutic era, translating clinical trial data to real-world clinical practice is often suboptimal. Postgraduate training and narrowly focused clinical specialisations reflect the traditional siloed approach to managing cardiovascular-metabolic disease that appears increasingly outmoded in the 21st century. It is our contention that greater inter-disciplinary collaboration allied to increased awareness of the continuum of cardiometabolic disease should enable clinicians to address this global public health threat more effectively. With this aim in mind, we have established an *International Cardiometabolic Working Group*. It is our hope to stimulate the interest of clinicians and clinical researchers across a range of medical specialties who share the vision of better care for people living with cardiometabolic diseases.

1. Introduction

The 21st century is witnessing progressive increases in cardiometabolic multiple long-term conditions (MLTCs, also known as multimorbidity) [1,2]. The commonest chronic conditions from the age of 20 years are dominated by non-communicable obesity-associated disorders including hypertension, diabetes, and cardiovascular disease [3]. Cardiometabolic disorders (Table), which share common pathophysiology and often cluster in affected individuals, conspire to elevate the risk of atherosclerotic cardiovascular disease (ASCVD) [4,5]. In recent years, a complex multi-directional pathological nexus of cardiovascular-kidney-metabolic disease has been recognized [6]. Within this disease continuum a multiplicity of pathological cardio-kidney, obesity-metabolic-kidney, and kidney-vascular associations exist [7,8]. The metabolic-vascular nexus extends to include metabolic liver disease, which is highly prevalent among people living with obesity and/or type 2 diabetes and is associated with higher rates of both ASCVD and CKD [9].

2. Trends in cardiometabolic disease

Epidemiology and pathophysiology must be considered in any holistic model of cardiovascular risk assessment [10]. In the USA, mortality attributable to ASCVD has been declining in response to public health initiatives, e.g., reductions in tobacco use and improved risk factor control [11]. However, the rate of decline has been abated and may even be showing signs of reversal in some population groups [11]. Moreover, global cardiovascular deaths increased from 12.4 million in 1990 to 19.8 million in 2022 [12]. This rise is considered to reflect global population growth and ageing with contributions from potentially preventable metabolic, environmental, and behavioural factors [12,13]. Progressively more people are living with cardiometabolic MLTCs that are closely associated with rising rates of obesity [13].

A recent report from the NCD Risk Factor Collaboration (NCD-RisC)

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in collaboration with the World Health Organization (WHO) noted that the total number of children, adolescents and adults worldwide living with obesity has now surpassed one billion [14]. Associated increases in the prevalence of associated cardiometabolic disorders are projected which will disproportionately affect racial and ethnic minorities, as well as less affluent communities in high-income countries [3,15]. Recent data suggest in excess of 500 million adults, i.e., 1 in 10, are living with diabetes [16]. Against this background, a recent report by the UK Health Foundation projected that the prevalence of major chronic illnesses in England, including diabetes and kidney disease, will increase by more than one-third by 2040 [17]. The projection is based on trends in risk factors including smoking, poor diet, inadequate physical activity, alcohol consumption and an ageing population. The authors of the report call for 'careful planning, investment and changes in how care is delivered'. While a comprehensive societal approach is required at the level of health care provision, a progressively greater burden of ill-health concomitantly mandates a multi-factorial approach to modifiable cardiometabolic risk [18].

3. Cardiovascular-renal-metabolic nexus of disease

Beyond type 2 diabetes, the list of disease states closely associated with excess total and ectopic fat extends to hypertension, CKD, dyslipidaemia, metabolic dysfunction-associated steatotic liver disease (MASLD), polycystic ovarian syndrome, obstructive sleep apnoea, heart failure, and venous thromboembolism [19,20]. Of particular concern from a public health standpoint is the rising burden of cardiometabolic disease associated with the global epidemic of obesity in youth [21] which carries particularly high risks of vascular complications [22].

4. A new era of therapeutics for cardiometabolic disorders

A comprehensive approach to the prevention and management of cardiometabolic disease is required. Clinical trials have demonstrated that development of type 2 diabetes in high-risk individuals can be averted by safe and effective nonpharmacological lifestyle and pharmacological measures [23,24]. For individuals with established cardiometabolic disease it is now possible to target a plurality of risk factors simultaneously through pharmacotherapeutic advances including sodium-glucose co-transporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists. In subjects with type 2 diabetes, SGLT-2 inhibitors improve glycaemic control while lowering blood pressure, reducing adiposity and providing cardio-renal protection [25]. The cardiometabolic benefits of SGLT-2 inhibitors extend beyond diabetes to high-risk individuals with heart failure or renal disease [26]. The unprecedented range of clinical benefits of injectable incretin-based medications have generated huge public interest, albeit while fuelling issues of limited supply and equity of access [27]. Beyond reducing adiposity, GLP-1 receptor agonists reduce ASCVD events, notably stroke, in people with type 2 diabetes [28]. The latter observation is noteworthy since neurologic disorders such as stroke are now the leading cause of disability-adjusted life-years (DALYs) in Asia [29]. However, some evidence from real-world diabetes practice suggests that the benefits of these agents may be lower than that reported in clinical trials [30]. Data on the class continue to accrue, with recent confirmation that the GLP-1 receptor agonist semaglutide reduces cardiovascular events in adults living with obesity and ASCVD in the absence of diabetes [31]. GLP-1 receptor agonists have also been shown to favourably modify the natural history of CKD [32]. The potential clinical applications of incretin-based drugs, possibly mediated via anti-inflammatory actions, extend to liver disease, sleep apnoea, and neurodegenerative conditions [33]. This awareness of modifiable cardiovascular risks allied to therapeutics that cut across multiple diseases needs to bridge effectively across clinical specialties.

Novel cholesterol-lowering agents and mineralocorticoid receptor antagonists form part of the increasingly multimodal therapeutic approach to cardiometabolic disease, but are costly [34]. More effective management of cardiometabolic disorders has the potential to reduce aspects of chronic morbidity and healthcare costs while extending lifespan [35]. Studies show that newer cardioprotective agents continue to be under-used particularly in those likely to benefit the most, even in centres of excellence [36–38]. Multiple barriers have been identified to the use of GLP-1 receptor agonists and other novel therapies including inconsistencies in guideline recommendations, safety concerns, patient characteristics, and concerns about costs [39,40]. Potential solutions have been proposed to overcome the hurdles to greater use of medications with proven cardioprotective properties [39]. Novel technologies such as machine learning have the potential to ensure closer alignment of clinical practice with evidence-based management while promoting precision medicine [41,42].

5. Translating evidence into clinical practice

As discussed, there has been an unprecedented expansion of disease-modifying pharmacotherapeutics that hold the promise of improving clinical outcomes for cardio-renal-metabolic disorders. To date, however, translation of these discoveries into clinical practice has been slow, incomplete, and inequitable [43]. The translation of evidence into practice may be best achieved through early and complete risk assessment (staging) and targeted interventions. Care should have its foundations in non-pharmacological lifestyle advice supplemented, where appropriate, by judicious use of pharmacological and/or metabolic/bariatric surgical interventions. Optimisation and coordination of the convoluted management of cardiometabolic disorders should improve clinical outcomes. Healthcare expenditure can be expected to be reduced by curtailing adverse ASCVD events, minimizing redundant testing via improved disease staging and reducing drug-drug interactions. To recapitulate, themes that unite clinicians supporting this approach are (a) the high and increasing global prevalence of cardiometabolic diseases (b) the burden of multiple non-communicable metabolic and vascular diseases (c) the demonstration of the capacity of intentional weight reduction and certain new drugs to ameliorate risk factors and improve multiple clinical outcomes as well as quality of life (d) the need to lessen the burden on patients attending multiple clinics.

6. Practical options to improve clinical care of cardiometabolic diseases

The pathological continuum of cardiometabolic disorders generates an impetus for clinicians to work together to reduce the burden of disease. Opportunities exist to improve coordination between primary care, cardiology, lipid, diabetes, renal, and hepatic services [44]. Local initiatives which promote team-based comprehensive care for patients with cardiometabolic disorders have been described; however, these generally remain isolated examples of best practice [45]. At the level of service provision, the traditional partitioning clinical services remains firmly entrenched with current health care systems designed around single-disease models. Accumulating evidence that this siloed approach to care is no longer fit for purpose has prompted proposals for the creation of multidisciplinary clinical teams [46].

In the light of rapidly evolving evidence, it is our contention that innovative models of clinical care are required to address the burgeoning global public health threat posed by cardiometabolic disorders (see Table 1). A recent international educational event at the Royal Society of Medicine in London confirmed a groundswell of support from cardiologists to endocrinologists, lipidologists, angiologists, renal physicians, and primary care clinicians for more effective and coordinated care of patients with cardiometabolic MLTCs. The event led to the creation of the *International Cardiometabolic Working Group*, an interdisciplinary coalition of clinicians and researchers with a shared vision. In pursuit of better care for people living with cardiometabolic MLTCs, we and others have made the case for a new focus on more comprehensive training in

Table 1
Definition of cardiometabolic disease.

For the purposes of this article[a] the major components of cardiometabolic disease include: • Excess adiposity (especially central and including ectopic lipid deposition) • Dyslipidaemia/hypertension management • Type 2 diabetes • Chronic kidney disease (reduced glomerular filtration rate, or albuminuria) • Atherosclerotic cardiovascular disease (ASCVD) • Heart failure (reduced and preserved ejection fraction) • Metabolic dysfunction-associated steatotic liver disease (MASLD) Other relevant disorders include female hyperandrogenism, male hypogonadism, and common (e.g., hypothyroidism) and rare (e.g., acromegaly) endocrine disorders that may increase the risk of cardiovascular disease. Additional factors that serve to exacerbate the health risks associated with cardiometabolic disease include unhealthy nutrition, tobacco use, and others such as air pollution, and global warming.

[a] The authors acknowledge potential limitations of this term which, nonetheless, has the advantage of being widely recognized in clinical practice.

Table 2
Postgraduate opportunities for training in cardiometabolic medicine.

Residency[a]
Fellowship[a]
Postgraduate courses in cardiometabolic medicine[b]
Local accreditation of clinical practices by an academic institution, e.g., Cardiometabolic Center Alliance https://cardiometabolicalliance.org
Certification[b] in subspecialty of cardiometabolic medicine
Board certification in cardiometabolic and lifestyle medicine by professional societies

[a] Or non-US equivalent.
[b] Preferably attracting endorsement by national and supra-national specialist societies. For example, the 2024 Postgraduate Course in Cardiometabolic Medicine endorsed by the European Society for Cardiology and European Atherosclerosis Society. https://www.zhh.ch/en/cardiometabolic-medicine.

relevant interrelated aspects of vascular-metabolic medicine [47–51]. This approach would involve the acquisition of expertise in the diagnosis and management of excess adiposity, hyperglycaemia, hypertension and dyslipidaemia as core features of cardiometabolic disorders. Greater awareness of initiators and promoters of non-communicable cardiometabolic diseases, e.g., the role of nutrition, could be provided during undergraduate medical education [52]. At postgraduate level, physicians seeking to expand their competence in cardiovascular-metabolic medicine could acquire knowledge and skills through rotations through cardiometabolic medicine during core residency and specialist training (Table 2) [53].

7. Potential hurdles to implementing comprehensive care for cardiometabolic disorders

We do not underestimate the barriers to improving the identification and management of modifiable cardiometabolic risk factors. How a new clinical speciality might be developed and accredited will vary between healthcare systems which may have distinctive existing models of care. In the USA, for example, preventive cardiology is more established as a speciality than in some other countries, such as the UK [54]. Of relevance to cardiovascular disease prevention, specific concerns have been expressed in the UK about the current absence of a path to accreditation in clinical lipidology [55]. A rigorous postgraduate education programme would include key components to equip clinicians to bridge across existing clinical specialties. The curriculum would include epidemiology, biostatistics (including evidence-based medicine), behavioural science and psychology alongside core knowledge of cardiology, angiology[1] and lipid metabolism (*see Graphical Abstract*). Clinical rotations through specialties such as nephrology and hepatology would expand and aid training in cardiometabolic diseases. Consideration would need to be given to the needs of children and older people many of whom are managed in primary care. Choices may be required as to which elements of training should be included. A case in point is reproductive endocrinology: male hypogonadism and female hyperandrogenism are associated with adverse cardiometabolic risk profiles yet remain underappreciated in terms of deleterious effects on clinical outcomes [19]. The metabolic-cardiovascular implications of mental health issues and the emerging subspecialty of cardio-oncology also merit greater attention [56,57].

The cardiometabolic clinical specialist should have the requisite knowledge and skills to coordinate management as patients transition between specialties and across the primary-secondary care interface. An invigorated focus on averting the development of cardiometabolic disease should consider not only primary prevention of ASCVD but also primordial prevention, i.e., avoiding the onset of modifiable risk factors for atherosclerosis [58].

Future work should include evaluation of new integrated models of care for people with cardiometabolic conditions. The prevalence of MLTCs and the variety of different combinations of diseases will in future make it increasingly difficult to deliver comprehensive care. In many countries, multi-disciplinary primary care teams are the gatekeepers of care who accrue in-depth longitudinal knowledge about their patients. Integrated care models for chronic diseases will need to focus care precisely to individuals with cardiometabolic MLTCs. There is a pressing need for healthcare providers and policy makers to generate evidence on high quality cost-effective alternatives that can achieve better patient outcomes while maintaining continuity of care [59]. Care models need to be sensitive to cultural and ethnic issues.

Multidisciplinary teams that could include nurse clinicians, nutritionists, physiotherapists, exercise trainers, prescribing pharmacists and physician associates would help create a sustainable clinical cardiometabolic service in the face of medical workforce limitations. There are several reported examples in diabetes and cardiovascular disease where such models of care have been shown to be cost-effective [60–62]. In parallel, as an interim phase while entrants undergo comprehensive training, clinicians could gain valuable insights through targeted learning via accredited educational modules [63]. An apposite example of online education that provides the fundamentals of this learning is the Cardiometabolic Health Congress Certificate Program in Cardiometabolic Medicine (https://www.cardiometabolichealth.org/professional-education/cmhc-foundations-of-cardiometabolic-health-certificate-course). Such an approach could fast track expansion of

[1] In some countries.

the pool of clinicians with expertise in managing multiple cardiometabolic conditions. A concerted multi-layered effort may be required involving clinicians and patient advocacy groups alongside national and international professional medical societies to make this vision a reality. Ensuring that care is equitable, accessible and patient-centric is essential. Aligned with this holistic approach is the potential for real world biomarker evidence to inform the development of new therapies and support precision medicine [19].

We invite clinicians and researchers from across the spectrum of relevant medical specialties who share our vision to consider contributing to the *International Cardiometabolic Working Group*. Expressions of interest and thoughts about how we can collectively advance the the aim of better care will be gratefully received at andrew.krentz@kcl.ac.uk.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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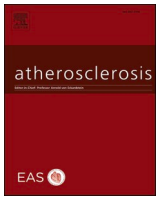

Corrigendum to "Rising to the challenge of cardio-renal-metabolic disease in the 21st century: Translating evidence into best clinical practice to prevent and manage atherosclerosis" [Atherosclerosis, Vol 396, (September 2024), 118528]

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