Towards a new order in cardiovascular medicine: re-engineering through global collaboration

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Introduction

The financial ‘meltdown’ that began in 2008 dramatically underscores the need for significant global changes in our fundamental institutions and interactions, and the field of medicine is no exception. Global ‘flattening’ encompassed by modern information and communication networks has increased our awareness of major health disparities at almost every level. At the same time, however, we have unprecedented access to knowledge that allows people to live longer and healthier lives. The field of cardiovascular medicine is particularly illustrative of this paradox. Despite decades of unprecedented improvements in prevention, treatment, and outcomes, cardiovascular medicine now faces a major global upswing in disease impact, driven by global demographic and cultural trends. Moreover, given the discipline’s emphasis on technological and pharmacological treatments, it accounts for a major portion of healthcare costs.

Outstanding emerging examples of local, national, and global collaboration among cardiovascular practitioners, however, suggest rapidly growing awareness of these challenges, as well as new opportunities for addressing them.1 In this article, we argue that leaders in the field of cardiovascular medicine have a fundamental responsibility to create, develop, and implement a global knowledge network that exemplifies the learning health system of the future.

The global impact of cardiovascular disease

Numerous studies document the effects of cardiovascular disease (CVD), as well as the impact of its treatment and prevention, on rates of death and disability among the world’s population. As life expectancies increase globally, the prevalence of ischaemic heart disease and heart failure will continue to grow even as age-specific risk drops due to application of existing measures for treatment and prevention.2,3 New and striking increases in obesity and diabetes mellitus threaten to compound the effects of age, creating a dramatic surge in CVD prevalence and potentially offsetting gains achieved through reductions in smoking and by the use of effective treatments aimed at lowering lipid levels and blood pressure. Less well appreciated is the continuing significant impact of congenital heart disease, which affects at least 1% of people worldwide. Accordingly, stemming the tide of CVD will become (or already is) a priority for most countries and their respective governments.

Heterogeneous impact at every level

Cardiovascular disease is increasingly a problem of the economically and socially disadvantaged. On the global stage, the vast bulk of the coming increase in CVD is expected to occur in low- and middle-income countries that lack awareness of or access to effective prevention and treatment measures. In this regard, the segmentation of populations by stage of evolution with regard to overall health, first articulated by Abdel Omran,4 has proved instructive (Table 1).5 In Stage I (dominated by diseases of pestilence and famine), rheumatic heart disease and nutritional cardiomyopathy are the leading cardiovascular problems. In Stage II, in which economic and cultural development reduce the impact of pandemics, hypertension and stroke become more important. In Stage III, as life expectancy increases, chronic
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Life expectancy, years</th>
<th>Dominant form of CVD</th>
<th>% deaths attributable to CVD</th>
<th>% world's population at this stage</th>
<th>Regions affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: pestilence and famine</td>
<td>Malnutrition and infectious diseases predominate</td>
<td>35</td>
<td>Rheumatic heart disease, cardiomyopathy caused by infection and malnutrition</td>
<td>5–10</td>
<td>11</td>
<td>Sub-Saharan Africa; parts of all regions except for high-income regions</td>
</tr>
<tr>
<td>Stage II: Receding pandemics</td>
<td>Improved nutrition and public health leads to increase in chronic diseases, hypertension</td>
<td>50</td>
<td>Rheumatic valvular disease, ischaemic heart disease, haemorrhagic stroke</td>
<td>15–35</td>
<td>38</td>
<td>South Asia; southern East Asia and Pacific; parts of Latin America and the Caribbean</td>
</tr>
<tr>
<td>Stage III: degenerative and human-created diseases</td>
<td>Increased fat and caloric intake; widespread tobacco use; chronic disease deaths exceed mortality from infections and malnutrition</td>
<td>60</td>
<td>Ischaemic heart disease; stroke (ischaemic and haemorrhagic)</td>
<td>&gt;50</td>
<td>35</td>
<td>Europe and Central Asia; northern East Asia and the Pacific; Latin America and the Caribbean; Middle East and North Africa; urban parts of low-income countries, especially India</td>
</tr>
<tr>
<td>Stage IV: delayed degenerative diseases</td>
<td>CVD and cancer are leading causes of morbidity and mortality; prevention and treatment avoids death and delays onset; age-adjusted CVD declines</td>
<td>&gt;70</td>
<td>Ischaemic heart disease; stroke (ischaemic and haemorrhagic); congestive heart failure</td>
<td>&lt;50</td>
<td>15</td>
<td>High-income countries; parts of Latin America and the Caribbean</td>
</tr>
</tbody>
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CVD, cardiovascular disease.
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diseases—atherosclerosis, obesity, and diabetes mellitus—emerge as leading causes of death and disability. In Stage IV, these long-term problems strike at increasing age while the number of older people rises, thereby increasing the prevalence of chronic disease even as age-specific incidence decreases. Economic progress in the past several decades has lifted numerous countries (and populations within countries) beyond Stages I and II and into Stages III and IV. Recently, it has become clear that some societies devolve into what has been termed ‘Stage V’, in which societal structures disintegrate, leading to the emergence of health problems such as alcohol and drug abuse. We suggest that an alternative Stage V would be the progressive reduction in CVD event rates through aggressive societal approaches to prevention such as those used in Scandinavia, where CVD event rates have dropped significantly in the wake of successful attempts to lower blood pressure and cholesterol levels and dramatically reduce cigarette smoking.

This phenomenon of heterogeneity in disease prevalence and outcomes can be charted at the national level and among countries that share a general economic stratum. It is also interesting that the different stages, previously observed at the national level, can be seen within regions and even cities. Murray et al. have written eloquently about the ‘Eight Americas’, in which clear patterns of distinct variability in longevity and health status emerge as a function of age and ethnicity. Within the United States, there are major regional differences in cardiovascular mortality and morbidity, with the highest rates in the South and parts of the Midwest, and the lowest in several other Midwestern states and in the mountain states of the West. Likewise, in Europe, major differences in disease prevalence can be seen among countries. These differences appear to be due to a mix of economic, educational, and environmental factors, although much work remains to be done to elucidate this issue. The arrival of fine-grained geospatial-temporal mapping (i.e., geographical information systems [GIS]) now allows us to visualize differences at the level of individual neighbourhoods. Figure 1 demonstrates the heterogeneity of CVD in local, national, and international terms. Figure 1A shows that within Durham County, NC (the home of Duke University), a distinct pattern of excessive CVD can be found in neighbourhoods that are less affluent and where levels of education are on average lower. These data, although transformed to prevent identification of individuals, nevertheless convey the salient point: CVD is not randomly distributed in populations, and we can now examine these spatial and environmental distributions at a very high degree of resolution. Figure 1B illustrates the variability of CVD prevalence by state in the United States, and Figure 1C shows variability among European countries. These issues, then, are common to all CVD specialists, whether they work in the wealthiest or least economically developed nations.

Thus, in the face of a heterogeneous and complex health issue of global extent, we propose the implementation of three transformative tools: quality systems, new approaches to clinical epidemiology, and information technology (IT) and informatics.

Harnessing the cycle of quality

The growth of the global CVD knowledge base has fostered a working model capable of improving clinical outcomes at all of the levels discussed earlier. As diagnostic and therapeutic approaches and technologies are developed, they undergo a series of evaluations, beginning with small proof-of-concept studies before evolving into larger-phase clinical trials. These studies in turn inform an understanding of the balance of therapeutic benefits and risks and are ultimately reflected in clinical practice guidelines, which are vested in professional societies such as the American Heart Association, European Society of Cardiology, and American College of Cardiology, or governmental bodies such as the National Boards of Health and Welfare, the National Institute for Clinical Effectiveness, and the Cochrane Institutes. Where definitive evidence exists, clinical practice guidelines can be distilled into performance measures that define actions of providers, practices, hospitals, and systems as beneficial or detrimental.

Performance measures are the underpinning of quality assessment, often incorporating an element of public reporting or differential reimbursement for quality. This measurement of practices and outcomes through registries, electronic health records, and personal health records enables a cycle of continuous learning and feedback. If this cycle of knowledge generation, integration, and feedback is to work on the grand scale now possible, the entire spectrum of providers as well as the public must learn to regard formal evaluation of decision-making, elucidation, and quantification of uncertainty, and contribution to scientific and clinical knowledge as routine aspects of interacting with the health system. The challenges of fostering probabilistic thinking in decision-making are well documented throughout society (including among physicians), but informed assessment of the balance of risk and benefit is critical to implementing research findings in practice. Equally important is widespread access to electronic information, given the sheer volume of rapidly accumulating research. While the paradigm for high-technology specialty care is relatively straightforward, implementing effective outpatient prevention will require continuous learning among patients, family members, and providers, including community health workers, at all levels of specialty expertise. However, linking fragmented parts of health care, such as transitions from emergency medical services to hospitals, or hospital discharges to outpatient clinics, provides a significant opportunity to improve care delivery.

As attention has increasingly focused on quality, some have mistakenly seen technological improvement and public health as diametrically opposed. Instead, effective research networks can guide technological development and implementation more effectively, so that a novel technology can be used appropriately when it provides significant benefit and eschewed when it provides the same or worse outcomes at a higher cost. At the same time, relatively simple strategies such as the cardiovascular polypill may offer a low-cost alternative means for economically disadvantaged populations to enjoy longer, higher-quality lives even when access to costly new technology is limited. In addition, the capacity of wireless technologies to provide information and monitoring of therapy at a very low cost provides a fascinating opportunity to use new technology to lower costs.

Examples of success in using research findings to drive quality improvement abound. In the field of prevention, the combination of risk factor improvements and primary and secondary prevention accounted for 67% of the reduction in cardiovascular mortality in the United States from 1980 to 2000. The INTERHEART...
demonstrated that a common set of risk factors account for a large proportion of risk of myocardial infarction in multiple countries. More recently, attention has focused on the high rate of hospital re-admissions after myocardial infarction and acute heart failure admissions in both the United States and Europe. Application of quality cycles will undoubtedly reduce these unacceptably high rates.

**Redefining clinical epidemiology**

Just as we are beginning to refine our general model of learning in the practice of medicine, a revolution in the understanding of the biology of health and disease is under way. In the coming decade, we will likely be able to stratify populations who appear to have the same risk factors or diseases into multiple subpopulations marked by differing risks of death and disability and differing responses to therapies. If we are to harness new biomedical science for the maximum benefit of our patients, we must merge disparate fields into a coherent whole (Table 2). Clinical epidemiology will evolve into a much more sophisticated observational science: biobanking will improve in quality, efficiency, and usability; and new technologies will be applied to systems biology, including measurement of genetic polymorphisms, the expression of those genes in tissues and cells, the proteomic composition of fluids, and the metabolome, consisting of a limited number of molecules that carry out the body’s metabolic activity, now characterize into distinct patterns. These evolving disciplines will provide a new understanding of factors defining differential natural history and response to treatment, ultimately serving as the basis for individually tailored treatment as a new paradigm in health care. While the biological disciplines will increasingly define the host response and the biological basis for intervention, social and environmental scientists must be intimately involved with defining interventions capable of improving the external factors that can change the risk of CVD and subsequently affect outcomes.

**The essential role of informatics and information technology**

Quality systems and the new clinical epidemiology depend on broad capabilities in informatics and information technology. We see this exemplified in the complex interplay of three basic types of health records: electronic health records owned by the practice or system providing care; personal health records owned by patients and families; and disease registries maintained by professional groups, governments, or health systems. Each has advantages and limitations.

Electronic health records will be essential for physicians, other providers, group practices, networks, hospitals, and health systems to share critical information across the patient care, organizational, and financial domains. Personal health records allow patients to involve different providers and health systems in their care and decision-making processes without being hindered by proprietary issues across provider entities. Indeed, major technology firms such as Google and Microsoft are developing personal health records that can be deployed across international boundaries. Disease registries can collect highly structured information that fuels insight into effective clinical practices: this circumvents the uncertainty that accompanies records designed for individual practitioners or patients. It will however be critical to weave these various records into a cohesive fabric, dubbed the ‘learning health system’ by the U.S. Institute of Medicine. In addition, these databases ideally should be integrated with biobanks at different stages of the disease process to provide information that will support both the individual patient’s treatment, as well as future research. In the traditional system, each patient encounter produces a transactional record specific to that encounter, while a separate (but partially overlapping) system gathers aggregate data about populations or cohorts entered into trials or observational studies. In contrast, in a learning health system, providers, patients, and administrators understand that the capture of practice information provides critical knowledge that in aggregate can be used to improve decision support, ultimately benefiting both the individual as well as future patients.

Clearly, managing privacy issues and overcoming public concern about unique patient identifiers will be critical to the success of the learning health system. If each person had a unique identifier, medical information could flow much more easily to the point of care, helping to prevent errors. Data could also flow directly to research repositories avoiding the need for expensive and burdensome personal contacts to gather routine information as part of clinical trials. However, people understandably require assurance that systematic failsafes are in place and can prevent medical information from being inappropriately accessed or otherwise misused.

| **Table 2** Challenges and opportunities facing cardiovascular medicine, and strategies for creating solutions that exemplify a learning health system |
|---|---|---|
| **The issue** | **The opportunity** | **The strategy** |
| Lack of definitive evidence to guide care | New knowledge generation | Continuous learning/quality care |
| Disease heterogeneity | New approaches to epidemiology | Novel intervention/new informatics approaches |
| Inadequate funding | Novel partnerships | Governments, industry, and foundations transcending conventional geographic and organization boundaries |
| Paucity of new leadership | Program development | Social networking/academic ‘Facebook’ |
**Funding strategies and partnerships**

Because CVD knows no geographic boundaries, we must combat it with an equally non-territorial approach. Multidimensional partnerships that combine intelligent information systems and basic human interactions are particularly needed. The professional cardiovascular societies have made a good start through joint scientific meetings, knowledge sharing, and collaborative efforts aimed at developing care guidelines and standardizing definitions, such as those embodied in the joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction.\(^2^3\) The multinational clinical trials of novel therapies, such as those undertaken by the Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (VIGOUR) Group and similar academic trialists’ networks, have over the last 20 years helped researchers collaborate across borders. Nonetheless, there remains a lack of understanding (and an accompanying lack of support) for the importance of these global networks in addressing global health issues. It is thus increasingly important that funding for research and education include integrated government, research foundation, and industry sources that transcend national boundaries.

The communication system for preventing and treating CVD should be built around knowledge repositories and biobanks. Most health systems and several countries are now building major data repositories that include key health data for populations, defined either by geographical location or by where they receive organized health care. By linking together these data sources and biobanks to enable quality improvement, disparities can be reduced and the whole system can be moved toward reducing death and disability from CVD.

**Fostering and mentoring the next generation**

Together with the funding of research and broad education, the development of future practitioners and leaders in cardiovascular medicine is a critical priority requiring the attention and creative energy of current leaders. Presently, cardiovascular training programs emphasize technical expertise with the vast technological armamentarium available to specialists. The knowledge needed to apply these tools is substantial, so the general approach is understandable, but we must somehow develop a parallel educational approach to prepare cardiovascular specialists for this new environment, in which understanding information and decision-making processes will prove critical to an informed use of ever-expanding technological capabilities.

In addition to the broad training of all practitioners, we must also develop a tier of future leaders who can guide these powerful approaches to more effective applications of current knowledge and spark the new ideas needed to prevent and treat the worldwide CVD epidemic. Given the global reach of the cardiovascular community, simply keeping up with the complex communications that occur within specialty areas can be daunting. One major unmet need is a ‘Facebook-like’ social networking application for cardiovascular medicine capable of linking both current and future leaders. Such a network would help foster the development of skills and connections needed for practitioners to advance and would help efface the economic, physical, and geopolitical barriers that have hindered communication and collaboration in the past. This approach will be especially critical in emerging economies, where the impact of CVD will be most profound and the academic and practice infrastructure is least developed.

**Summary**

Cardiovascular disease is a major worldwide health threat, and the need for prevention and treatment cannot be met solely by specialists, or even by specialty-trained teams that extend beyond the limited number of physicians. While cardiovascular specialists should strive to provide high-quality, technologically sophisticated specialty care and seek to develop our academic and practice progeny in a carefully orchestrated, intensive effort, we should also lead the transition to a modern learning health system. This system will involve the global population and span national boundaries and cultural differences, allowing access to new knowledge through carefully assimilated data collected as part of practice and fed back through electronic systems. Cardiovascular specialists trained to understand this new, information-dense world can both provide excellent specialty care for sick patients, as well as proctoring the knowledge base with populations and non-specialist practitioners who will benefit from implementing practices that have been proven effective.

**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

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**References**

Cardiomyocyte disintegration during Anderson–Fabry’s disease

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A 65-year-old man was admitted to our hospital because of syncope. On examination he was haemodynamically stable. Laboratory findings revealed positive cardiac enzymes, and Holter registration demonstrated multiple episodes of non-sustained ventricular tachycardia. Transthoracic echocardiography showed a reduced left ventricular systolic function with concentric hypertrophy and a binary endocardial appearance (Panel A, arrow). Late enhancement imaging on cardiac magnetic resonance revealed abnormal mid-myocardial enhancement basal to mid-inferolateral (Panel B, arrow). Heart catheterization excluded significant coronary stenosis and subsequent endomyocardial biopsy showed diffuse vacuolization of cardiomyocytes on haematoxylin–eosin staining (Panel C, arrows) and multi-lamellar myelin-like bodies on electron micrograph (Panel D, arrow) suggestive of Anderson–Fabry’s disease.

Accumulation of multi-lamellar myelin-like bodies causes the vacuolization and subsequent cardiomyocyte damage leading to cardiac enzyme and gadolinium leakage from the cardiomyocytes. The diagnosis of Fabry’s disease was confirmed by detection of the reduced α-galactosidase A enzyme activity in peripheral leucocytes. The patient received an implantable cardioverter-defibrillator and is currently being treated with α-galactosidase A enzyme replacement therapy.