Cardiovascular disease on a global scale: defining the path forward for research and practice

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During the 2006 World Congress of Cardiology meeting in Barcelona, the Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (VIGOUR) group held a symposium examining potential approaches to understanding and controlling the explosive worldwide growth of cardiovascular disease and its attendant morbidity and mortality. Over the last 20 years, the global nature of many problems in health care has become much more evident. In the realm of health, this has meant that countries across the globe have started to experience the same kinds of behavioural shifts (overeating, reduced physical activity and smoking), and with them massive increases in cardiovascular risk factors, observed over the last century particularly in North America and Western Europe. This VIGOUR symposium focused on what actions can be taken now to prepare for this future in which prevention and treatment of cardiovascular disease will be a major public health issue in a much larger proportion of the world’s countries. The participants focused on four major areas where they saw important opportunities: (i) the development of high quality, contemporaneous data sources that can be used to study and improve the processes, treatments and outcomes of cardiovascular diseases globally; (ii) the feasibility and resource/health economic implications of any proposed potential solutions need to be carefully defined; (iii) models/systems must be identified that can be used to guide effective interventions targeting health problems of large populations at an affordable price; (iv) academic research organizations need to assume a more active role in the health-care system both through their traditional activities in discovery research and developing evidence-based medicine along with translation of research findings into effective interventions that improve the public health.

KEYWORDS
Cardiovascular diseases; Epidemiology

Introduction

During the 2006 World Congress of Cardiology meeting in Barcelona, the Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (VIGOUR) group held a symposium examining potential approaches to understanding and controlling the explosive worldwide growth of cardiovascular disease and its attendant morbidity and mortality. Since the mission of the VIGOUR group is to enhance cardiovascular health through research into the creation, evaluation, and implementation of novel prevention and treatment strategies developed through global collaboration, the subject of this symposium is foundational to the group’s activities.1 The joining of the European Society of Cardiology meeting and the World Heart Federation meeting was a particularly propitious venue for this undertaking since the resulting 2006 World Congress of Cardiology was the largest cardiovascular research and educational dialogue conducted to date among countries representing the full spectrum of economic and health accomplishments.

The present paper is a distillation of the presentations and discussions from the 2006 meeting, updated to include evolving insights of the group stimulated by the symposium.

The problem briefly stated

Not so long ago, it was generally held that cardiovascular diseases, particularly those related to atherosclerosis, hypertension, and diabetes were problems unique to the ‘developed world.’ When technology freed us from much of the drudgery and dangers that characterized the lives of our ancestors, the argument went, we were able to replace active lives with inactive ones with no loss of productivity and to consume calories out of proportion to our
Europe. Although 12.4% of all deaths worldwide are due to cardiovascular disease, this proportion is expected to rise to 16.3% by 2020 largely as a result of the modern epidemic in the 'BRIC countries' (Brazil, Russia, India, China). This epidemic is characterized by a rapid increase in chronic diseases such as diabetes, obesity, and cardiovascular disease.

Health-care spending vs. life expectancy for several countries. Data from the Organization for Economic Co-operation and Development. http://www.oecd.org/document/30/0,3343,en_2649_201185_12968734_1,1_1_1,00.html (accessed 13 August 2007). Figure 1

Steady-state needs. 'Progress' in the food industry gave us new prepared foods that promoted obesity and, in some cases, were frankly atherogenic. Progress in the communication and entertainment industries has given us the ability and desire to spend a greater portion of each day in an inactive state. Higher caloric intake coupled with lower physical activity have led to the well-publicized epidemic of obesity, now evident in the youngest generations as well as in the adult populations. Further damage was done over the last century by the mass acceptance of tobacco addiction as a desirable cultural norm.

The wealthiest countries of the world have used technology in the form of novel drugs, devices, and surgical procedures to mitigate some of the damage done by these 'friendly fire' consequences of contemporary cultural trends, albeit at great expense and with the overall effect of palliation rather than cure or full prevention. A continued puzzle to these countries is the repeated observation that vast differences in the amount of investment in health-care technology does not translate readily into a measurable impact on public health statistics (Figure 1). For example, Cuba, a relatively poor country, spends about $229 per capita on health care, whereas Canada spends $3173 and the USA spends $6069. Yet the life expectancy for males in Cuba is 75 years, whereas that in Canada is 78 and that in the USA is 79. The corresponding figures for females are 79, 83, and 80 years.

Over the last 20 years, the global nature of many problems in health care has become much more evident. In a general sense, 'globalization' is the process whereby the activities and characteristics of daily life are being standardized around the world. In the realm of health, this has meant that countries across the globe have started to experience the same kinds of behavioural shifts (overeating, reduced physical activity, and smoking), and with them massive increases in cardiovascular risk factors, observed over the last century particularly in North America and Western Europe.

Although 12.4% of all deaths worldwide are related to cardiovascular disease, currently the bulk of these are in countries with the highest per capita gross domestic product (GDP). However, it is projected that the less wealthy countries currently experiencing a rapid growth in economic wealth, such as Brazil, Russia, India, and China (the 'BRIC countries'), will constitute an increasing proportion of the world's cardiovascular deaths such that by 2020 the overall proportion of deaths due to ischaemic heart disease will have grown to 16.3% from 12.4% largely as a result of this contribution.

The VIGOUR symposium focused on four major areas where they saw important opportunities to prepare for this future in which prevention and treatment of cardiovascular disease will be a major public health issue in a much larger proportion of the world's countries (Table 1). First, high quality, contemporaneous data sources must be developed that can be used to study and improve the processes, treatments, and outcomes of cardiovascular diseases globally. Second, the feasibility and resource/health economic implications of any proposed potential solutions need to be carefully defined in each geographic region. Third, models/systems that can be used to guide effective interventions targeting health problems of large populations at an affordable price should be identified. Finally, academic research organizations (AROs) need to assume a more active role in the health-care system both through their traditional activities in discovery research and developing evidence-based medicine (EBM) along with translation of research findings into effective interventions that improve the public health.

Table 1 Steps along the path to mitigate the modern epidemic of cardiovascular diseases

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<tr>
<th>Step 1</th>
<th>Develop high-quality contemporary data sources that characterize the processes and outcomes of care.</th>
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<td>Step 2</td>
<td>Evaluate the resources use/cost, cost effectiveness and system-level costs of novel initiatives.</td>
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<td>Step 3</td>
<td>Model community and country or system level interventions after systems already shown to work, when possible.</td>
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<td>Step 4</td>
<td>Redefine the role of Academic Medical Centers to serve as the focal point for ideas and resources targeted at the translation of medical discoveries into interventions that improve the health of communities.</td>
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The problem of nomenclature

When discussing the whole world, one rapidly finds the need to employ some shorthand terms that can reduce the complexities of contemporary life to a manageable taxonomy. Starting in the 1950s, the 'Third World' became a widely used label for countries that were aligned neither with the capitalist North American/Western European bloc nor with the socialist Soviet eastern bloc. These unaligned countries, many recently emerging from colonial rule, were generally characterized by poverty, poor public health, low educational attainment, and generally poor quality of life. In more recent years, the less politically charged terms 'developing countries' and 'developed countries' have taken hold in the academic literature. Even a cursory analysis of the problem, however, shows how unsatisfactory this classification is. Part of the difficulty lies in using a binary classification to describe a complex multidimensional construct. The term 'newly industrialized countries' has been proposed to cover a group of countries including China, India, Mexico, and the Persian Gulf states. A somewhat more nuanced approach is currently reflected in the United Nations.
Human Development Index (HDI) that ranks almost all countries of the world on a numerical weighted scale from 1.0 (best) to 0 (worst). The index components include life expectancy, literacy, education, and standard of living. On the basis of 2004 data, 63 countries are currently considered to have a high HDI (1.0 to 0.80), including Sweden, Canada, Australia, the USA, Belgium, and New Zealand as well as South Korea, the Czech Republic, Hungary, Argentina, Kuwait, Poland, Mexico, and Cuba. Eighty-two countries have a medium-level HDI (0.79 to 0.50), including the Russian Federation, Brazil, Saudi Arabia, Peru, Jordan, Iran, China, India, Vietnam, Pakistan, Ghana, and Sudan. The countries in the lowest tier of the HDI (0.50) are mostly in sub-Saharan Africa but also include Haiti and Yemen.

Although differences in these factors can be easily quantified among countries, most nations have a version of this same issue within. The study of disparities in health outcomes has taught some important lessons. In some of the economically fastest growing countries, as significant numbers of people move into the range of wealth and education where they can take advantage of state-of-the-art medical care, many millions of other people in those countries will live in conditions equivalent to those seen in countries at the lowest HDI. Thus, there is tremendous opportunity to apply what is being learned in global health research back into countries even in the highest HDI group.

Developing the evidence: integrating trials and registries

Although the epidemiological data from the lower HDI countries (mentioned earlier) is not as reliable or as complete as one would wish, the evidence for a growing epidemic of cardiovascular disease is persuasive. Given the global relevance of the problem, then, where do we look for remedies?

Large-scale observational studies provide one relatively inexpensive, and therefore attractive, source. When used to study the distribution of potentially modifiable risk factors, such observational studies play a valuable role. However, their value in developing evidence on the effectiveness of therapies is less certain. Observational studies over the last decade have suggested, for example, that estrogen replacement in post-menopausal women, vitamin E, and folate/vitamin B6 all have prognostic benefit when used for secondary prevention. The attractiveness of such information stems from the fact that these therapies appear powerful, are widely applicable, and are relatively inexpensive. However, when tested in randomized trials not only have these therapies failed to live up to the potential suggested by earlier observational analyses but also in some cases a previously unsuspected potential for harm has been uncovered. Where the major confounders are well understood and carefully measured, observational analyses can provide the same answer as carefully conducted clinical trials. Such confirmation of having ‘gotten it right’ is, however, only possible in retrospect. We can never be sure, in the absence of clinical trial confirmation, that the next observational treatment analysis we do is free from important confounding.

One aspect of observational studies that is particularly relevant to lower HDI countries is the focus on relatively simple, available, and affordable therapies. In other words, developing strategies that depend on expensive new drugs may be highly irrelevant for countries that are still grappling with basic public health problems. Certainly, some members of the country who have acquired sufficient personal wealth may be candidates for the best of contemporary medicine, but islands of ’high-technology’ medicine in a sea of inadequate health care will not advance the general public health.

Even when armed with the evidence from well-done randomized trials, the application of results to new patients seen in a given practice setting is not straightforward. Trial primary results expressed in relative terms, such as relative risk reductions or treatment hazard ratios answer the critical question of whether the therapy in question is statistically significantly better than the control therapy. In other words, ‘does the therapy work at all?’ This is a critical first step, but it is not (or should not be) the end of the story. If the therapy in question reduced mortality by, say, 20% on a relative basis, the value of this therapy for individual patients depends on their absolute risk without such treatment. A 2% 5-year mortality rate that is reduced by 20% (to 1.6%, representing four per 1000 more survivors at the end of 5 years) may represent an imperceptible benefit to many patients. The same relative reduction applied to a 10% 5-year mortality rate (yielding 20 per 1000 more survivors at the end of 5 years) may be viewed by patients and doctors as more substantial. Furthermore, when the affliction is a common one that affects the lives of thousands of individuals, a small absolute benefit may translate into a large overall public health impact. If the therapy in question is both inexpensive and low risk, selecting who to treat based on magnitude of expected benefit may not be necessary. However, most therapies used in modern cardiovascular medicine have a sufficient risk and/or cost to underscore the relevance of the question as to which patients should be selected from among the potentially eligible.

Given that most of the current clinical trial data published were generated in the highest HDI countries, one may ask whether the results are also relevant to those providing treatment in lower HDI countries. If not, where should one get the necessary evidence? Conversely, with contemporary trials now enrolling more and more patients in the lower HDI countries to meet enrollment quotas at an acceptable cost, are the results of such trials still relevant to the high HDI countries as well?

Some insights can be obtained from the example of the HERO 2 (The Hirulog and Early Reperfusion or Occlusion) trial, which compared bivalirudin vs. unfractionated heparin in ST-elevation myocardial infarction (MI) patients receiving streptokinase in 46 countries. Overall results showed a reduction in reinfarction but no effect on total mortality. Initial tests for heterogeneity based on geographic region suggested possible differences in treatment effect on mortality, but consistent benefit on reinfarction across geographic region. Further analysis showed that participating regions other than Western Europe (i.e. Latin America, Eastern Europe, Russia, Asia) all had higher than the expected mortality rates given the baseline risk profiles of the enrolled patients (Figure 2). The explanation for
Exploring regional heterogeneity in outcomes and treatment effects offers an important new opportunity for focused clinical research within specific geographic areas. Large registries can play a critical role in such investigations. Specific examples of issues that can be addressed by such registries include regional variations in: (i) inappropriate temporal delays in the use of mechanical intervention with percutaneous coronary intervention or fibrinolytic therapy in ST-elevation acute MI, (ii) glycoprotein IIb/IIIa overdosing or anti-thrombotic therapy that results in excess bleeding, and (iii) the so-called treatment risk paradox whereby patients at lowest risk receive expensive co-intervention with catheterization and revascularization more frequently than those who are at greatest risk and from whom the greatest benefit would be expected. In addition, comprehensive screening and creation of a registry of all patients during the time of enrolment in clinical trials of new interventions is particularly helpful in developing insights into the genesis of international differences in clinical trial results.

Developing the evidence: proof of concept vs. generalizability

Differences in clinical trial results and the paucity of data on many therapies from the lower HDI countries is not the only challenge facing those who desire to stem the epidemic of global cardiovascular disease. Numerous studies have now pointed out that clinical trials lack adequate enrolment of many important patient subtypes. One of the largest deficiencies is in the very oldest cardiovascular patients, a group seen with increasing frequency in clinical practice. Many clinical trial populations in cardiovascular disease now have mean ages in the low to mid-60s, with most of the patients under age 75. Sometimes this occurs due to specific exclusion of those over age 75. More often, older patients are not enrolled due to individual decision-making at each study site. Commonly, such decision-making may reflect uncertainty on the part of the patient’s clinician about whether very elderly patients will adequately understand the process of consent, be able to comply with continuing therapy, or be at increased hazard and hence unable to demonstrate the treatment benefits proposed for the therapy under study. Pharmaceutical companies doing Phase III clinical trials to gain regulatory approval for marketing of a new drug may wish to exclude patients with complex co-morbidities, such as chronic kidney disease, due to uncertainty about the degree to which the comorbidity will interfere with the demonstration of the expected therapeutic benefit.

In both these examples, one driving force for the creation of clinical trials that exclude key groups seen in practice is the conflict between proof of concept and generalizability. Investigators and sponsors designing clinical trials often have the goal of demonstrating that a particular new therapy works. They therefore design trials that maximize the chances of showing a positive result, if the therapy is really effective, by enrolling ‘ideal’ subjects who are believed most likely to respond in the expected way. Clinicians, on the other hand, care for all the complex patients who do not make it into clinical trials. They want to know whether the therapies that work well in ‘ideal’ populations...
also work, perhaps in a form that is adjusted in dose or timing, in elderly patient populations, or in patients with renal disease, chronic obstructive pulmonary disease, or other important and prevalent comorbidities.

Such pragmatic questions are not easily answered with the available evidence. Often, extrapolation from younger and healthier patients is the best that can be done. One instructive example is the use of fibrinolytic therapy in the elderly, where evidence of higher risk from intracranial haemorrhage may lead clinicians to withhold treatment. Risk is clearly increased in the elderly, and the absolute magnitude of benefit is also typically increased. Using the concept of net clinical benefit (lives saved minus patients with major disabling stroke), despite an excess in—usually fatal—intracranial haemorrhage, the absolute net clinical benefit for elderly ST-elevation MI patients treated with thrombolysis is greater than that in younger patients (who have much lower risk of both death and intracranial haemorrhage). However, even in the largest clinical trials, uncertainty about benefit exists in the eldest subsets since not enough of them are enrolled to estimate treatment effects with precision.

Renal disease increases the risk from cardiovascular disease substantially. As with advanced age, our current understanding of treatment selection issues and the most appropriate dosing to achieve the optimal efficacy–safety balance is distressingly incomplete. Similar issues are raised by the growing prevalence and incidence of diabetes, which is now seen in about one-third of patients with acute coronary disease.

**Efficient allocation of finite health-care resources**

Across the spectrum of high HDI countries, there is a greater than two-fold variation in health spending as a percentage of the GDP, but, as mentioned earlier, little relation to overall health outcomes based on these expenditures. Further, the economist Uwe Reinhardt has suggested that about 90% of the international variation in health spending can be statistically ‘explained’ by the country GDPs. In short, as a country becomes more affluent, its citizens spend more on health care. Economics has little to say, however, about which country is spending the ‘correct’ amount, although it has much to say about the relative efficiency of that spending to produce more health.

One interesting effect of globalization on medicine is the internationalization of norms for defining evidence and for defining excellence in practice. North American and European physicians agree much more than they disagree on what is clinically effective in cardiovascular medicine. Hence, when a new trial persuasively identifies a therapy as effective, the result may be a redefinition of what constitutes high quality medicine. Individual countries, many of which are not able to increase health spending as readily as the USA, are then left with the problem of figuring out how to pay for this ‘high quality’ care.

For pharmaceuticals, the common approach to generalization of results is to assume that all patients who meet eligibility criteria should receive the therapy in question. As a consequence, patients who survive a hospitalization for acute coronary syndrome, for example, may leave the hospital with a bag full of expensive medicine. Their physician is discouraged from making any sort of individualized regimen by administrators who keep score of how often all elements of EBM are being employed. Current AHA/ACC/ESC guidelines do not take into account the affordability of the treatments they recommend. As a consequence, individual countries often use their professional societies to craft ‘country-specific’ guidelines that can take better account of the fiscal limitations not acknowledged by the international guideline documents. Guideline writing committees and EBM experts defend their ‘one size fits all’ approach by pointing out that ‘opening the door’ for clinicians to be able to justify not using EBM is an invitation to go backwards to the earlier era where each doctor decided what he or she thought was effective and acted accordingly. Most clinicians are clearly ill equipped to make such customized judgements. However, acting as if fiscal limitations are not real or are not important does little to advance the efficient use of available resources. Frank acknowledgement and discussion of the problem is the first step in developing data needed to make better decisions under such limitations.

But although partitioning of treatment benefit for pharmaceutical therapy is discouraged, it has long been the norm for surgical therapy. Consider the example of coronary artery bypass grafting (CABG) surgery. Yusuf et al. showed in a meta-analysis of CABG vs. medicine that in seven clinical trials involving 2649 patients with coronary artery disease (CAD), CABG improved survival overall out to 12 years. However, we do not use these results to justify recommending CABG for all CAD. We know, from further analyses, that the survival benefit of CABG is large in left main patients and moderate in three-vessel disease patients, and we consider these patients frequently for surgery. Patients with less severe CAD, on the other hand, derive much less absolute benefit from CABG and are generally treated with more conservative measures. Of course, the major difference between pharmacological therapy and surgery is the level of up-front therapeutic risk, but the principles described in the previous section relating to relative and absolute benefit also apply to drug therapy as well as surgery.

In the case of pharmacological prevention therapy, the cost of therapy is typically the same whether the patient treated is a low-risk primary prevention patient or a high-risk secondary prevention subject. However, for the higher risk subject, there is often a partial offset of the cost of therapy due to the prevention of expensive morbid events, such as MIs, hospitalizations, and coronary revascularizations. In addition, the number needed to treat (NNT) is much lower in the high-risk secondary prevention subgroups. The net result is that the cost to produce a unit of benefit (such as an extra quality adjusted life year or extra survivor free of major events) is much more favourable for secondary prevention and is generally more a function of patient baseline risk than treatment cost.

Where treatment cost becomes more important is in assessing the impact of a new therapy on the health-care budget of a country, region, or health-care system. The fact that a therapy may provide good value for money (i.e. is cost-effective by conventional benchmarks) is of little relevance to countries that cannot afford to increase spending on health care. And although it might seem
logical that adoption of new therapies should be accompanied by the retirement of older therapies, freeing up resources to pay for the new treatments, this seems to happen only infrequently in medicine.

Regarding the unique problems of pharmacological prevention therapy in lower HDI countries, Gaziano et al. recently performed a cost-effectiveness analysis on the use of aspirin plus generic ACE-inhibitor, statin, and calcium channel blocker or beta-blocker from the perspective of six developing world geographic regions. They found that such a combination regimen was likely to be very cost-effective for secondary prevention in all regions. In addition, the regimen also looked economically attractive for primary prevention in patients with a high absolute risk for future cardiovascular events.

These results emphasize that treatment and prevention approaches will need to be adjusted for the region and the resource level. We cannot define one treatment standard for cardiovascular disease that involves the most expensive resource level. We cannot define one treatment standard for cardiovascular disease that involves the most expensive

One approach to this difficulty is to encourage more development of carefully constructed regression models that can partition treatment benefit according to relevant patient risk factors. Such models could address the inefficiencies reflected in large values for NNT as well the desirability of balancing probability of benefit with the probability of harm, the latter being sometimes summarized in the number needed to harm. The advantages are that properly constructed models are more reliable than physicians: given the same set of patient characteristics, they will output the same predictions day after day. In this regard, they may surpass physicians, particularly less experienced ones. However, they cannot use information that was not included in the database in which they were developed, a constraint that physicians do not have. Formal experiments comparing expert physicians and statistical prediction models suggest a tie in accuracy with greater reliability for the models.

This activity of partitioning treatment benefit, which mimics the physician’s intuitive judgements on which patients have favourable risk–benefit ratios for a given treatment, must be distinguished from the formal tests of heterogeneity in treatment effect that are undertaken in major clinical trials. In this latter activity, the focus is on identifying subgroups of patients in whom the treatment does or does not work, a qualitative question. In the treatment benefit partitioning referred above, one can assume that the treatment works in all patients. What differs is the amount of absolute benefit provided. This latter quantity is what patients, and their doctors, are most concerned about in making decisions.

Dynamic quality improvement: Sweden as a model

Within the high HDI countries, Sweden provides a model of what can be done to improve the quality of cardiovascular care operating from a moderately restricted health-care budget, using the aforementioned tools along with international clinical practice guidelines.

Sweden is a country of ~9 million that spends about 9% of its GDP on health care. The country has developed unique national registries of cardiovascular care, including the RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions), which has been collecting information since 1995. This data resource allows the development of a unique 10-year perspective on quality of care defined as adherence to guidelines in appropriately targeted patients using three metrics: the use of coronary angiography in ACS, primary PCI in ST-elevation MI in patients <80 years, and the frequency with which ACE-inhibitor therapy was employed after MI. The RIKS-HIA data demonstrate striking uptake in the use of these indicators of quality of care across 20 000 acute MI admissions representing over 95% of admissions to Swedish CCUs since 1995. Commensurate with this, there has been a steady decline in 30-day mortality for both men and women across various age strata providing good indirect evidence that greater application of guideline-based interventions results in overall improvement in health outcomes amidst a broader Western European community possessing a well-organized health system. Moreover, using a semi-quantitative ‘quality index’ that incorporates revascularization, anti-thrombotic, and antiplatelet treatment and other secondary prevention measures, the RIKS-HIA data also demonstrate that an educational programme can enhance the number of guideline-based therapies applied which in turn is associated with a decline in 30-day mortality.

A similar relationship between quality of care measured this way and outcome following hospitalization for acute coronary syndrome was recently shown by Peterson et al. in the international CRUSADE registry.

Academic institutions developing global solutions

The case of Sweden is a powerful demonstration of the central role of relevant data and supportive information technologies in contemporary high-quality cardiovascular care. Whether operating in the higher or lower HDI countries, little progress can be achieved on the problem of global cardiovascular disease without these tools. In their absence, we are still working within the 19th century framework of Osler and other pioneers of modern academic medicine.

In Sweden, the collection of national performance data is a joint effort among government, academia, and practitioners. In much of the world, however, the role of academia in the future of medicine is not so clear. In addition to training medical practitioners of all types, there appear to be four research areas where academia’s role is still strong in medicine: (i) investigator-driven fundamental discovery research, (ii) translational bench to bedside research and the iterative continuous loop that characterizes this process, (iii) evaluative research driven, for example, by consumers of health care, and (iv) research into quality of care and the development of systems engendered by the need to assess and improve outcomes.

In the USA and many other high HDI countries, the system in which health research is undertaken is fragmented and inefficient, characterized by both silos and barriers. As a consequence, the typical time from basic discovery to
implementation of the discovery as a useful clinical tool is an unduly long 15-20 years and, in some cases, it may be twice that. On-going initiatives, including the CTSA (Clinical and Translational Science Awards) programme started by the US National Institutes of Health and the US Congress, are attempting to transform the process of biomedical research in academic medical centres in order to provide a network of organizations that can drive a more integrated and efficient flow of research. In this model, the academic medical centre functions as an ARO that takes more coordinated ownership of the multiple steps in translation of basic discovery to the clinic, both at a community and a global health level. For some functions, networks of academic centres and their associated practice groups may be joined to form a virtual ARO. Such, in fact, is the concept behind the VIGOUR organization.\textsuperscript{13}

One unfortunate irony is that pockets of low HDI populations can be found in the USA and some large Western European inner cities in the veritable shadows of our massive biomedical academic establishments funded by the taxpayers. Some of these academic health-care institutions are in the vanguard of developing a new relationship with their communities. The new vision emerging for the academic centre places it as the centre for creative thought about health in the community, not isolated from it, but serving it and learning from it how to improve cardiovascular health in ways that do not require great affluence or high education and can take account of cultural differences and sensitivities.

Another area of change for academic centres is their relationship with the for profit pharmaceutical and medical device industries. Academic centres clearly cannot develop innovative medical technologies (either drugs or devices) by themselves. As suggested above, they have complementary skills to industry but both must be partners in the effort to improve human health. The interface between clinician scientists, the health industry, individual patients, and collective society needs to be seen as complementary. AROs can contribute by participating meaningfully in early human studies, generation of new knowledge, and evaluation and translation of that knowledge into the community incorporating new technologies that can reduce the cost per unit of improved health and as such provide an enhanced model of health care.

Conclusions

The VIGOUR organization is dedicated to cultivating a network of academics, clinicians, statisticians, and health service researchers who can develop and implement effective solutions to the growing global epidemic of cardiovascular disease. We will generate, explore, and develop broad-spectrum approaches adaptable to a wide variety of practice settings and health-care budgets. A core technology enabling such adaptive approaches will be high-quality dynamic registries that help monitor the dissemination of technologies and assess-ment of quality of care, while providing the infrastructure for effectiveness trials. The imperative has emerged for AROs to fulfill their social contract with their parent society. The timing is right, the need great, and the opportunities abundant.

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