Dr Rutherford asks: You have been a leader in the field of implementation science. Could you explain this type of research?

Dr Patel replies: Combatting chronic diseases is now recognized as a leading challenge facing most of the world, with the brunt of the burden being borne by low- and middle-income countries. To achieve affordable and effective health care, the local social, cultural, physical (institutions, workforce, and resources), and political environment all have to be evaluated and navigated. What we are really doing is identifying strategies to change behavior. How people will respond is generally informed by their own experiences, values, norms, and learning. We try to incorporate an understanding of these factors as part of the process of developing healthcare interventions and evaluating their outcomes.

In Australian primary healthcare settings, you have tested computer-guided interventions in high-risk populations to increase healthcare capacity. Under what circumstances might this be a feasible strategy?

Some years ago, we conducted a series of studies focusing on evidence-practice gaps in primary health care for cardiovascular diseases in Australia. Despite the availability of substantial resources, we found that only about half of individuals at high risk for cardiovascular events were prescribed an optimal combination of preventive therapies. To address this problem, we developed a technology-based platform, named HealthTracker, that has provider and patient tools to support real-time evidence-based management of diseases. The complex algorithm behind the decision support tool is an amalgamation of many guidelines relevant to cardiovascular disease prevention and management. This system offers integration with electronic medical records; highly individualized point-of-care management and specific advice about further tests and treatment; an interactive risk communication tool to enhance the patient’s understanding of the potential benefits of lifestyle and medical treatment strategies; an audit tool to summarize specified performance or qual-
ity indicators and real-time lists of patients not meeting such indicators; a performance feedback portal that allows ranking and comparison of providers and services according to specified performance indicators; and a content-rich consumer portal to support lifestyle change and medication adherence.

The effectiveness of the provider-facing component of HealthTracker was evaluated in a cluster randomized trial in Australian primary care practices. Its use was not mandated or monitored, but the intervention was associated with significant improvements in risk factor screening and treatment of undertreated high-risk individuals. A crucial factor in its success was integrating the system with the patient’s electronic medical care to eliminate the manual input of data. We recognize that the political and social context is critical in supporting the adoption and sustainability of quality improvement interventions such as HealthTracker.

**What roles do the healthcare system and reimbursement policy play in the success (or lack of success) of these programs?**

In Australia, as in other parts of the world, primary care visits are subsidized by the government on a fee-for-service basis. There is widespread awareness that this mode of reimbursement is not well suited to support effective prevention and management of chronic diseases and payment models are changing. Quality improvement initiatives are much more likely to be successful if reimbursement models, at least in part, support their goals. We are waiting, and hoping, this will become a reality soon in Australia!

**You have made important contributions regarding the cardiovascular polypill. Could you describe how this started, what you have learned, and where this is heading?**

We theorized that the availability of polypills might reduce the costs and complexity in prescribing for high-risk individuals so they receive optimal combinations of preventive therapies that are universally recommended by current guidelines: potentially, the low-hanging fruit for polypill use. In parallel with developing HealthTracker we have conducted research on cardiovascular polypills (fixed-dose combinations of aspirin, a statin, and 2 blood pressure-lowering drugs) over the past 5 years. The GAP trial evaluated the effectiveness of a polypill-based strategy, in comparison with usual care, in 623 participants from 33 Aboriginal Community Controlled Health Services and mainstream general practices in Australia. The intervention was associated with a substantial improvement with medication adherence and cost savings to consumers and the Australian government.

Using the same protocol with minor adaptations, the European Commission funded the UMPIRE trial that evaluated the polypill-based strategy in 1002 patients from India, the United Kingdom, Netherlands, and Ireland. After a median of 15 months follow-up, the polypill-based strategy was associated with significant improvements in adherence to optimal therapy, and lower blood pressure and total cholesterol levels, as well. Patient data from Kanyini GAP, UMPIRE, and a New Zealand health system study were combined in a prospectively defined meta-analysis. These analyses included data from 3140 patients and confirmed significant improvements in medication use, blood pressure, and LDL levels, with little heterogeneity between countries in these results. Although the improvements in blood pressure and cholesterol were small on an individual level, the benefits could be substantial if applied across large populations. These findings have been used to apply for inclusion of polypills in the WHO Essential Drug List. We are also evaluating a strategy of early use (initial treatment or after failed monotherapy) of a low-dose combination pill of 3 blood pressure-lowering medications, versus usual care, for the management of hypertension.

To address the obvious gap of initial, and long-term, adherence to prescribed drugs and other evidence-based interventions, we are embarking on a cluster randomized trial including 70 Australian general practices and data from at least 4200 undertreated patients who are at high risk of cardiovascular disease. We will develop, and evaluate, a complex therapeutic intervention that integrates HealthTracker, polypill-based strategies, and a pharmacy-based medication adherence program.

Our research with polypill-based strategies is another case study of global solutions for global problems. Although the process of actual implementation is likely to vary substantially among different settings, the potential effectiveness of polypill-based strategies is demonstrably similar in countries at vastly different stages of economic development and with highly heterogeneous health systems.

**What are the barriers to adoption of the polypill in clinical practice?**

We have found that a polypill-based approaches are well accepted by patients, especially those on multiple separate medications. Although provider acceptability was high, some providers felt the availability of only 2 versions (doses) of the polypill limited flexibility to match patient variability. For our most recent trial, we have developed 8 polypill versions that can be used, a necessary compromise between providing flexibility while...
maintaining the simplicity of the polypill prescription. However, adoption of polypills into routine care will need a lot more than generating the necessary evidence to introduce these into the market. Cardiovascular polypills are currently marketed in several countries globally, yet their uptake has been relatively poor. We are currently trying to understand some of the reasons for this observation. There are no easy solutions to these very complex problems.

**Obviously there is no cookbook approach to improving cardiovascular health in diverse populations, and I wonder what you have learned from your similar efforts in Europe, India, and China?**

There is no one-size-fits-all approach to improving health across diverse populations, but our research suggests that, although certain aspects of our approach are generalizable, the solutions require adaptation to the local context. In recent years we have conducted studies, extending our technology-based decision support system developed in Australia to low- and middle-income countries now bearing the brunt of cardiovascular diseases globally. In India, healthcare workforce shortages are a major challenge, especially in rural communities. With colleagues in India, we have been working within rural districts in the state of Andhra Pradesh for >10 years in supporting NPHWs to identify individuals at high cardiovascular risk, to initiate referrals to primary healthcare physicians, and later to perform follow-up visits with patients to reinforce lifestyle changes and medication adherence. This is supported by a mobile tablet-based electronic decision support system for the NPHW and the doctor, a shared electronic medical record, and a program to support long-term medication adherence. In a stepped-wedge cluster randomized trial, we are currently evaluating the proportion of individuals at high risk of cardiovascular disease who achieve blood pressure targets in >80,000 individuals from 54 villages.4 We are extending this research to the Northern Indian state of Haryana where NHPWs have a different level of education than those in Andhra Pradesh, and a district in East Java, Indonesia, as well. We consider it important to determine whether such interventions can be successfully adapted and implemented across a variety of different health systems.

In recognizing the reality of multimorbidity of chronic diseases, we are moving beyond cardiovascular diseases, and among other conditions are also focusing on diabetes mellitus and common mental disorders. For example, in China, we are evaluating a similar system of tools to support family health promoters, often children of remote elderly parents, and community doctors to provide coordinated care for patients with type 2 diabetes mellitus.

**The themes of diversity within populations, poverty, cultural trustworthiness of health providers, lack of transportation, and limited numbers of healthcare professionals recur in many parts of the world. What are the approaches to mitigating these factors?**

Particularly extensive barriers exist in rural communities of low- and middle-income countries where vertical disease-specific programs, with a focus on acute episodic care, have dominated the landscape. In our pilot study of the NPHW-led intervention in rural India, we found that system barriers at every step of the care process can inhibit a successful outcome. This included large distances that needed to be traveled to access care, healthcare provider absenteeism, insufficient supplies of essential drugs, and perceived role conflicts and power imbalance with the introduction of new technology. Although the intervention redesign in collaboration with district administrators helped mitigate some of these factors (e.g., tracking and ensuring drug supply, doctors visiting villages periodically, performance incentives for healthcare providers), broader health system reform will be critical to reach more individuals and achieve long-term sustainability of improved health care. Over time our goal is to obtain a detailed understanding of both barriers and methods of facilitating care to inform policy makers who seek reform.

**In China, major healthcare reforms are under way. You were involved in introducing clinical pathways for the management of acute coronary syndromes in 75 hospitals throughout China. What did you learn from this experience?**

We have been fortunate to partner with an eminent Chinese cardiologist, Professor Gao Runlin, and the Chinese Cardiac Society to implement a program of research aimed at promoting evidence-based care of ACS. The observational phase in many centers in mainland China (CPACS-1) showed large gaps in evidence-based practice with undertreatment of high-risk individuals and overuse of more expensive technologies and invasive strategies in individuals at low risk for adverse outcomes.

CPACS-2 was a cluster randomized trial of a clinical pathways–based intervention for suspected ACS management evaluated in 75 level hospitals (3500 patients)
throughout China. The intervention was associated with some improvements in care (receipt of early revascularization and secondary prevention treatments), but not for most other quality-of-care performance indicators. In-depth interviews identified 5 key system-level barriers to effective implementation: (1) leadership support for implementing quality improvement, (2) variation in the capacity of clinical services and quality improvement resources, (3) fears of patient disputes and litigation, (4) healthcare funding constraints and high out-of-pocket expenses, and (5) patient-related factors. Although the results of the trial were disappointing, we were gratified that through integrated process evaluations we were able to identify context-specific health system barriers to successful implementation that need to be addressed to achieve improved patient outcomes. Some, such as fear of litigation or violence against healthcare providers, can only be addressed through broader societal policies. However, many findings from CPACS-2 substantially influenced modifications to the intervention used in CPACS-3, an ongoing stepped-wedge cluster randomized trial of a more complex multifaceted intervention involving training, decision support, clinical pathways, and performance incentives in resource-limited hospitals.

What do you view as the major challenges and opportunities for implementation research in cardiovascular disease?

To achieve the 25×25 goals (25% reduction of premature mortality from noncommunicable diseases by 2025) set by the World Health Assembly in 2013, a number of targets including risk factor control and availability of essential drugs and technologies have been defined. This is therefore prime time for implementation science. However, through our own work we have quickly learned that the delivery of health care in different countries and systems is complex. Insufficient understanding of how broader system components interact with a particular healthcare delivery innovation or therapy, and vice versa, will seriously impede the impact of care, and the scalability and sustainability, as well. Implementation science is still in its relative infancy but is increasingly used by those who plan and fund healthcare delivery. Implementation research is hard work, characterized by using many different methods to study new ideas in complex, messy, real-world environments, but the potential payback for underserved populations is definitely worth the effort! In that regard, I would like to acknowledge the important and often leading contributions of many colleagues and trainees in Australia, India, China, and elsewhere, without whom this work would not be possible.

Abbreviations Used in This Article

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndromes</td>
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<td>CPACS</td>
<td>Clinical Pathways in Acute Coronary Syndromes</td>
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<td>GAP trial</td>
<td>Kanyini Guidelines Adherence with the Polypill</td>
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<td>LDL</td>
<td>low-density lipoprotein</td>
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<td>NPHW</td>
<td>nonphysician healthcare worker</td>
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<td>UMPIRE trial</td>
<td>Use of a Multidrug Pill in Reducing Cardiovascular Events</td>
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<td>WHO</td>
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DISCLOSURES

None.

FOOTNOTES

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REFERENCES


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Anushka Patel and John D. Rutherford

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