Reduction of strategies, including educational initiatives and pushing the food industry for reduction of trans fat moieties from food products. Similarly, efforts will also be made to work with the food industry for reducing the salt intake of Americans, by a variety of strategies, including educational initiatives and pushing for extensive disclosure of sodium content on food packaging. By addressing such key risk factors, MHI aims to prevent 1 million myocardial infarctions and strokes over the next 5 years.2,5

Table 1 summarizes the key principles and strategies of MHI.

Targeting End Results Instead of Surrogates: A Major Paradigm Shift
There is little doubt about the link between key cardiovascular risk factors and cardiovascular problems, and, thus, targeting the major cardiovascular risk factors is the rational strategy for reducing the burden of CVD and stroke; however, it is improving outcomes, not merely optimizing risk factors, that is the ultimate goal of this program.2 Major concerns have recently been raised about the mismatch between the control of cardiovascular risk factors and outcomes improvement.7 Mechanistically targeted health interventions may not always lead to predicted benefits. This issue could be owing to the complexity of the disease cause-clusters (Figure 1), unforeseen pleiotropic effects of the intervention that offset or reverse the predicted benefit (see Table 2 and Figure 2), or a combination of both.

Aspirin for the Right Patients
Use of aspirin has been among the most widely suggested recommendations for reducing the risk of vascular events. Nevertheless, as any other drug therapy, aspirin use is associated with potential harmful effects, and the benefit-to-risk ratio should be always kept in mind. Even though some investigators have recently questioned the magnitude of benefit from preventive aspirin therapy,11-13 there is ample evidence to suggest that aspirin use reduces cardiovascular events in most high-risk subgroups.10,14-16 Therefore, proper case selection for aspirin therapy is key to maximize preventive effects and minimize adverse events.

Lowering Blood Pressure May Not Be Enough
Some antihypertensives are effective in controlling blood pressure but may not reduce,4 or may even increase, cardiovascular events.17 In a systematic review, Carberg et al assessed the effects of atenolol on cardiovascular mortality and morbidity: Pooled results from placebo-controlled trials demonstrated remarkable control of blood pressure with atenolol, with no improvements in all-cause or cardiovascular mortality. Myocardial infarctions were not reduced, although there was a marginal reduction in strokes. Data comparing atenolol with other antihypertensives showed similar control of blood pressure but significantly less efficacy in CVD and mortality reduction with atenolol, compared with other

The Million Hearts Initiative: Aims, Objectives and Tools
The Million Hearts Initiative (MHI) is an ambitious national campaign that aims to reduce the incidence of CVD and stroke. Led by the Department of Health and Human Services, in collaboration with multiple governmental and private sector organizations, MHI will foster nationwide efforts to target major cardiovascular risk factors including hypertension, dyslipidemia, smoking, and obesity, as well as encouraging the implementation of preventive measures such as prescription of aspirin to patients at risk of CVD or stroke. Efforts will also be made to work with the food industry for reduction of trans fat moieties from food products. Similarly, MHI aims to reduce the salt intake of Americans, by a variety of strategies, including educational initiatives and pushing

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Table 1. Main Principles of the Million Hearts Initiative

<table>
<thead>
<tr>
<th>MHI Targets</th>
<th>Description</th>
<th>Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>A large number of at-risk patients do not receive aspirin for primary or</td>
<td>• Multiple collaborative strategies, including education, quality</td>
</tr>
<tr>
<td>Blood</td>
<td>secondary prevention of CVD, or adequate blood pressure control, or</td>
<td>measurement, better use of health information technology, and financial</td>
</tr>
<tr>
<td>pressure</td>
<td>treatment for dyslipidemia.</td>
<td>incentives to adhere to adequate use of aspirin, antihypertensives,</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td>and cholesterol-lowering therapy</td>
</tr>
<tr>
<td>Smoking</td>
<td>Active and passive smoking are associated with multiple detrimental health</td>
<td>• More detailed information and prominent warnings about the health</td>
</tr>
<tr>
<td>Dietary</td>
<td>intake, some studies suggest a link between increased dietary sodium and the</td>
<td>hazard of cigarette smoking</td>
</tr>
<tr>
<td>sodium</td>
<td>the risk of hypertension.</td>
<td>• Efforts and grants for smoking prevention</td>
</tr>
<tr>
<td>intake</td>
<td></td>
<td>• Efforts and grants for smoking cessation</td>
</tr>
<tr>
<td>Dietary</td>
<td>Some studies suggest a link between increased dietary fat and the risk of</td>
<td>• More extensive disclosure of sodium contents of food products for</td>
</tr>
<tr>
<td>trans fat</td>
<td>hypertension.</td>
<td>consumers</td>
</tr>
<tr>
<td>intake</td>
<td></td>
<td>• Multiple educational plans for the public and healthcare professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to advocate reduced-salt intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Collaborative works with the industry to reduce the trans fat moly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in industrial food products</td>
</tr>
</tbody>
</table>

MHI indicates the Million Hearts initiative; CVD, cardiovascular disease.

antihypertensives.8 In a recently published clinical trial, Haller et al randomized patients with type 2 diabetes to olmesartan versus placebo. Olmesartan was associated with improved blood pressure control and reduced microalbuminuria but at the cost of increased cardiovascular mortality.17

Dyslipidemia Pharmacotherapy: A One-Horse Race for Statins?

Likewise, there is little clinical evidence to indicate that drug therapies other than statins for dyslipidemia translate into improved clinical outcomes.18 Many clinical trials have shown no clinical benefit (and have, at times, suggested harm) for several available or investigational lipid-lowering drugs.19-22 From the myriad of studies evaluating the effects of fibrin acid derivatives, only 1 has shown benefits in reducing a composite of death from coronary heart disease, nonfatal myocardial infarction, and stroke. Notably, that study was conducted in the prestatin era.18 Results of the AIM-HIGH trial of niacin as an add-on to statin therapy in patients with atherosclerotic cardiovascular disease showed improvements in all lipid levels but no clinical benefits from niacin therapy. Until the results from HPS2-THRIVE are available, the use of niacin as a lipid-lowering agent in clinical practice will remain debatable; however, AIM-HIGH has cast a shadow of doubt on the usefulness of niacin therapy for patients with cardiovascular problems. Even though the rationally derived benefits of many of the investigational medications seem undisputable, experience has, not infrequently, suggested the opposite. The ILLUMINATE trial was a study of torcetrapib, an inhibitor of cholesteryl ester transfer protein, and showed marked improvement in the high-density lipoprotein levels, associated with concomitant reduction in the low-density lipoprotein levels. Torcetrapib, however, led to increased cardiovascular events and all-cause death; presumably, because of its unexpected effect of raising aldosterone and blood pressure levels.22 Subsequently, the DEFINE trial, testing anacetrapib, another inhibitor of cholesteryl ester transfer protein, showed similar improvements in the lipid profile but no change in blood pressure during the follow-up period. Unfortunately, however, the sample size of DEFINE was not sufficient to assess the role of anacetrapib on patients’ outcomes.23 Postmenopausal estrogen replacement therapy is an intervention that was once widely used for cardiovascular protection, on the basis of observational evidence and also on the mechanistic basis that it is known to reduce low-density lipoprotein levels and to raise high-density lipoprotein levels. Results from the Women’s Health Initiative trial showed marked improvements in lipid levels, but postmenopausal estrogen therapy led to excess risk of cardiovascular disease, which was, in large part, owing to increased rates of stroke and pulmonary embolism.24 In fact, estrogen has multiple effects beyond alterations in the lipid profile, including its effects on the coagulation cascade. Such therapy exemplifies how targeted interventions to address a risk factor might have multiple consequences in a complex cause-cluster model (Figure 2).

Smoking Cessation: Promising Efficacy Versus Safety Concerns

Smoking is such a powerful cardiovascular risk factor that it is easy to assume that any intervention that increases smoking cessation must be beneficial; however, with drug interventions, there is always a potential for harm, which must be weighed against the evidence for benefit.10,26 Varenicline is known to improve the abstinence rate 2-fold compared to placebo; however, after 24 weeks of follow-up, only one fourth of patients using varenicline had maintained smoking abstinence. This issue is important, since all patients might be put at risk of potential adverse drug effects, including cardiovascular and neuropsychiatric problems, whereas only a minority might receive the benefit.27

Dietary and Weight-Lowering Strategies: Less Is Not Always Better

Lastly, whereas certain dietary habits such as the Mediterranean diet and regular physical activity have consistently shown clinical benefits,28-31 the safety and efficacy of some other diet programs for reducing cardiovascular risk have been questioned.32 The MHI advocates the restriction of trans fats as an intervention to reduce stroke and acute myocardial infarction (AMI). To date, no randomized controlled trial, with hard clinical end points, has compared the
Probable Models for Human Disease

I) The factor and the outcome track together, no evidence of causality exists.

II) The factor is a necessary and sufficient cause for the outcome. An example is exposure to f. tularensis, and development of clinically detectable infection.

III and IV) The factor is a necessary but not a sufficient cause (does not lead to the outcome by itself). Infections in immunocompromised people are examples. The infective microorganism, the factor, is the necessary cause. A combination of other conditions may lead to immunodeficiency and hence development of the outcome (clinically apparent infection).

V) The factor can participate in the cause cluster, but is neither a necessary nor a sufficient cause (G, D and E together lead to the outcome in the absence of the factor). Majority of cardiovascular disease risk factors (including hypertension, dyslipidemia, smoking) lie in this category.

Figure 1. Depending on the causal model, interventions aimed at factors (sometimes the surrogate end points) have different consequences on the outcome. Targeting a surrogate may not affect the outcome (pathway I), may certainly affect the outcome (pathways II, III, IV), or may have a partial effect (pathway V). Importantly, health interventions may have pleiotropic effects that lead to manipulation of not only the targeted factor (surrogate) but also other role players in the disease cause-cluster (see figure 2).

Table 2. Real World Examples of the Gap Between Improvements of Risk Factor and Outcomes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intervention</th>
<th>Intermediary End Point</th>
<th>Cardiovascular Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Atenolol</td>
<td>Atenolol was effective in reducing blood pressure.</td>
<td>No benefit compared with placebo, increased mortality compared with other antihypertensives8</td>
</tr>
<tr>
<td>Obesity</td>
<td>Sibutramine</td>
<td>Sibutramine led to significant weight loss.</td>
<td>Increased cardiovascular events with sibutramine9</td>
</tr>
<tr>
<td>Smoking</td>
<td>Varenicline</td>
<td>Varenicline is more effective than placebo for smoking cessation.</td>
<td>Increased cardiovascular events with varenicline compared with placebo10</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Several drug classes, including niacin, fibrates, cholesterol absorption inhibitors, and CETP inhibitors</td>
<td>Improved lipid profile, including improved HDL-C, reduced LDL-C, and reduced triglyceride levels</td>
<td>No consistent clinical benefit except for statins; suggestions of harm for some available or investigational drugs</td>
</tr>
</tbody>
</table>

CETP indicates cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Effects of Health Interventions on Intermediate Factors and Outcomes

I) The intervention affects the surrogate endpoint which, in turn, affects the terminal outcome. An example is treatment of hypertension (surrogate) with agents that reduce cardiovascular events (terminal outcome).

II) The intervention affects the surrogate but not the terminal outcome. An example could be dyslipidemia therapy by most of the fibric acid derivatives. No effects are seen on cardiovascular events (terminal outcome).

III) The intervention affects both the surrogate, and other factors in the cause cluster (pleiotropism). The net effect is not fully explained by the surrogate. For example, post-menopausal hormone replacement therapy improves dyslipidemia (targeted surrogate). However, it also affects the coagulation, leading to increased vascular events. Statins show beneficial pleiotropism and their benefits are not fully explained by the lipocentric theory.

IV) The intervention affects the surrogate but the surrogate cannot affect the outcome. By pleiotropic effects, the intervention can alter other factors that modify the outcome. The outcome may or may not subsequently lead into a change in the levels of the surrogate (dashed arrow).

Figure 2. Our view is limited to believe in beneficial effects of interventions due to a simple causal relationship between the surrogate and the outcome. If drug A, for example, is capable to control a risk factor, we assume it will confer benefit; however, any intervention may elicit complex and unpredictable alterations to homeostasis. Such complexity may ultimately alter the end results. Therefore, an intervention may be beneficial, neutral, or harmful; irrespective of how it affects one surrogate end point.

a relatively small number of Francisella tularensis or Shigella species organisms and subsequent development of clinically apparent infection (Figure 1: II)\textsuperscript{41,42}; however, the majority of human diseases follow a cause-cluster pattern wherein a complex interplay between several risk factors and host characteristics, genetic or environment-related, lead to development or prevention of an outcome (Figure 1: III–V). Accordingly, strategies targeted at 1 part of the cause-cluster may not necessarily improve outcomes, because such interventions might also affect other role players in the cause-cluster; and even if the intervention is successful, the observed benefit cannot be extrapolated to all other interventions thought to affect the same risk factor in the cause-cluster model.\textsuperscript{43} Understanding of disease mechanisms and the use of cutoff number approaches have brought certain advancements in patient care and preventive medicine: Elevated blood pressure and dyslipidemia, for example, are known to contribute to CVD and stroke. Nevertheless, controlling these surrogates, which sometimes set arbitrary definitions for health and disease, does not necessarily mean that outcomes will improve.

Therefore, in targeting the strategies to improve clinical outcomes, care should be exercised to select only evidence-based interventions that positively affect the definable outcomes of direct importance to the population, and not the surrogates per se.\textsuperscript{44-46} Mechanistic approaches to implementation of preventive and therapeutic health strategies may only be justifiable in serious conditions where no experimental clinical data relating to clinically important outcomes are available.

Moreover, as depicted in Figure 2, many interventions can have pleiotropic effects. In this sense, the benefits and harms of implementing such health interventions cannot be fully measured under trajectories of a single surrogate end point, even if the surrogate is causally linked with the terminal outcome.
Accordingly, it is prudent to track the terminal outcome rather than, or in addition to, intermediate end points.

**Aligning the Intervention With the Desired Outcome**

MHI is an aspiring collaborative effort that can provide unprecedented grounds to significantly reduce the burden of cardiovascular disease and stroke. The key ABCS principles (Aspirin for high-risk patients, Blood pressure control, Cholesterol control, and Smoking cessation) of MHI, if targeted appropriately, would undoubtedly prevent some CVD and stroke and save hundreds of lives. As discussed above, proper use of aspirin for wisely selected at-risk patients would be of benefit for primary and secondary CVD prevention. Thanks to the Patient Protection and Affordable Care Act and the MHI campaign, the Centers for Medicare and Medicaid Services have accepted coverage for intensive behavioral counseling for CVD prevention. Treatment of hypertension and dyslipidemia by correctly selected strategies can likewise be effective and efficient for CVD and stroke prevention. MHI strategies for promoting information about the hazards of smoking, creating smoke-free public places and workplaces, and facilitating the smoking cessation plans would also be of multiple cardiovascular and noncardiovascular health benefits.

Influenced by economic constraints and an ever-growing list of available healthcare options, we are challenged to choose effective and affordable interventions that are equally accessible to a wide range of patients. Since the efforts of MHI aim to help over 100 million Americans, we believe that preparation of sets of evidence-based recommendations could be a key step. These recommendations would target all MHI stakeholders, including both healthcare providers and lay people, and would focus on each of the key cardiovascular risk factors. For the greater success of this population-based campaign, which we all look forward to, the best policy should be to focus on using strategies that have been directly shown to be effective and efficient. Consideration of the end results and the means to achieve them should be specifically applied to the pharmacist-led campaign to provide hypertension control recommendations (eg, choice of drugs), as well as the strategies to be used by the CDC and the Agency for Healthcare Research and Quality to improve ABCS delivery. In this sense, proper use of the National Heart, Lung, and Blood Institute support for guidelines-driven evidence-based cardiovascular risk prevention programs could be very helpful. From the long list of available medications to improve the lipid levels, for example, only statins have shown consistent benefits in improving outcomes. The availability of many statins, including the imminent widespread availability of generic atorvastatin, makes this class of drugs the preferred option for lipid-lowering therapy. Besides shifting huge expenditures toward cost-effective strategies, defining clear recommendations will put a security firewall between MHI’s efforts and the potentially conflicting role of the medical drug and device industry in promoting therapeutic and preventive strategies of uncertain benefit.

**The Challenge to Monitor the Success of MHI**

The success of the MHI program will be monitored using the quality measures that are associated with MHI, which are largely measures of process. But tools are also needed to track clinical outcomes so that a better understanding emerges of the real impact of the measures adopted, as this effort is moving forward. Monitoring the results of MHI by predefined standardized analyses, such as by comparing the annual trends of cardiovascular risk factors and those of the outcomes, could be very helpful for assessing the success of this initiative. This would be in harmony with MHI’s focus on the use of electronic health record systems, facilitating the tracking of quality measures and outcomes, as well as with the planned contribution of the Agency for Healthcare Research and Quality to support surveillance of cardiovascular events. We propose that monitoring the results at 4 levels would provide the most beneficial information: (1) adherence to interventions; (2) control of risk factors; (3) safety and efficacy outcomes; and (4) impact on disparities. This way, the effectiveness of the initiative in achieving the predetermined goals, as well as the accountability for further investments on the initiative, could be dynamically observed. Moreover, it would provide opportunities to fine-tune interventions where necessary. In the imperative era of treatment based on outcomes, not only is it crucial to manage hypertension, dyslipidemia, smoking, and obesity but also how to do so in line with the current best evidence. Whereas the Italian philosopher Niccolò Machiavelli said that “the end justifies the means,” we would like to highlight that “getting to the end is achieved through justified means.”

**Conclusion**

Cardiovascular disease and stroke remain the major cause of death and disability in the United States. The Million Hearts Initiative is an aspiring campaign that can bring about a dramatic decline in the incidence and burden of CVD and stroke. For its greater success, we suggest that, besides being goal-directed, MHI should be means-directed. MHI could, in fact, be a great opportunity to shift the clinical practice paradigm from targeting the risk factors to that of end results. The complexity of human disease cause-clusters mandates the selection of justified means for getting to well-defined ends.

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**Disclosures**

None.

**References**


Key Words: acute myocardial infarction ■ prevention ■ primary prevention ■ stroke ■ Million Hearts Initiative
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