Invited Commentary

Translating the Secondary Prevention Therapeutic Boom Into Action

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For decades, patients with ischemic heart disease (IHD) and myocardial infarction (MI) have been treated with a "classic prevention cocktail," including aspirin, P2Y12 inhibitor, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and statin therapy. Widespread use of this secondary prevention regimen has been partially responsible for the reduction in cardiovascular (CV) mortality in the United States.[1] Yet, despite this, patients with IHD still face up to 5% to 10% annual risk for recurrent events.[2] This residual risk has spurred the development of multiple new therapies, including novel antithrombotic regimens, nonstatin lipid-lowering therapies, anti-inflammatory agents, and cardioprotective antidiabetic agents. While the emerging CV prevention therapeutics will provide many treatment opportunities for clinicians and their patients, it also raises many questions for contemporary cardiac care. What constitutes the optimal combination of CV prevention therapies? Can such strategies be routinely implemented? If so, will patients be able to afford and durably maintain these regimens?

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In this issue of *JAMA Cardiology*, Mortensen and colleagues[3] outline the magnitude of these challenges. Using data from the Copenhagen General Population Study, the authors examined a community-based sample of 6292 patients with IHD and 2277 with prior MI. The investigators then queried how many of these individuals were eligible for 12 novel CV preventive therapies based on their trial inclusion criteria. Their findings were striking: 80% of patients with IHD and 99% of those with prior MI were eligible to receive at least 1 new drug, while 37% and 80%, respectively, were eligible for 4 or more new therapies. As high as they are, these projections still may be an underestimate, as the investigators applied trial enrollment criteria rather than assuming clinicians may prescribe drugs in a more liberal off-label fashion in routine practice.

In this time of nearly overwhelming choices, treatment decisions should ideally be guided by scientific evidence. As noted by the study authors, each of the 12 novel drugs had demonstrated in their clinical trials significant CV benefits when added to standard medical care. However, it is challenging to ascertain which of these drugs provided a greater comparative benefit, as each were evaluated in different patient populations with varying trial designs, end points, and durations of follow-up. Additionally, studies to date have looked at these agents individually and have not investigated whether some combination of these new prevention drugs could provide synergistic benefits. Fully defining the optimal combination of preventive therapies is a daunting problem, as these 12 new agents can be combined in myriad combinations. Furthermore, while clinical trials commonly just add a new medication to the existing standard of care regimen, it is possible that the new drug could obviate the need for prior ones considered standard. For example, will aspirin continue to be the foundation for CV antithrombotic therapy when newer, more potent, and/or potentially safer options exist?

Given the lack of existing trial evidence to directly compare novel agents, Mortensen and colleagues[3] provide indirect estimates of the potential population health benefits associated with adopting each novel preventive medication. Applying the relative risk reduction results from the drug trials and multiplying this by estimates of community-based use patterns and CV event rates, the investigators estimated the potential association of these novel drugs with 5-year major CV events or deaths. Such analyses indicate that the antithrombotic strategy from the COMPASS trial appeared to have the greatest potential to improve population health. While interesting, such estimates do not consider the differences between efficacy measured in the trial vs the effectiveness of these new drugs in community practice, nor do they consider the potential adverse events associated with the widespread use of the novel therapy (eg, bleeding events). Finally, on the patient level, the benefits of any new preventive therapy will likely vary depending on the patient's underlying risk and comorbid illness. Thus, drug selection patterns will likely need to be personalized.

Even if there were trials to define the optimal preventive regimen, adopting and implementing this evidence into clinical practice will likely happen slowly. The old adage that it takes 17 years from drug discovery to widespread use has stayed constant over time, underscoring the stagnant process of translating discovery to practice. Despite the billions of dollars spent yearly by pharmaceutical companies on prescriber detailing and direct-to-consumer marketing,[4] the scientific breakthroughs of the last decade remain unrealized for most eligible patients. The cost of novel therapies is often cited as a major hurdle to widespread adoption. When first released, a year's worth of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy had a yearly retail price of more $14 000; 1 year of a sodium-glucose transport protein 2 (SGLT2) agent can retail for more than $6000 per year and canakinumab can cost up to $200 000 per year. Facing such prices, insurers have initiated difficult authorization policies and high patient copays that have limited access to novel prevention treatments. Combined, such strategies have been effective in preventing adoption. For example, fewer than 0.5% of PCSK9 inhibitor-eligible patients are receiving a prescription for PCSK9 inhibitors following US Food and Drug Administration approval[5]; fewer than 10% of those eligible to receive an SGLT2 are taking the drug and treatment with canakinumab for CV indications is likely close to nil.[6] That said, drug prices are fluid and competition (and lack of adoption) often forces price modification: facing poor sales, both manufacturers of PCSK9 drugs recently dropped their price by 60%.

Cost alone cannot fully explain the slow adoption of preventive treatments. Although aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins are generic and cost pennies a day, studies continually show underuse of these among eligible patients.[6] Other studies have found that providing patients with free medications only marginally affects rates of longitudinal drug persistence and does not reduce CV events.[7]

Novel approaches are needed to improve the implementation of evidence-based medications. To date, multifaceted strategies that combine clinician education, real-time feedback, performance incentives, policy changes, and patient engagement strategies have proven most effective. Moving forward, using the electronic health record to identify treatment-eligible patients and alert clinicians of care opportunities seems promising. Additionally, various digital tools are providing platforms to deliver behavioral interventional strategies aimed toward fostering better patient and clinician engagement to improve preventive care.

In conclusion, the study by Mortensen and colleagues[3] provides an important summary of the new and exciting time we are entering in CV disease prevention. It is remarkable to realize that 12 novel therapies have recently been added to our prevention arsenal. Even more remarkable is that multiple others, such as a synthetic small interfering RNA against PCSK9, an apolipoprotein (a) inhibitor, and additional cardioprotective antidiabetic drugs, are on the not-so-distant horizon. Combined, clinicians and patients will have many therapeutic options available to profoundly lower cardiovascular disease risk. While there is still a need for ongoing clinical trials to define optimal drug combinations, the focus of investigators and sponsors alike must turn toward improving the use of the effective medications already at our fingertips.

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