Published in final edited form as:

JAMA Cardiol. 2020 February 01; 5(2): 215–216. doi:10.1001/jamacardio.2019.4959.

Translating the Secondary Prevention Therapeutic Boom into Action

Michael G. Nanna, MD¹, Eric D. Peterson, MD, MPH¹

¹Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

For decades, patients with ischemic heart disease (IHD) and myocardial infarction (MI) have been treated with a ‘classic prevention cocktail’ including aspirin, P2Y₁₂ inhibitor, beta-blocker, ACEi/ARB and statin therapy. This secondary prevention regimen has been partially responsible for the dramatic reduction in cardiovascular (CV) mortality in this country¹. Yet, despite this, IHD patients still face up to 5-10% annual risk for recurrent events². This ‘residual risk’ has spurred the development of multiple new therapies including novel antithrombotic regimens, non-statin lipid lowering therapies, anti-inflammatory agents, and cardioprotective anti-diabetic agents. While the blossoming of novel CV prevention therapeutics will provide a plethora of treatment opportunities for clinicians and their patients, it also raises many important questions for contemporary cardiac care. What constitutes the optimal combination of CV prevention therapies? Can such strategies be routinely implemented? And, if so, will patients be able to afford and durably stay on these regimens?

In this issue of *JAMA Cardiology*, Mortensen & colleagues³ outline the magnitude of these challenges. Using data from the Copenhagen General Population Study, the authors examined a community-based sample of 6,292 patients with IHD and 2,277 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 IHD patients and 99% of those with prior MI were eligible for at least one new drug, while 37% and 80%, respectively, were eligible for four 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 significant CV benefit when added to standard medical care. However, it is challenging to ascertain which of these drugs provided greater comparative benefit as each were evaluated in different patient populations with varying trial designs, endpoints, 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 therapy is a

daunting problem as these 12 new agents can be combined in a myriad of unique 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 provide readers with indirect estimates of the potential population health benefits associated with adoption of 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 impact of these novel drugs on 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 take into account the differences between efficacy measured in the trial versus 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 (e.g. 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, our drug selection patterns will likely need to be personalized.

Even if there were trials to define the optimal preventive regimen, adoption and implementation of this evidence into clinical practice will likely be quite slow. The old adage that it takes 17 years from drug discovery to widespread use has stayed disturbingly 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 marketing⁴, the scientific breakthroughs of the last decade remain unrealized by the majority of eligible patients. Cost of novel therapies is often cited as a major hurdle to widespread adoption. When first released, a year's worth of PCSK9 inhibitor therapy had a yearly retail price of over \$14,000; one year of an SGLT2 agent can retail for more than \$6,000/year and canakinumab can cost up to \$200,000/year. Facing such prices, insurers have initiated difficult authorization policies and high patient co-pays that have limited access to novel prevention treatments. Combined, such strategies have been quite effective in preventing adoption. For example, less than 0.5% of PCSK9-inhibitor eligible patients are receiving a prescription for PCSK9-inhibitor following FDA approval⁵; less than 10% of those eligible for an SGLT2 are on drug and treatment with canakinumab for CV indications is likely close to nil⁶. That said, drug prices are fluid and competition (and lack of adoption) often forces price modification: facing poor sales, both manufactures of PCSK9 drugs recently dropped their price by 60%.

Cost alone cannot fully explain slow adoption of preventive treatments. Even though aspirin, beta-blockers ACE-inhibitors, and statins are generic and cost pennies a day, studies continually show under-utilization of these among eligible patients⁶. Other studies have found that providing patients with 'free' medications only marginally impacts rates of longitudinal drug persistence and does not reduce cardiovascular events⁷.

Novel approaches are needed to improve implementation of evidence-based medications. To date, multifaceted strategies that combine provider education, real-time feedback, performance incentives, policy change and patient engagement strategies have proven most effective. Moving forward, use of the electronic health record (EHR) to identify treatment-eligible patients and alert providers of care opportunities seems promising. Additionally, a variety of digital tools are providing platforms to deliver behavioral interventional strategies aimed toward fostering better patient and provider engagement in order to improve preventive care.

In conclusion, the study by Mortensen & colleagues³ provides an important summary of the new and exciting time we are entering in cardiovascular 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 siRNA against PCSK9, an apolipoprotein (a) inhibitor, and additional cardioprotective anti-diabetic drugs, are on the not-so-distant horizon. Combined, clinicians and patients will have an extraordinary abundance of 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 utilization of effective medications already at our fingertips.

Acknowledgments

CONFLICT OF INTEREST DISCLOSURES

MG Nanna: Dr. Nanna is supported by the NIH training grant T-32-HL069749-15.

ED Peterson: Research Grant: Significant; Amgen, Sanofi, Astrazeneca, Merck. Consultant/Advisory Board; Modest; Amgen. Astra Zeneca, Merck, Bayer, Amarin, Novo Nordisk and Sanofi. Dr Peterson is also a founding partner in Swift Implementation Science, Inc

REFERENCES

1. Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129(14):1483–1492. [PubMed: 24573352]
2. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *Jama*. 2010;304(12):1350–1357. [PubMed: 20805624]
3. Mortensen MB, Blaha MJ, Nordestgaard BG. Eligibility and Preventive Potential for New Evidence-Based Cardiovascular Drugs in Secondary Prevention: Results From a Contemporary General Population *JAMA cardiology*. In Press.
4. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. *Jama*. 2019;321(1):80–96. [PubMed: 30620375]
5. Karalis DG, Mallya UG, Ghannam AF, Ellassal J, Gupta R, Boklage SH. Prescribing Patterns of Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors in Eligible Patients With Clinical Atherosclerotic Cardiovascular Disease or Heterozygous Familial Hypercholesterolemia. *The American journal of cardiology*. 2018;121(10):1155–1161. [PubMed: 29548678]
6. Arnold SV, de Lemos JA, Rosenson RS, et al. Use of Guideline-Recommended Risk Reduction Strategies Among Patients With Diabetes and Atherosclerotic Cardiovascular Disease. *Circulation*. 2019;140(7):618–620. [PubMed: 31174429]
7. Wang TY, Kaltenbach LA, Cannon CP, et al. Effect of Medication Co-payment Vouchers on P2Y12 Inhibitor Use and Major Adverse Cardiovascular Events Among Patients With Myocardial

Infarction: The ARTEMIS Randomized Clinical Trial. *Jama*. 2019;321(1):44–55. [PubMed: 30620370]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript