Title
Improving Statin Noncompliance: If You Build It, Will They Come?

Journal
Canadian Journal of Cardiology, 35(7)

ISSN
0828-282X

Authors
Sparrow, Robert T
Ferreira-Legere, Laura
Udell, Jacob A
et al.

Publication Date
2019-07-01

DOI
10.1016/j.cjca.2019.05.011

Peer reviewed

Canadian Journal of Cardiology 35 (2019) 813–815

Editorial

Improving Statin Noncompliance: If You Build It, Will They Come?

Robert T. Sparrow, MD,[a] Laura Ferreira-Legere, RN, MScN,[b] Jacob A. Udell, MD, MPH,[b,c,d] and David D. Waters, MD[e]

[a] Faculty of Medical Science, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[b] ICES, Toronto, Ontario, Canada

[c] University of Toronto, the Cardiovascular Division, Department of Medicine, Women's College Hospital, Toronto, Ontario, Canada

[d] Peter Munk Cardiac Centre, Toronto General Hospital, Toronto, Ontario, Canada

[e] Division of Cardiology, Zuckerberg San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, California, USA

See article by Chen et al., pages 884–891 of this issue.

Few things are as certain in cardiology as the knowledge that statins reduce cardiovascular (CV) events in at-risk individuals. Statins have significantly reduced the risk of death, myocardial infarction, stroke, and the need for coronary revascularization in dozens of high-quality clinical trials.[1] Risk reduction is proportional to low-density lipoprotein cholesterol (LDL-C) lowering; specifically, each 1 mmol/L reduction in LDL-C lowers CV events by 22%.[1] Other drugs that reduce LDL-C, including ezetimibe[2] and proprotein convertase subtilisin-kexin type 9 inhibitors,[3] have also been shown to reduce CV events, albeit with less impressive clinical trial evidence. Although guidelines in this area often differ with respect to details, they all endorse statin therapy for subjects at intermediate or high risk of a CV event.[4]

On the basis of this information, one might expect that most patients with atherosclerotic CV disease (ASCVD) would be treated with a statin, perhaps 90%. As shown in the report from Chen et al.[5] in this issue of the *Canadian Journal of Cardiology*, reality falls far short of this expectation. These investigators linked 5 large databases in the province of Alberta to identify 281,665 patients with a new ASCVD diagnosis from 2011 to 2015. Only 77.9% of these patients had an LDL-C measurement, and of those with a measurement, only 65.9% were treated with a statin. Among those treated who had a follow-up LDL-C measurement, 36.6% did not achieve the modern Canadian target of either < 2 mmol/L or a 50% LDL-C reduction. Goal achievement improved from low to moderate to high-intensity statin use. Adherence, defined as taking at least 80% of medication, was similar across the 3 statin intensities and averaged 60.2%.

Chen et al. characterize their findings as "a remarkable treatment gap," and we certainly agree. They detail how this gap is not unique to Alberta, but extends to the rest of Canada,[6] as well as to the United States, Europe, and most other places that have been studied. Differences among geographic locations might result from differences in patient populations studied (primary vs secondary prevention), differences in methods, differences in practice patterns, differences in the culture of therapy compliance, and variations in guideline implementation.

On the basis of these findings, approximately one-third of ASCVD patients are untreated, one-third are treated but do not achieve their LDL-C targets, and one-third are treated to goal. If we assume that the patients not treated to goal obtain approximately half of the potential event reduction from treatment, then overall, approximately half of the potential CV event reduction from statins is being forfeited. Over the lifetimes of our patients with ASCVD, this is a huge missed opportunity. Is there anything that we can do to narrow this gap?

Approaches to Improving Statin Compliance

Thankfully, a number of options are available. Statin-prescribing initiatives can be broadly categorized as either patient-focused or physician-focused. Both approaches have previously been implemented, with mixed results. The good news is that many of the positive interventions have the applicability and feasibility to be widely implemented across various health care settings.

Patient-centred programs generally involve educational outreach along with an offer of ASCVD risk assessment to illustrate the benefits of statin therapy. The method of education delivery has been shown to be a key factor in an

Received for publication May 9, 2019. Accepted May 9, 2019.

Corresponding author: Dr David D. Waters, Division of Cardiology, Room 5G1, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, San Francisco, California 94110, USA. Tel.: +1-415-420-6646.

E-mail: David.Waters@ucsf.edu

See page 815 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.05.011

intervention's effect on statin use. For example, a 2013 trial in which patients were mailed personalized information about risk reduction from use of statins more than doubled the rate of statin prescriptions after 9 months (odds ratio, 2.13; 95% confidence interval [CI, 1.22-3.72).[7] In contrast, electronic and phone-based education programs have generally been ineffective.[8] Although electronic communication is an emerging trend in health care, ASCVD patients might not be the optimal demographic target to engage strongly with smartphones and apps without the commitment of additional resources.

In comparison, interventions targeting physicians have been broader in scope and have encompassed various techniques, such as educational initiatives, audit and feedback systems, and point-of-care decision support tools. Physician education often seems like the obvious, straightforward choice of intervention. Yet, in a recent review of 8 trials of physician education, none showed a benefit on statin prescribing.[9] This unanimous verdict suggests that either physicians are not educable, or more likely, that a lack of knowledge is not the roadblock to improved prescribing.

There is definitely not a one-size-fits-all, magic bullet approach to improving statin compliance. Combining multiple modalities; for example, point-of-care tools with audit and feedback systems, and involving nurses or pharmacists, appears to increase the chance of a successful intervention. In the **T**reatment **o**f Cardiovascular **R**isk in **P**rimary Care Using **E**lectronic **D**ecision Supp**o**rt (TORPEDO) trial,[10] of 10,308 patients, an electronic health record alert system, physician risk communication tool, and audit program that allowed physicians to view their performance against peers, were all combined in a single intervention. Although the proportion of ASCVD patients who received all guideline-recommended medications was not significantly different (56.8% vs 51.2%; $P = 0.12$; odds ratio, 1.11; 95% CI, 0.97-1.27), the intervention more than tripled the rate of new statin prescriptions after 17 months (19.2% vs 4.7%, $P < 0.001$; odds ratio, 3.22; 95% CI, 1.77-5.88).

These results bring to light an important principle: time and energy, not knowledge, is the real barrier to statin prescribing. Physicians generally possess adequate knowledge of ASCVD treatment guidelines, but the many health needs and perceptions of ASCVD patients, short appointments, and competing demands on physician time all combine to impede statin prescribing. These and other interventions show that reminder systems to identify undertreated patients, and tools to streamline the treatment discussion process and encourage patient empowerment through education, can lead to robust improvements. It is time to lighten the burden on physicians and encourage implementation of systems and programs around them to help improve their prescribing practices.

One example of a more robust approach is the ongoing Canadian Institutes of Health Research-funded **C**ommunity **H**eart **O**utcomes **I**mprovement and **C**holesterol **E**ducation **S**tudy (CHOICES) trial that is aiming to randomize and compare metrics, including statin prescribing, between health regions where patient- and physician-oriented implementation programs are initiated along with standard care.[11]

Compliance Lessons From Non-Statin Studies

Moving on to patients themselves, 2 recent large clinical trials have shed light on why patients might or might not neglect their medication. The first issue studied was patient cost: in circumstances in which patients pay for part or all of their drug cost, poor compliance has previously been attributed to this factor. In the **A**ffordability and **R**eal-World Antiplatelet **T**reatment **E**ffectiveness After **M**yocardial **I**nfarction **S**tudy (ARTEMIS),[12] 301 US hospitals that enrolled 11,001 post-acute coronary syndrome patients randomized them to usual care or to co-payment vouchers for clopidogrel or ticagrelor for 1 year (median voucher value $137 for a 30-day supply). The co-primary outcomes were patient-reported persistence with P2Y12 inhibitor (defined as continued treatment without gap in use $\geq$ 30 days) and MACE (death, recurrent myocardial infarction, or stroke) at 1 year.

Patient-reported persistence with P2Y12 inhibitors at 1 year was higher in the intervention than in the control group (87.0% vs 83.8%; $P < 0.001$; adjusted difference, 2.3%; 95% CI, 0.4%-4.1%). There was no significant difference in MACE at 1 year between intervention and usual care groups (10.2% vs 10.6%; $P = 0.65$. The difference in persistence is perhaps smaller than what one would expect; in fact, nearly one-third of patients provided with vouchers did not use them. ARTEMIS suggests that although medication cost might contribute to noncompliance, it does not appear to be the dominant factor.

In the Visualization of Asymptomatic Atherosclerotic Disease for Optimum Cardiovascular Prevention (VIPVIZA) trial,[13] 40-, 50-, or 60-year-old Swedes with 1 or more classic CV risk factors underwent carotid ultrasound examination and were randomized to a control group or to an intervention group. The intervention group patients and their physicians viewed a pictorial representation of the ultrasound results. A total of 3532 individuals were enrolled. The primary outcomes, **F**ramingham **R**isk **S**core (FRS) and European **S**ystematic **Co**ronary **R**isk **E**valuation (SCORE), were assessed after 1 year. At 1 year FRS (1.07; 95% CI, 0.11-2.03; $P = 0.0017$) and SCORE (0.16; 95% CI, 0.02-0.30; $P = 0.0010$) were significantly better in the intervention group. Much of the difference could be attributed to greater statin use and lower LDL-C levels in the intervention group.

Several features of the VIPVIZA intervention probably contribute to its success; it is directed to the patient and the physician, it depicts the underlying silent atherosclerotic process, it provides patient-specific results and risk level, and subsequent treatment can be directed at multiple risk factors. These lessons can be applied to future studies of statin prescribing.

Concluding Comments

Although previous studies show inroads to close the statin treatment gap, more work still needs to be done. The existing trials to date are relatively few in number and quite heterogeneous in their populations, interventions, and analysis, limiting the generalizability to new practice areas. Cost-benefit analyses also have not been performed, and the question of whether incremental improvements in statin compliance are worth the time and money invested in the interventions has not been analyzed.

To a degree not seen with other CV drugs, statins are often the subject of news stories and internet postings that minimize their benefits and exaggerate their adverse effects. In a nationwide prospective cohort study from Denmark, negative statin-related news stories were shown to decrease statin persistence and increase myocardial infarction and CV mortality.[14] Patient education must therefore often counter preexisting patient biases and overcome fears of adverse effects.

W.P. Kinsella, coincidentally from Alberta, wrote "*Shoeless Joe*," a magically surrealistic baseball story that was adapted into the 1989 film "Field of Dreams."[15] In it, a young corn farmer played by Kevin Costner, hears a voice telling him to build a baseball diamond in his cornfield. "If you build it, they will come," the voice said, referring to the ghost baseball players from the Chicago Black Sox scandal, and also to the fans who would watch them play.

A large authoritative database of statin trials has been built for us. It does not answer all of our questions, but it clearly indicates that ASCVD patients benefit from statin treatment. Will they come? More work is needed to find ways to encourage them to do so!

Disclosures

D.D.W. has received remuneration for participation in clinical trial committees from pharmaceutical companies that develop or market cholesterol drugs. The remaining authors have no conflicts of interest to disclose.

References

1. Cholesterol Treatment Trialists' Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
2. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.
3. Waters DD, Hsue PY. PCSK9 inhibition to lower LDL-cholesterol and reduce cardiovascular risk: great expectations. Circ Res 2015;116:1643-5.
4. Waters DD. Cholesterol lowering guidelines: from whence we came and where we are now. Can J Cardiol 2019;35:590-7.
5. Chen G, Farris MS, Cowling T, et al. Treatment and low-density lipoprotein cholesterol management in patients diagnosed with clinical atherosclerotic cardiovascular disease in Alberta. Can J Cardiol 2019;35:884-91.
6. Alabousi M, Abdullah P, Alter DA, et al. Cardiovascular risk factor management performance in Canada and the United States: a systematic review. Can J Cardiol 2017;33:393-404.
7. Persell SD, Lloyd-Jones DM, Friesema EM, Cooper AJ, Baker DW. Electronic health record-based patient identification and individualized mailed outreach for primary cardiovascular disease prevention: a cluster randomized trial. J Gen Intern Med 2013;28:554-60.
8. Webster R, Li SC, Sullivan DR, et al. Effects of internet-based tailored advice on the use of cholesterol-lowering intervention. J Med Internet Res 2010;12:e42.
9. Nguyen T, Nguyen HQ, Widyakusuma NN, et al. Enhancing prescribing of guideline-recommended medications for ischaemic heart diseases: a systematic review and meta-analysis of interventions targeted at healthcare professionals. BMJ Open 2018;8:e018271.
10. Peiris D, Usherwood T, Panaretto K, et al. Effect of a computer-guided, quality improvement program for cardiovascular disease risk management in primary health care: the treatment of cardiovascular risk using electronic decision support cluster-randomized trial. Circ Cardiovasc Qual Outcomes 2015;8:87-95.
11. CANHEART. CANHEART CHOICES Community Heart Outcomes Improvement and Cholesterol Education Study. Available at: http://www.canheart.ca/choices/. Accessed May 8, 2019.
12. 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;321:44-55.
13. Näslund U, Ng N, Lundgren A, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. Lancet 2019;393:133-42.
14. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J 2016;37:908-16.
15. Wikipedia. Field of Dreams. Available at: https://en.wikipedia.org/wiki/Field_of_Dreams. Accessed April 29, 2019.