Systematic Review/Meta-analysis

Proportion and Risk Indicators of Nonadherence to Statin Therapy: A Meta-analysis

Mark Lemstra, PhD, David Blackburn, PharmD, Alex Crawley, BSP, and Ryan Fung, BSP
College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

See editorial by Feldman and Campbell, pages 531-533 of this issue.

ABSTRACT
Background: Nonadherence to chronic disease medications is important. A growing body of literature suggests that better delivery of established therapies would save more lives than would discovery of innovations. Our first objective was to quantify the proportion of adherence to statin medications. The second objective was to provide estimates of risk indicators associated with nonadherence to statin medications.

Methods: We performed a systematic literature review and meta-analysis of all studies published between database inception and June of 2011 that reviewed adherence, and risk indicators associated with nonadherence to statin medications.

Results: In the end, 67 studies met our inclusion and exclusion criteria and passed our methodological-quality evaluation. Among observational studies, 49.0% (95% confidence interval [CI], 48.9%-49.2%) of patients were adherent to statin medications at 1 year of follow-up. Among randomized trials, 90.3% (95% CI, 89.8%-90.8%) of patients were adherent to statin medications at 1 year of follow-up. The association between 147 variables and adherence to statin medications was determined. After meta-analysis, only 6 variables were associated with nonadherence to statin medications: primary prevention (rate ratio = 1.52; 95% CI, 1.50-1.53); new statin users (rate ratio = 1.46; 95% CI, 1.33-1.61); copayment (rate ratio = 1.28; 95% CI, 1.09-1.50); lower income status (rate ratio = 1.26; 95% CI, 1.16-1.37); fewer than 2 lipid tests performed (rate ratio = 1.38; 95% CI, 1.16-1.64), and not having hypertension (rate ratio = 1.16; 95% CI, 1.12-1.21).

The effectiveness of interventions for enhancing adherence to chronic medication remains surprisingly weak. This is a concern because effective ways to help patients follow their treatment plans could improve health outcomes. For example, among patients who suffered an acute myocardial infarction, 1-year mortality rates were 25% lower for those who adhered to statin medications. As such, some suggest that better delivery of established therapies would actually save more lives than would the discovery of innovations.

The authors of an editorial on chronic medication adherence suggest that adherence rates range from 43% to 78%, physicians’ ability to recognize nonadherence is poor, and interventions to improve adherence have demonstrated mixed and limited results.

A recent Cochrane meta-analysis reviewing the effectiveness of interventions to improve adherence to lipid-lowering medications concluded that adherence rates range from 25% to 80%. The authors conclude that reliable indicators of adherent behaviour to statin therapy have not been found.
Conclusions: This study provides some insight into the extent of non-adherence by study type along with 6 risk indicators associated with nonadherence to statin medications.

Methods
A systematic literature review was performed by accessing the databases PubMed, PsychINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central, Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHSEED), Health Technology Assessment Database (HTAD), and EMBASE, from database inception till June of 2011.

All relevant Medical Subject Headings and free-text terms describing cardiovascular disease were combined with terms describing statins by their generic and proprietary name, adherence, and risk indicators (Supplemental Table S1). Reference sections of each article were reviewed for additional papers. Papers that were not published were not included in our search.

The following inclusion and exclusion criteria were used.

Inclusion criteria:
1. Published article that determined the proportion of adherence to statin therapy during a defined period
2. Observational cohort study (prospective or retrospective) or randomized controlled trial (RCT)
3. Use of a validated tool for measurement of adherence to statins
4. Published in English language

Exclusion criteria:
1. Opinion papers, letters to the editor, case reports, or case studies
2. Studies with fewer than 50 participants

Titles were reviewed initially for relevance and to remove duplication. Remaining articles were subject to full abstract review. The remaining articles were then subjected to a full-article review, along with methodological quality evaluation by a panel of 3 reviewers (M. L., A. C., and R. F.). Unanimous agreement was sought, but a majority of 2 out of 3 reviewers was used to determine initial approval or rejection.

For RCTs, the Delphi list was used to evaluate methodological quality. A score of 5 out of 8 was required for a randomized trial to be accepted. For observational studies, a scale with 8 questions was used to evaluate methodological quality, with a score of 5 out of 8 required for acceptance (Supplemental Table S2).

The statistical basis for the meta-analysis was taken from Fleiss. Complete details on this statistical basis, along with its assumptions, have been described previously in other meta-analyses published by the principal investigator. Four or more articles were required for meta-analysis. Only random effects models are displayed.

Sensitivity analysis reviewed the individual influence of a study by repeating the meta-analysis without studies with the largest and smallest relative weights. If this analysis produced little change in inference (less than 15% change in rate ratio), inclusion of the study would not warrant caution in the interpretation. Sensitivity analysis also included study design, country of origin, prospective vs retrospective studies, and measure used to calculate adherence.

Results
A review of PubMed, PsychINFO, CINAHL, Cochrane Central, DARE, NHSEED, HTAD, and EMBASE identified 1574 articles. From this, 991 articles were removed for lack of relevance. Another 69 articles were removed because of duplication. After full abstract review, 295 articles were removed after the inclusion and exclusion criteria were applied. The remaining 219 articles were subjected to methodological quality review, and as a result, 152 articles were rejected. In the end, 67 articles (53 cohorts and 14 RCTs) were accepted for meta-analysis (Supplemental Table S3). All decisions were unanimous. The summary appears in Figure 1.

Of these 67 studies, the most common follow-up duration was 12 months; 27 studies (24 cohorts and 3 RCTs) had data on adherence at 1 year. Among the 24 cohorts, with a total sample size of 635,758, 49.0% (95% confidence interval [CI], 48.9%-49.2%; range, 24%-87.5%) of patients were at least 80% adherent to statin medications at 1 year of follow-up. Among the 3 randomized trials, with a total sample size of 14,604, 90.3% (95% CI, 89.8%-90.8%; range, 84.5%-97.7%) of patients were adherent to statin medications at 1 year of follow-up.

Country of origin did not help describe the wide range of values. Prospective vs retrospective comparisons were not possible because only 1 prospective cohort had data at 1 year. Analyzing by measure used to calculate adherence revealed that “proportion of days covered” (PDC) resulted in 38.6% adher-
ence (95% CI, 38.5%-38.8%), whereas “discontinuation” resulted in 68.6% adherence (95% CI, 68.4%-68.8%) at 1 year of follow-up. However, sensitivity analysis of removing the largest study from each group resulted in adherence of 56.0% (95% CI, 55.8%-56.2%) for PDC and 57.0% (95% CI, 56.5%-57.6%) for discontinuation measures.

The second-most-common follow-up duration was 6 months. Among the 7 cohorts, with a total sample size of 80,742, 54.8% (95% CI, 54.4%-55.1%; range, 30%-87.0%) of patients were adherent to statin medications at 6 months of follow-up. Only 1 randomized trial had data at 6 months and, as such, was not pooled.

A total of 33 studies did not have adherence data at 6 or 12 months of follow-up. Among these remaining cohorts, the lowest adherence measured was 19% at 3 months, while the highest adherence was 88%, also at 3 months’ follow-up. Among the RCTs, the lowest adherence was 65.6% at 6 months, while the highest adherence was 95%, at an average duration of follow-up of 4.8 years.

The second objective was to provide estimates of risk indicators associated with adherence to statin medications. In total, the association between 147 variables and adherence to statin medications was reviewed. In the end, 6 variables were associated with nonadherence to statin medications (Fig. 2 and Supplemental Fig. S1).

The most important variable was primary vs secondary coronary heart disease prevention. For 18 studies, with a total sample size of 982,487, patients who were dispensed statin medications for primary prevention, in comparison with secondary prevention, were 52% more likely to be nonadherent (rate ratio = 1.52; 95% CI, 1.50-1.53).

For 7 studies, with a total sample size of 857,155, new statin users, in comparison with experienced or previous statin users, were 46% more likely to become nonadherent (rate ratio = 1.46; 95% CI, 1.33-1.61).

Among 6 studies with a total sample size of 884,643, patients required to make a copayment when their statin medications were dispensed were 28% more likely than others to be nonadherent (rate ratio = 1.28; 95% CI, 1.09-1.50).

Analyzing 11 studies with a total sample size of 1,194,722, patients who were of lower income status were 26% more likely to become nonadherent (rate ratio = 1.26; 95% CI, 1.16-1.37) than those who were not of lower income status.

For 8 studies with a total sample size of 325,346, patients who had fewer than 2 lipid tests performed were 38% more likely to be nonadherent (rate ratio = 1.38; 95% CI, 1.16-1.64) than were patients who had 2 or more lipid tests. Because investigation of variables post index date can be problematic, a subanalysis of lipid testing before and during treatment found that patients with fewer than 2 lipid tests prior to commencing treatment (3 studies) were 29% more likely to become nonadherent than were others (rate ratio = 1.29; 95% CI, 1.01-1.64), whereas patients who received fewer than 2 lipid tests during treatment (5 studies) were 44% more likely than others to become nonadherent (rate ratio = 1.44; 95% CI, 1.14-1.81). Among 17 studies with a total sample size of 625,739, patients without hypertension were 16% more likely to become nonadherent (rate ratio = 1.16; 95% CI, 1.12-1.21) than were patients with hypertension.

Tests of homogeneity of variance for the 6 variables associated with nonadherence were all $P < 0.001$. This suggests highly significant heterogeneity among the studies. Stratification by country of origin, observational study vs RCT, prospective vs retrospective study, and measure of adherence did not alter estimates to a significant degree. However, 1 variable, hypertension, was the only variable to have studies with negative estimates. Two studies found that not having hypertension increased adherence to statin therapy, contrary to the results of the other 15 studies.
ing these 2 studies modified the rate ratio only from 1.16 to 1.18 (95% CI, 1.13-1.23).

Sensitivity analysis removed the studies with the largest and smallest relative weights within each of the 6 variables. The only variable with significant change was primary prevention. Removing 1 study with a rate ratio of 1.76, but with a relative weight of 0.25, altered the rate ratio from 1.52 to 1.44 (95% CI, 1.43-1.46).

In the end, 141 variables had either negative or inconsistent associations with adherence to statin therapy.

Discussion

Among observational studies, 49.0% of patients were adherent to statin medications at 1 year of follow-up, in comparison with 90.3% of patients in randomized trials. After meta-analysis, only 6 variables were associated with nonadherence to statin medications: primary prevention, new statin users, co-payment, lower income status, fewer than 2 lipid tests performed, and not having hypertension.

There are a number of explanations for the wide difference found between RCTs and observational studies. First, a number of RCTs had a run-up phase whereby nonadherent patients were removed prior to randomization. Second, highly selective inclusion and exclusion criteria restricted randomization to as little as 8% of the original sample. Third, patients in the randomized trials received more follow-up visits, more-frequent lipid testing, more direct observation, and more follow-up of medication adherence.

An editorial on adherence to chronic disease medications concluded that differences found between experimental studies and real-world clinical settings were due to selection bias of study subjects and the rigorous attention participants receive. Other explanations might include free medications and informed consent prior to participation. Our study found that adherence to statin medications within observational studies was almost half that observed in RCTs.

To date, reliable indicators of adherent behaviour to statin therapy have not been found. Because of a well-defined search strategy, our meta-analysis is consistent with the literature. Co-payment for medications is known to be an issue, as 10% of Canadian patients report nonadherence due to medication cost alone. Lower income status might also increase nonadherence due to affordability, although low income status has also been associated with nonadherence to other health-seeking behaviours. Patients who have a low perceived risk of disease, like those prescribed chronic medications for primary prevention, have been found to be less likely to adhere to their medications. Similarly, patients with a concurrent diagnosis of hypertension, along with dyslipidemia, would likely have increased perceived risk of heart disease. Also, receiving less lipid testing before statin therapy reflects a lack of knowledge of the disease prior to treatment. Receiving less lipid testing after initiating statin therapy could reflect a number of issues, including poor patient-provider relationship. Finally, experienced statin users might be more adherent than new statin users because of a selection process whereby previously nonadherent subjects were not prescribed statins again.

The main limitation of our meta-analysis was the inclusion of studies with wide variability and heterogeneity in measurement of adherence, definition of adherence, and study design. For example, RCTs predominantly use discontinuation (quitting), whereas observational studies predominantly use PDC (poor execution) as an adherence measure. Discontinuation (nonpersistence) might fulfill only part of the full definition of nonadherence, which includes intermittent use. However, similar adherence rates of 56% for PDC and 57% for discontinuation measures were observed among observational studies after we removed the largest study within each group. Second, the primary objective of the RCTs was drug efficacy, whereas
the primary objective of the cohorts was medication adherence. Third, although our meta-analysis identified 6 variables associated with statin nonadherence, the extent to which adherence would be improved if these variables were addressed remains unclear. Fourth, our interpretation is limited to variables previously reviewed. It is possible, if not likely, that other, untested associations exist. For example, other patient-related, disease-specific, clinic organizational, and social factors could impact adherence, as could factors related to the provider-patient relationship. That said, it is clear that many variables routinely collected through administrative health care utilization databases offer little insight into statin nonadherence.

The known effectiveness of interventions for enhancing adherence to chronic medication remains surprisingly weak. The interventions that have been shown to be somewhat effective have all been complex, expensive, and time intensive and have resulted in limited improvement toward better adherence and treatment outcomes. It is possible that this lack of effectiveness is due to lack of knowledge of the actual risk indicators of chronic medication adherence. This study provides some insight into factors associated, and not associated, with nonadherence to statin medications.

In summary, better treatment of cardiovascular risk factors could result in substantial reduction in morbidity and mortality of Canadians. Knowledge of which factors do not predict adherence (eg, age and gender) and of those that do might aid clinical management. Although some variables cannot be changed, such as primary prevention, new statin use, lack of comorbidities, or lower income status, greater attention (including testing) can be provided by clinicians to patients known to be more likely to be nonadherent to statin therapy.

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Supplementary Material
To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2012.05.007.