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Systematic Review/Meta-analysis

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

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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).

RÉSUMÉ

Introduction : La non-observance du traitement médicamenteux de la maladie chronique est importante. Une littérature de plus en plus vaste suggère qu'une meilleure offre de traitements établis sauverait plus de vie que le ferait la découverte d'innovations. Notre premier objectif était de quantifier la proportion d'observance au traitement par une statine. Le second objectif était de fournir l'estimation d'indicateurs de risque associés à la non-observance au traitement par une statine.

Méthodes : Nous avons effectué une revue de la littérature et une méta-analyse de toutes les études publiées entre la création de la base de données et juin 2011 sur l'observance au traitement par une statine et les indicateurs de risque associés à la non-observance de ce traitement.

Résultats : À la fin, 67 études ont répondu aux critères d'inclusion et d'exclusion et réussi notre évaluation de qualité méthodologique. Parmi les études d'observation, 49,0 % (intervalle de confiance [IC] de 95 %, 48,9 %-49,2 %) des patients suivaient rigoureusement leur traitement par une statine après 1 an de suivi. Parmi les essais aléatoires, 90,3 % (IC de 95 %, 89,8 %-90,8 %) des patients suivaient rigoureusement leur traitement par une statine après 1 an de suivi. Le lien entre les 147 variables et l'observance au traitement par une statine a été déterminé. Après la méta-analyse, seulement 6 variables ont été associées à la non-observance au traitement par une statine: la prévention primaire (ratio des taux = 1,52; IC de 95 %, 1,50-1,53); les nouveaux utilisateurs de statines (ratio des taux = 1,46; IC de 95 %, 1,33-1,61); la quote-part (ratio des taux = 1,28; IC de 95 %, 1,09-1,50; un plus faible revenu (ratio des taux = 1,26; IC de 95 %, 1,16-1,37); moins de 2 bilans lipidiques effectués (ratio des taux = 1,38; IC de 95 %, 1,16-1,64) et le fait de ne pas souffrir d'hypertension (ratio des taux = 1,16; IC de 95 %, 1,12-1,21).

The effectiveness of interventions for enhancing adherence to chronic medication remains surprisingly weak.[1] This is a concern because effective ways to help patients follow their treatment plans could improve health outcomes.[1] For example, among patients who suffered an acute myocardial infarction, 1-year mortality rates were 25% lower for those who adhered to statin medications.[2] As such, some suggest that better delivery of established therapies would actually save more lives than would the discovery of innovations.[3,4]

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.[5]

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

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Conclusions: This study provides some insight into the extent of nonadherence by study type along with 6 risk indicators associated with nonadherence to statin medications.

Conclusions : Cette étude donne un aperçu de l'étendue de la non-observance au traitement par le plan d'étude ainsi que 6 indicateurs de risque associés à la non-observance au traitement par une statine.

for primary or secondary prevention, while demographic factors such as age and gender have proven to be poor predictors.[6]

A meta-analysis reviewing adherence by study design has never been published. However, a review of indicators of nonadherence to statins has been attempted once.[7] This study had limitations, including (1) being a subanalysis of a larger study, (2) applying search filters to limit the volume of literature reviewed, (3) not including randomized trials, (4) excluding studies because they did not use multivariate analysis, and (5) not subjecting studies to a methodological quality review.[7] Because of the methodology, the authors concluded that age and gender were associated with nonadherence, which is inconsistent with the literature.[6] Self-limiting the volume of literature reviewed resulted in too few studies available for statistical pooling.[7]

Our first objective was to quantify the proportion of adherence to statin medications by study design (randomized trial vs observational study). The second objective was to provide estimates of 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 in order to apply inclusion and exclusion criteria. 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.[8] This scale includes all the questions used by the Cochrane Collaboration to assess bias.[6] A score of 5 out of 9 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).[9]

The statistical basis for the meta-analysis was taken from Fleiss.[10] Complete details on this statistical basis, along with its assumptions, have been described previously in other meta-analyses published by the principal investigator.[11-13] 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).[2,14-79] 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 635,578, 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-

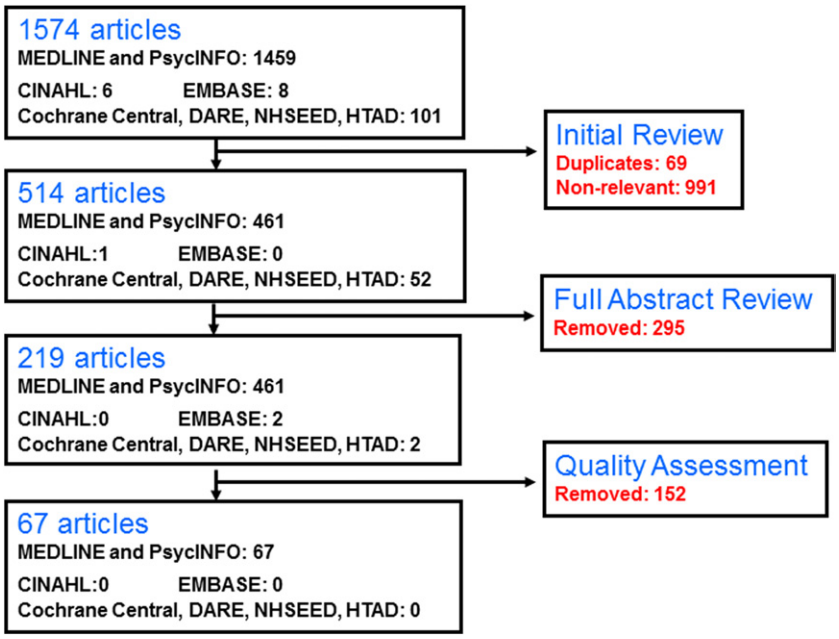

Figure 1. Systematic literature review process. CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHSEED, National Health Service Economic Evaluation Database.

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 be 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. Remov-

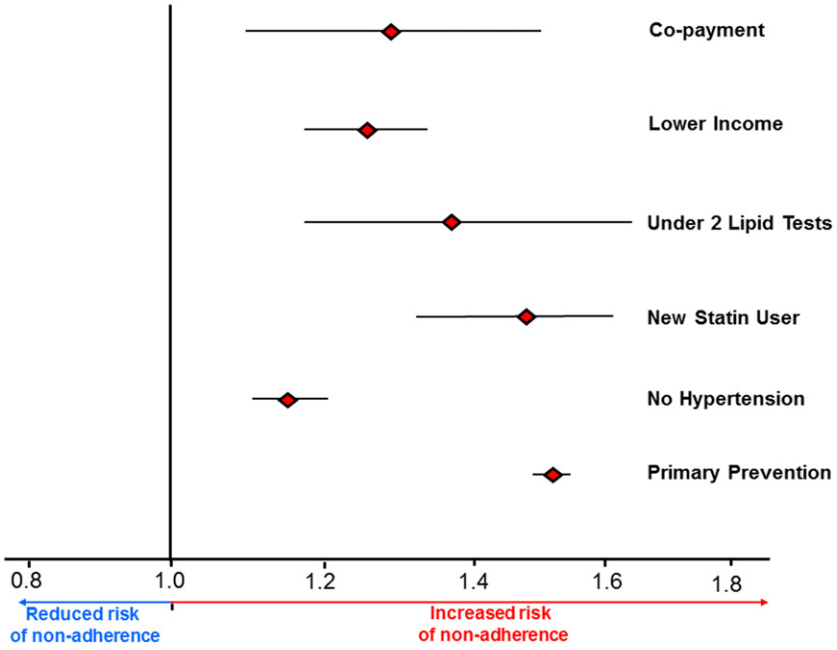

Figure 2. Variables associated with nonadherence to statin medications.

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 rigourous attention participants receive.[5] 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.[6] 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.[80] 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.[81-83] 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.[5] Similarly, patients with a concurrent diagnosis of hypertension, along with dyslipidemia, would likely have increased perceived risk of heart disease.[84] Also, receiving less lipid testing before statin therapy reflects a lack of knowledge of the disease prior to treatment.[85] Receiving less lipid testing after initiating statin therapy could reflect a number of issues, including poor patient-provider relationship.[86] 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 fulfil 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.[1] 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.[1] 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.[87] 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.

Disclosures

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References

1. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2005;4:CD000011.
2. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA 2007;297:177-86.
3. May C, Montori V, Mair F. We need minimally disruptive medicine. BMJ 2009;339:485-7.
4. Ting HH, Shojania KG, Montori VM, Bradley EH. Quality improvement: science and action. Circulation 2009;119:1962-74.
5. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
6. Schedlbauer A, Davies P, Fayey T. Interventions to improve adherence to lipid lowering medication. Cochrane Database Syst Rev 2010;3:CD004371.
7. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother 2010;44:1410-21.
8. Verhagen AP, de Vet HCW, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemio1 1998;51:1235-41.
9. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007;36:666-76.
10. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121-45.
11. Lemstra M, Bennett N, Neudorf C, et al. A meta-analysis of school based marijuana and alcohol prevention programs in targeting adolescents aged 10-15 years old. Addict & Res Theory 2010;18:84-96.
12. Lemstra M, Bennett N, Neudorf C, et al. A systematic review of drug and alcohol use by socioeconomic status in adolescents aged 10-15 years. Can J Public Health 2008;99:172-7.
13. Lemstra M, Neudorf C, D'Arcy C, Kunst A, Warren L, Bennett N. A systematic review of depressed mood and anxiety by socioeconomic status in adolescents aged 10-15 years. Can J Public Health 2008;99:125-9.
14. Abraha I, Montedori A, Stracci F, Rossi M, Romagnoli C. Statin compliance in the Umbrian population. Eur J Clin Pharmacol 2003;59:659-61.
15. Abughosh SM, Kogut SJ, Andrade SE, Larrat P, Gurwitz JH. Persistence with lipid-lowering therapy: influence of the type of lipid-lowering agent and drug benefit plan option in elderly patients. J Manage Care Pharm 2004;10:404-11.
16. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA 1998;279:1458-62.
17. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002;288:455-61.
18. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. Pharmacoeconomics 2004;22(suppl 3):13-23.
19. Blackburn DF, Dobson RT, Blackburn JL, Wilson TW. Cardiovascular morbidity associated with nonadherence to statin therapy. Pharmacotherapy 2005;25:1035-43.
20. Bouchard MH, Dragomir A, Blais L, Berard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary prevention. Br J Clin Pharmacol 2007;63:698-708.
21. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. Arch Intern Med 2007;167:847-52.
22. Bushnell CD, Zimmer LO, Pan W, et al. Persistence with stroke prevention medications 3 months after hospitalization. Arch Neurol 2010;67:1456-63.
23. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther 2005;27:1639-46.
24. Chan DC, Shrank WH, Cutler D, et al. Patient, physician, and payment predictors of statin adherence. Med Care 2010;48:196-202.

25. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. J Natl Med Assoc 2003; 95:17-27.

26. Chodick G, Shalev V, Gerber Y, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clin Ther 2008; 30:2167-79.

27. Choudhry NK, Brennan T, Toscano M, et al. Rationale and design of the Post-MI FREEE trial: a randomized evaluation of first-dollar drug coverage for post-myocardial infarction secondary preventive therapies. Am Heart J 2008;156:31-6.

28. Coberley C, Morrow G, McGinnis M, et al. Increased adherence to cardiac standards of care during participation in cardiac disease management programs. Dis Manage 2008;11:111-8.

29. Donnelly LA, Doney AS, Morris AD, Palmer CN, Donnan PT. Long-term adherence to statin treatment in diabetes. Diabet Med 2008;25: 850-5.

30. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. J Gen Intern Med 2004;19:638-45.

31. Evans CD, Eurich DT, Lamb DA, et al. Retrospective observational assessment of statin adherence among subjects patronizing different types of community pharmacies in Canada. J Manage Care Pharm 2009;15:476-84.

32. Gislason GH, Rasmussen J, Abildstrøm S, et al. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. Eur Heart J 2006;27:1153-8.

33. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovasc Disord 2006;6:48.

34. Hoeks SE, Scholte op Reimer WJ, van Gestel YR, et al. Medication underuse during long-term follow-up in patients with peripheral arterial disease. Circ Cardiovasc Qual Outcomes 2009;2:338-43.

35. Hudson M, Rahme E, Richard H, Pilote L. Comparison of measures of medication persistency using a prescription drug database. Am Heart J 2007;153:59-65.

36. Hudson M, Richard H, Pilote L. Parabolas of medication use and discontinuation after myocardial infarction—are we closing the treatment gap? Pharmacoepidemiol Drug Saf 2007;16:773-85.

37. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002; 288:462-7.

38. Kamal-Bahl SJ, Burke T, Watson D, Wentworth C. Discontinuation of lipid modifying drugs among commercially insured United States patients in recent clinical practice. Am J Cardiol 2007;99:530-4.

39. Kopjar B, Sales AE, Pineros SL, Sun H, Li YF, Hedeen AN. Adherence with statin therapy in secondary prevention of coronary heart disease in veterans administration male population. Am J Cardiol 2003;92:1106-8.

40. Lachaine J, Rinfret S, Merikle EP, Tarride JE. Persistence and adherence to cholesterol lowering agents: evidence from Regie de l'Assurance Maladie du Quebec data. Am Heart J 2006;152:164-9.

41. Larsen J, Andersen M, Kragstrup J, Gram LF. High persistence of statin use in a Danish population: compliance study 1993-1998. Br J Clin Pharmacol 2002;53:375-8.

42. McGinnis BD, Olson KL, Delate TM, Stolcpart RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. Am J Manag Care 2009;15:689-95.

43. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 2007;28:154-9.

44. Perreault S, Blais L, Dragomir A, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. Eur J Clin Pharmacol 2005;61:667-74.

45. Perreault S, Blais L, Lamarre D, et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol 2005;59:564-73.

46. Samant ND. Clinical and Economic Impact of Statin Therapy Compliance on Hyperlipidemic Patients With Concomitant CHD Risk Factors [dissertation]. Baltimore: University of Maryland School of Pharmacy; 2010.

47. Schneeweiss S, Patrick AR, Maclure M, Dormuth CR, Glynn RJ. Adherence to statin therapy under drug cost sharing in patients with and without acute myocardial infarction: a population-based natural experiment. Circulation 2007;115:2128-35.

48. Shah ND, Dunlay SM, Ting HH, et al. Long-term medication adherence after myocardial infarction: experience of a community. Am J Med 2009; 122:e7-13.

49. Simpson RJ Jr, Signorovitch J, Birnbaum H, et al. Cardiovascular and economic outcomes after initiation of lipid-lowering therapy with atorvastatin vs simvastatin in an employed population. Mayo Clin Proc 2009; 84:1065-72.

50. Smith CS, Cannon CP, McCabe CH, Murphy SA, Bentley J, Braunwald E. Early initiation of lipid-lowering therapy for acute coronary syndromes improves compliance with guideline recommendations: observations from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial. Am Heart J 2005;149:444-50.

51. Tuppin P, Neumann A, Danchin N, et al. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. Arch Cardiovasc Dis 2010;103:363-75.

52. Valuck RJ, Williams SA, MacArthur M, et al. A retrospective cohort study of correlates of response to pharmacologic therapy for hyperlipidemia in members of a managed care organization. Clin Ther 2003;25:2936-57.

53. Vanelli M, Pedan A, Liu N, Hoar J, Messier D, Kiarsis K. The role of patient inexperience in medication discontinuation: a retrospective analysis of medication nonpersistence in seven chronic illnesses. Clin Ther 2009;31:2628-52.

54. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol 2008;66:110-6.

55. Wei L, MacDonald TM, Watson AD, Murphy MJ. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. Pharmacoepidemiol Drug Saf 2007;16: 385-92.

56. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart 2002;88:229-33.

57. Winkelmayer WC, Levin R, Setoguchi S. Associations of kidney function with cardiovascular medication use after myocardial infarction. Clin J Am Soc Nephrol 2008;3:1415-22.

58. Ye X, Gross CR, Schommer J, Cline R, St Peter WL. Association between copayment and adherence to statin treatment initiated after coronary

heart disease hospitalization: a longitudinal, retrospective, cohort study. Clin Ther 2007;29:2748-57.

59. Eagle KA, Kline-Rogers E, Goodman SG, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. Am J Med 2004;117:73-81.

60. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke 2010;41:397-401.

61. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis 2006;185:394-9.

62. Mann DM, Allegrante JP, Natarajan S, Halm EA, Charlson M. Predictors of adherence to statins for primary prevention. Cardiovasc Drugs Ther 2007;21:311-6.

63. Melloni C, Alexander KP, Ou FS, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. Am J Cardiol 2009;104:175-81.

64. Muhlestein JB, Horne BD, Bair TL, et al. Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. Am J Cardiol 2001;87:257-61.

65. Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: Prospective Pravastatin Pooling (PPP) Project. Circulation 2002;105:2341-6.

66. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative G. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757-67.

67. Dart A, Jerums G, Nicholson G, et al. A multi-center, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. Am J Cardiol 1997; 80;39-44.

68. Downs JR, Clearfield M, Tyroler HA, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS): additional perspectives on tolerability of long-term treatment with lovastatin. Am J Cardiol 2001;87:1074-9.

69. Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a national registry: results of the first myocardial infarction risk reduction program. Clin Ther 2001; 23:970-80.

70. Margolis KL, Dunn K, Simpson LM, et al. Coronary heart disease in moderately hypercholesterolemic, hypertensive black and non-black patients randomized to pravastatin versus usual care: the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT-LLT). Am Heart J 2009;158:948-55.

71. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006;368:1155-63.

72. Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1996;156:2085-92.

73. Pedersen TR, Faergeman O, Kastelein JJ, et al.; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial [erratum appears in JAMA 2005;294:3092]. JAMA 2005;294: 2437-45.

74. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. NEJM 1996;335:1001-9.

75. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation 1995;92:1758-64.

76. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. NEJM 1995;333: 1301-7.

77. Stacy JN, Schwartz SM, Ershoff D, Shreve MS. Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: results of a randomized clinical trial in a managed care setting. Popul Health Manag 2009;12:241-54.

78. Tikkanen MJ, Holme I, Cater NB, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged < 65 versus ≥ 65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol 2009;103:577-82.

79. Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. Ann Intern Med 2003;138:98-104.

80. Law M, Cheng L, Dhalla I, Heard D, Morgan S. The effect of cost on adherence to prescription medications in Canada. CMAJ 2012;184:297-302.

81. O'Malley AS, Forrest CB, Mandelblatt J. Adherence of low-income women to cancer screening recommendations. J Gen Intern Med 2002; 17:144-54.

82. Celano M, Geller RJ, Phillips KM, Ziman R. Treatment adherence among low-income children with asthma. J Pediatr Psychol 1998;23: 345-9.

83. Orlandi MA. Promoting health and preventing disease in health care settings: an analysis of barriers. Prev Med 1987;16:119-30.

84. Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication in inflammatory bowel disease. Am J Gastroenterol 2003;98: 1535-44.

85. Glanz K, Rimer B, Viswanath K, eds. Health Behavior and Health Education. 4th ed. San Francisco, CA: Jossey-Bass, 2008.

86. Vik SA, Maxwell DJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. Ann Pharmacother 2004;353:487-97.

87. Grover S, Coupal L, Kouache M, Lowensteyn I, Marchand S, Campbell N. Estimating the benefits of patient and physician adherence to cardiovascular prevention guidelines: the MyHealthCheckup Survey. Can J Cardiol 2011;27:159-66.

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.