A STUDY OF CORONARY HEART DISEASE PREDICTION

Ms. Suganya. R.*1, Mrs. Geetha. S*2.,

*1M.Phil Research Scholar, Department of Computer Science Muthurangam Government Arts College (Autonomous), Vellore, TamilNadu, India.
*2Assistant Prof, Department of Computer Science Muthurangam Government Arts College (Autonomous), Vellore, TamilNadu, India.

Introduction

Atherothrombotic disease is the leading cause of mortality among individuals in the United States, with heart disease and stroke contributing to approximately 23.7% and 5.1% of deaths, respectively, in 2011.1 Approximately 7.6 million and 6.6 million adults have experienced myocardial infarction (MI) or stroke, respectively.2 Peripheral arterial disease (PAD), a strong predictor of cardiac and cerebrovascular mortality,3 is another life-threatening condition that affects 8.5 million (~7.2%) US adults over the age of 40 years.4 Hospitalizations for atherothrombotic disease occur with high frequency. In 2009, 1.35 million individuals were hospitalized for coronary heart disease (CHD). Approximately 691 000 hospitalizations per year have been attributed to acute ischemic stroke. Another ~1 million individuals were discharged from the hospital for heart failure in a single year.[7] Fortunately, rates of CHD and cerebrovascular dis- ease have shown a trend toward decline during the last several years.[1] Age-adjusted mortality from CHD also decreased, by 66% in men and 67% in women, from 1980 to 2009.[5] Likewise, age-adjusted mortality from stroke has declined, from 48.0 to 37.9 persons per 100 000, from 2005 to 2011.

Overall reductions in mortality rates have been attributed, at least in part, to the availability of effective pharmacologic therapies, including antiplatelet therapies (e.g., aspirin),8 antihypertensive therapies (e.g., ß-blockers and angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]),9,10 and dyslipidemia treatments (e.g., statins).11 However, despite the substantial progress that has been made in reducing the rate of cardiovascular disease (CVD)-related mortality, nonadherence to medications for CVD prevention, including aspirin, continues to negatively impact patient out- comes,12–15 adding to the already high burden of these diseases on the healthcare system.16

The term adherence is often considered in a variety of contexts (e.g., lifestyle modifications, evidence-based guidelines, medication); however, a sizable body of published evidence has focused on medication adherence. This narrative review summarizes the data from primary research and review papers that examined patient adherence to medications for secondary prevention of CVD events (with a focus on aspirin), as measured by prescription refill data, electronic medication monitors, pill counts, and physiologic markers. Implications of medication nonadherence in the chronic treatment of CVD are substantial; therefore, understanding the barriers to adherence and the implications of suboptimal adherence is vital to improving treatment compliance and health outcomes in this large patient population.

METHODS

The PubMed database was searched for English-language articles with no time limitation up to June 21, 2015, using the following key words: “adherence,” “compliance,” “secondary prevention,” and “cardiovascular disease.” Additional database searches were performed using the following search strings: (“adherence” OR “compliance”) AND “secondary prevention” AND “cardiovascular disease.” Outcomes of the primary literature search yielded a total of 201 publications, from which approximately 25% (52) were ultimately selected for further consideration (41 original articles and 11 reviews). Articles that contained adherence data only in the setting of primary prevention, lacked data on medication adherence (e.g., focus on guideline adherence), emphasized quality-of-care outcomes, or focused on outcomes of acute interventions were excluded. Application of these delimiters led to the exclusion of approximately 90% of the 52 citations.

Consultation of more recent review articles and treatment guide- lines for general information on medication adherence for secondary prevention of CVD was also performed. Lastly, bibliographies from included articles and guidelines were manually reviewed for additional relevant studies. A majority of the literature cited the current manuscript was identified from manually reviewing previous publications on topic of adherence in the secondary prevention of CVD.

2.1 Prevalence of medication nonadherence

Patients are considered adherent to treatment when they actively, voluntarily, and collaboratively participate in the choice and goals of therapy, as well as planning and implementation of the treatment regimen.[17] In the literature, medication adherence rates of 80% are generally considered adequate for patients with established CVD or at risk for CVD.[18] Thus, in this context, medication adherence rates <80% should be considered suboptimal to varying degrees, depending on the

level of importance of a drug class to clinical response by disease state (e.g., adherence to glucose-lowering medications in patients with diabetes).

Poor adherence to medications for secondary prevention of cardiovascular (CV) events and mortality may be especially deleterious. A number of studies and meta-analyses have reported adherence rates of ~60% to 75% for chronic treatments for secondary preven- tion in CVD, with aspirin having one of the lowest reported rates of adherence (65%) among these therapies (Figure 1).[19–23] In one meta- analysis, adherence (based on pharmacy prescription refill data) to medications for secondary prevention during a median 24-month period was 66%.[19] Although some between-drug class variability was evident, there was generally no statistical difference, suggesting that adherence was not linked to any specific drug class.

Another study, of 1114 patients with various clinical manifestations of vascular disease (e.g., critical limb ischemia, claudication, acute limb ischemia), reported adherence rates of 64% to 91% for aspirin, 43% to 83% for statins, and 49% to 66% for ACE inhib- itors.[21] Lastly, long-term (10-year) adherence rates for patients with CVD taking aspirin, statins, or combination aspirin plus sta- tin therapy for secondary prevention were 60%, 64.5%, and 76.0%, respectively.[23]

A retrospective study of prospective data from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) and Translating Research Investigating Underlying Disparities in AMI Patients Health Status (TRIUMPH) registries (n=6838), both of which included patients with acute MI, showed that only up to 61.5% of patients reported "persistence" (i.e., self-reported medication use) with their prescribed secondary prevention regi- men after 12 months.[24] The persistence rate was even lower among patients at intermediate (59.3%) or high risk (45.9%) of a CV event.[24] Aspirin was the only secondary prevention medication that was associated with a significantly increased risk of lack of persistence in both intermediate-risk (relative risk [RR], 0.96; 95% confidence interval [CI], 0.95–0.99) and high-risk (RR, 0.92; 95% CI, 0.89–0.95) patients when compared with their low-risk counterparts.[24]

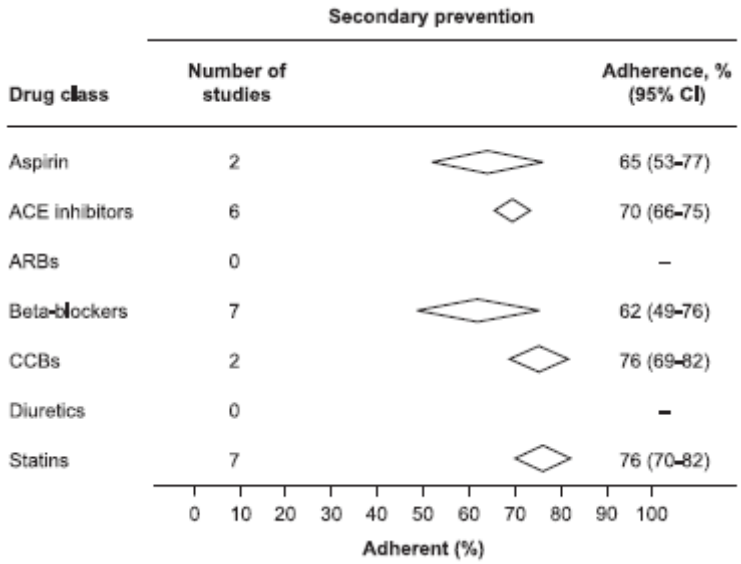

FIGURE 1 Summary of patient adherence in secondary prevention of CVD. Adherence is suboptimal for all medication classes in secondary prevention settings. Adapted with permission from Naderi SH, et al.[19] ACE; angiotensin-converting enzyme, ARB; angiotensin receptor blocker, CCB; calcium channel blocker, CI; confidence interval

2.2. **Health outcomes of nonadherence in secondary prevention of CVD**

Nonadherence is associated with higher morbidity and mortality, resulting in ~130 000 (41% of 320 000) avoidable deaths each year in the United States.[19] A systematic review of adherence in patients with established CVD found that for every 10% increase in medical adherence, an additional 6.7% of CV events could be prevented over 10 years.[22] In terms of reducing blood cholesterol levels to prevent atherosclerotic CVD, it has been suggested that patient adherence to medications is the single greatest opportunity to improve lowering of low-density lipoprotein cholesterol (LDL-C).[25]

In high-risk patients hospitalized with acute MI and subsequently discharged on aspirin, ß-blockers, statin therapy, or a combination of all three medications, mortality was highest among patients who discontinued use of all medications (hazard ratio, 3.8; 95% CI, 1.9–7.7; Figure 2).[26] However, discontinuation of any of these treatments increased the risk of mortality, with nearly 2-fold and 3-fold increases seen with discontinuation of aspirin and statin therapies, respectively.[26]

The large observational study, the Reduction of Atherothrombosis for Continued Health (REACH) registry, followed 37 154 patients with atherothrombotic disease of coronary, cerebrovascular, and/or PAD origin for 1 year to assess medication adherence, which was deter- mined based on patient self-report. The primary outcome was a composite endpoint of CV mortality, MI, or stroke at 4 years.[14] Only 46.7% of patients at baseline and 48.2% at 1 year were fully adherent with guideline-recommended medications for secondary prevention, such as antiplatelet agents, lipid-lowering therapies, and antihypertensive agents. At the time of enrollment, aspirin was the most commonly administered antiplatelet agent, used by 84% of patients. Patients who were fully adherent at baseline and 1 year had the lowest incidence

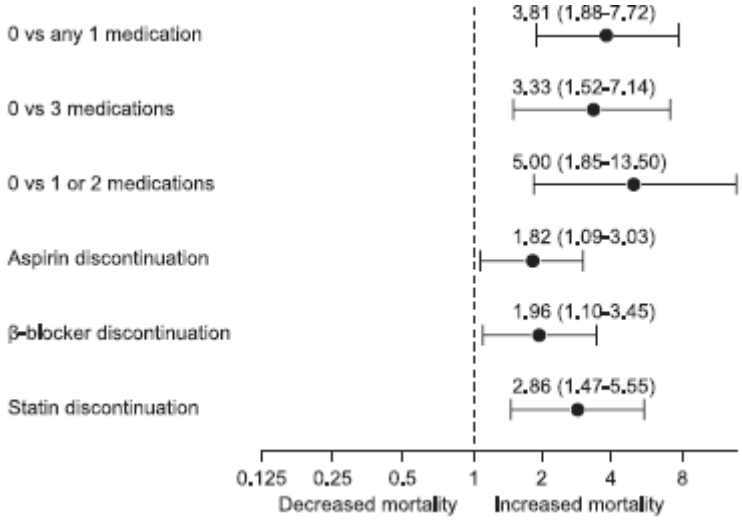

FIGURE 2 Mortality risk by medication adherence subgroup. Adjusted hazard ratios for patient subgroups. Error bars represent 95% confidence intervals. Discontinuation of any treatment for myocardial infarction was associated with an increased 12-month mortality rate.

of all-cause mortality vs those who were non adherent at both time points (*P*<.0001). Conversely, nonadherence to medications at base- line or 1 year increased the risk of all-cause and CV mortality at 4 years by approximately 30% (*P*<.001).[14] Those who were consistently non- adherent (i.e., no adherent at baseline and at 1 year) and negative converters (those who were compliant at baseline but nonadherent at 1 year) fared worst (Figure 3).[14] Cumulative incidence of CVD, MI, or stroke showed a similar trend.[14]

Aspirin

Aspirin is regarded as first-line antiplatelet therapy for secondary prevention and as primary prevention of CV events in select patients[27]; therefore, patient adherence to aspirin therapy has been evaluated in many studies. In a meta-analysis of six trials that evaluated withdrawal of aspirin therapy among patients with known CHD, nonadherence or discontinuation of aspirin imparted a 3-fold increased risk of over- all (odds ratio, 3.1; 95% CI, 1.8–5.6; *P*=.0001) thrombotic events and a 2-fold increase in the risk of coronary artery disease (odds ratio, 1.8; 95% CI, 1.5–2.2) and coronary artery bypass grafting (odds ratio, 2.4; 95% CI, 1.6–3.1).[15] In patients who experienced a CV event, the mean time from aspirin withdrawal to occurrence of the event was 10.7 days, which mirrors complete turnover of platelet population (i.e., the platelet life cycle).[15] Among the 3 studies that enrolled patients who had acute coronary syndrome or were taking secondary prevention therapies for CVD, risk of adverse thrombotic events was increased nearly 2-fold (1.8; 95% CI, 1.5–2.2; *P*<.00001) in patients who discontinued or were not adherent to the aspirin regimen.[15]

2.3 High-risk populations: diabetes mellitus

In contrast to the declining rates of CHD and cerebrovascular disease mentioned earlier, prevalence of diabetes is on the rise. If current epidemiologic trends hold true, one in three US adults will likely develop diabetes in their lifetime.[28] Patients with type 1 or 2 diabetes have high long-term risk for a CV event,[29] and risk of CV mortality is approximately 1.7-fold higher in this group, compared with those without diabetes.[30] In addition, the complexity of therapies[30] for management of diabetes and its comorbidities presents challenges to patient adherence.

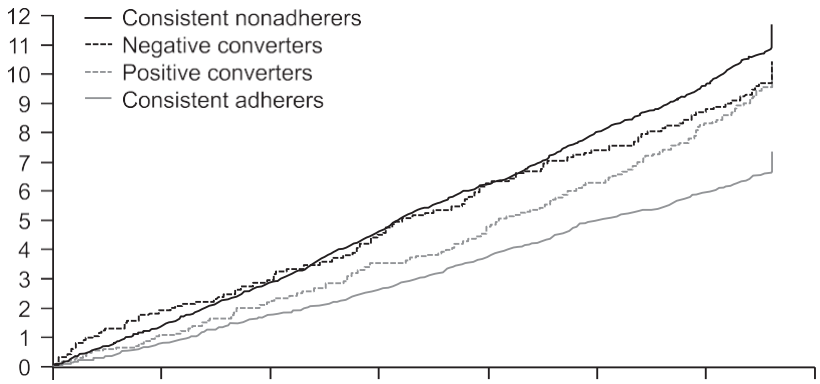

FIGURE 3 Kaplan–Meier summary of all-cause mortality in patients grouped according to adherence to antiplatelet therapy, lipid-lowering therapy, and antihypertensive therapy at baseline and at 1 y. Consistent no nadherers were no nadherent at baseline and at 1 y, whereas consistent adherers were adherent at baseline and at 1 y.

Treatment-related factors affecting adherence

In patients taking chronic therapy for CVD, frequency of dosing was inversely related to adherence: the higher the dosing frequency, the lower the patient adherence.[36–38] In a study of 91 patients with diabetes using oral antidiabetic agents, adherence to oral treatments taken 3 times daily was 38%, compared with 79% for once-daily therapy.[36] Patients with pulmonary embolism and deep vein thrombosis were 62% more likely to be adherent to their once-daily treat- ment than those who received twice-daily dosing (*P*<.001 for both comparisons).[37]

In a study of 1.08 million adults with a prescription for a once-daily or twice-daily antidiabetic, antihyperlipidemic, antiplatelet, or cardiac agent, 1-year adherence (measured as the medication possession ratio [MPR]) was higher for once-daily vs twice-daily dosing, with the greatest difference observed for antiplatelet agents (Table 1).[38] In this case, twice-daily treatments, primarily aspirin/dipyridamole, cilostazol, and ticlopidine, were associated with a 42% worsening in adherence (*P*<.01 vs once-daily treatment). This equated to an approximately 30% improvement in patient compliance with use of once-daily therapy.[38]

A 2010 observational study examined 340 patients at risk for or with confirmed CVD who were receiving low-dose aspirin (75– 325 mg/d).[39] Patients were assessed for the impact of upper gastrointestinal (GI) symptoms on nonadherence (defined as low-dose aspirin intake of <75% during a 3-month period). Most (75%) patients were low-dose aspirin-naïve at study entry, with no upper GI symptoms reported during the previous 14 days. Approximately two-thirds of patients (65%) were taking low-dose aspirin as secondary prevention or high-risk primary prevention. Among aspirin-naïve patients, the onset of upper GI symptoms was rapid, with 19% reporting symp- toms on Day 1 of the study, which increased to 46% during Week 1 (cumulative). Overall, 61 (18%) patients were nonadherent to low- dose aspirin during the 3-month period. Importantly, patients with upper GI symptoms during the day were significantly less likely to be adherent to aspirin regimens (P<.01). Other therapeutic classes used in the treatment of CVD are likewise associated with adverse effects (to a variable extent), including statin-induced myalgia, ACE inhibitor-induced cough, and ß-blocker-induced fatigue; these adverse effects have been known to result in nonadherence or out- right discontinuation.

Patient-related factors affecting adherence

Patient perceptions of the brevity of their illness or of how critical a medication may be to health or survival are subjective and may be influenced by a number of factors, including the degree to which patients understand their disease state and a lack of perceived need or benefit from recommended medication(s). The latter may be especially true for patients taking antiplatelet medications (e.g., aspi-rin) for in-stent thrombosis, statin therapy for dyslipidemia, or therapy for hypertension, because clinical symptoms of disease are not always outwardly evident for individuals in these populations.[34] Patients with diabetes, for example, may perceive their glucose-lowering therapy to be more important to disease management than antihypertensive or lipid-lowering therapies

CONCLUSION

The causes of poor or suboptimal adherence to drug therapies are multifactorial, involving patient perceptions and preferences, socioeconomic considerations, and a range of disease- or treatment-specific factors. Patient age and mental health and smoking status can impact treatment adherence,[33,34] as can a patient's perception of the severity of his or her illness.[34,43] It is common for patients to perceive OTC treatments as being less important or effective compared with prescription drugs.[44,45] In addition, frequency of dosing has been noted to influence adherence, with a higher dosing frequency associated with lower patient adherence rates.[38] As well, concerns about drug toxicity or occurrence of adverse effects may impact patients' compliance with their therapeutic regimens.[18,34] Inadequate healthcare cov- erage, low income

status, or high out-of-pocket costs can also affect adherence.[34] In addition, many high-risk patient groups, such as those with diabetes, are less likely to adhere to twice-daily or thrice-daily dosing.

Although the causes of nonadherence are complex and multi- factorial, adherence programs coupled with treatment regimens that involve less frequent dosing and fewer adverse effects are likely to offer the best chance for achieving successful outcomes. Because of the OTC status of aspirin, an effective and established antiplatelet therapy for secondary prevention of cardiovascular disease, adherence is likely further diminished through lack of perceived benefit, as well as deficiencies in terms of setting expectations during patient counseling. Assessment of the value of improving adherence to OTC prevention

REFERENCES

1. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: leading causes of morbidity and mortality and asso- ciated behavioral risk and protective factors–United States, 2005- 2013. MMWR Surveill Summ. 2014;63:3–27.

2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American heart association. Circulation. 2015;131:e29–e322.

3. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbid- ity and mortality implications. Circulation. 2006;114:688–699.

4. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med. 2007;32:328–333.

5. Ford ES, Roger VL, Dunlay SM, Go AS, Rosamond WD. Challenges of ascertaining national trends in the incidence of coronary heart dis- ease in the United States. J Am Heart Assoc. 2014;3:e001097.

6. Smith EE, Saver JL, Alexander DN, et al. Clinical performance mea- sures for adults hospitalized with acute ischemic stroke: performance measures for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3472– 3498.

7. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke sta- tistics–2014 update: a report from the American Heart Association. Circulation. 2014;129:e28–e292.

8. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.

9. Larochelle P, Tobe SW, Lacourciere Y. beta-Blockers in hypertension: studies and meta-analyses over the years. Can J Cardiol. 2014;30:S16– S22.

10. Tuppin P, Neumann A, Danchin N, et al. Evidence-based pharmaco- therapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitaliza- tion. Arch Cardiovasc Dis. 2010;103:363–375.

11. Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol. 2013;20:641–657.

12. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic con- trol, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tay- side Scotland. Medicines Monitoring Unit. Lancet. 1997;350:1505– 1510.

13. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonad- herence on hospitalization and mortality among patients with diabe- tes mellitus. Arch Intern Med. 2006;166:1836–1841.

14. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med. 2013;126:693–700.

15. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006;27:2667–2674.

16. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med.2005;353:487–497.

17. Delamater A. Improving patient adherence. Clin Diabetes. 2006;24:71– 77.

18. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its impor- tance in cardiovascular outcomes. Circulation. 2009;119:3028–3035.

19. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125:882–887.

20. Herlitz J, Toth PP, Naesdal J. Low-dose aspirin therapy for cardiovas- cular prevention: quantification and consequences of poor compli- ance or discontinuation. Am J Cardiovasc Drugs. 2010;10:125–141.

21. Chen DC, Armstrong EJ, Singh GD, Amsterdam EA, Laird JR. Adher- ence to guideline-recommended therapies among patients with diverse manifestations of vascular disease. Vasc Health Risk Manag. 2015;11:185–192.

22. Becerra V, Gracia A, Desai K, et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. BMJ Open. 2015;5:e007111.

23. 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;66:110–116.

24. Shore S, Jones PG, Maddox TM, et al. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocar- dial infarction. Heart. 2015;101:800–807.

25. Ray KK, Kastelein JJ, Boekholdt SM, et al. The ACC/AHA 2013 guide- line on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncer- tain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J. 2014;35:960–968.

26. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006;166:1842–1847.

27. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary pre- vention of cardiovascular disease: antithrombotic therapy and pre- vention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e637S– e668S.

28. Centers for Disease Control and Prevention. Diabetes: successes and opportunities for population-based prevention and control. 2015. Available at: http://www.cdc.gov/chronicdisease/resources/publica- tions/AAG/ddt.htm. Accessed June 3, 2015.

29. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recom- mendations for patient-centered management of dyslipidemia: part 1-full report. J Clin Lipidol. 2015;9:129–169.

30. Miller BR, Nguyen H, Hu CJ, Lin C, Nguyen QT. New and emerging drugs and targets for type 2 diabetes: reviewing the evidence. Am Health Drug Benefits. 2014;7:452–463.

31. Rodriguez F, Cannon CP, Steg PG, et al. REACH Registry Investigators. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic dis- ease: findings from the REACH Registry. Clin Cardiol. 2013;36:721–727.

32. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long- term adherence with cardiovascular drug regimens. Am Heart J. 2006;151:185–191.

33. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113:203–212.Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. Circulation. 2010;121:1455–1458.

34. Davis EM, Packard KA, Jackevicius CA. The pharmacist role in pre- dicting and improving medication adherence in heart failure patients. J Manag Care Spec Pharm. 2014;20:741–755.

35. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. Diabetes Care. 1997;20:1512–1517.

36. Laliberté F, Bookhart BK, Nelson WW, et al. Impact of once-daily versus twice-daily dosing frequency on adherence to chronic med- ications among patients with venous thromboembolism. Patient. 2013;6:213–224.

37. Bae JP, Dobesh PP, Klepser DG, et al. Adherence and dosing fre- quency of common medications for cardiovascular patients. Am J Manag Care. 2012;18:139–146.

38. Pratt S, Thompson VJ, Elkin EP, Naesdal J, Sorstadius E. The impact of upper gastrointestinal symptoms on nonadherence to, and discontin- uation of, low-dose acetylsalicylic acid in patients with cardiovascular risk. Am J Cardiovasc Drugs. 2010;10:281–288.

39. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Soci- ety Consensus Panel Statement on Assessment. Aetiology and Man- agement. Eur Heart J. 2015;36:1012–1022.

40. Vegter S, de BP, van Dijk KW, Visser S, de Jong-van den Berg LT. The effects of antitussive treatment of ACE inhibitor-induced cough on therapy compliance: a prescription sequence symmetry analysis. Drug Saf. 2013;36:435–439.