REVIEW

Benefits of statin therapy and compliance in high risk cardiovascular patients

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Abstract: Cardiovascular disease (CVD) remains the top cause of global mortality. There is considerable evidence that supports the mortality and morbidity benefit of statin therapy in coronary heart disease (CHD) and stroke, both in primary and secondary prevention settings. Data also exist pointing to the advantage of statin treatment in other high-risk CVD conditions, such as diabetes, CKD, CHF, and PVD. National and international clinical guidelines in the management of these CVD conditions all advocate for the utilization of statin therapy in appropriate patients. However, overall compliance to statin therapy remains suboptimal. Patient-, physician-, and economic-related factors all play a role. These factors need to be considered in devising approaches to enhance adherence to guideline-based therapies. To fully reap the benefits of statin therapy, interventions which improve long-term treatment compliance in real-world settings should be encouraged.

Keywords: cardiovascular disease, statin therapy, coronary heart disease, long-term treatment compliance

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for nearly 30% of the annual global mortality.[1] In the United States, where the disease is highly prevalent, over one third of the population has one or more types of CVD. Coronary heart disease (CHD) affects nearly 18 million Americans. As the predominant cause of death from CVD, it is estimated that over one million individuals suffer from acute CHD events each year in the United States. Stroke, the second leading cause of death from CVD, has a prevalence of nearly 6.5 million, and over 600,000 new stroke cases are diagnosed annually in the United States.[2] Other forms of high-risk CVD conditions are common as well. Approximately 5 million Americans have been diagnosed with heart failure (HF), and around 8 million Americans with peripheral vascular disease (PVD). Diabetes mellitus, a major CVD risk factor and CHD-equivalent, afflicts approximately 5.5 million individuals in the United States.

Dyslipidemia is one of the major CVD risk factors, and cholesterol-modifying therapy has well-established benefits in the primary and secondary prevention of CHD and stroke. As such, lipid-lowering therapy, primarily with the HMG-CoA-reductase inhibitors (statins), has become the mainstay of therapeutic guidelines for the management of these conditions.[3,4] There is also a growing body of evidence supporting the benefit of statin therapy in other CVD conditions such as heart failure (HF), PVD, and chronic kidney disease (CKD). Furthermore, statin therapy has already been an integral part of the standard management of diabetes mellitus, a major CVD risk factor and CHD-equivalent.[5]

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Although the burden of CVD remains high, mortality has been on a declining trend, which is largely attributed to evidence-based therapies – especially risk-reduction strategies, including the use of statins. Despite the known benefits, however, a significant proportion of high risk patients with CVD still do not receive the recommended regimens of lipid-modifying therapy, and many others discontinue treatment after being initiated on statin therapy. Improving the compliance to guideline-based therapies by both patients and physicians could potentially further reduce the public health and economic burden imposed by CVD.

Lipids, CVD risk, and statins

The relationship between abnormal plasma cholesterol fractions and increased CVD risk was described up to 60 years ago, when the role of the different lipoproteins in atherosclerosis was just being elucidated.[6] The modern concept of atherogenesis highlights the crucial roles these lipoproteins play in the atherosclerotic process. One of the earliest steps in atheroma formation involves the infiltration of the dysfunctional vascular endothelium by low-density lipoprotein cholesterol (LDL), the most atherogenic of the lipoproteins. The LDL in the vessel wall becomes oxidized and is taken up by macrophages forming the classic foam cells. This process further stimulates lipid deposition and incites the inflammatory cascade that leads to the formation of the atherosclerotic plaque. On the other hand, the high-density lipoprotein cholesterol (HDL) promotes reverse transport of cholesterol from lipid-laden macrophages in the vascular wall, and has anti-inflammatory effects, thereby inhibiting the progression of atherosclerosis and potentially inducing regression of the atherosclerotic plaque.[7] In various conditions where levels of LDL are abnormally high or levels of HDL are low, the atherosclerotic process is enhanced, increasing the risk of development of CVD.

Statins exert their LDL-lowering effect primarily through the inhibition of the HMG-CoA-reductase enzyme, which mediates the first committed step in the mevalonate pathway of cholesterol synthesis. To a lesser degree, these agents also decrease triglyceride levels, probably through inhibition of its synthesis in the liver and enhancement of lipoprotein lipase enzyme activity in the adipocytes.[8] Statins also have modest HDL-raising properties, which are postulated to result from the activation of peroxisome proliferator-activated receptors, leading to Apo-A1 gene induction.[9] It is also theorized that lipid-independent effects of statins contribute to some degree to their anti-atherothrombotic properties. A few of these purported pleiotrophic effects include modulation of inflammatory response, improvement of endothelial function, and inhibition of coagulation.[10]

The earliest statin commercially developed, lovastatin, was released for clinical use in 1987. Several other agents have been marketed since. Clinical data for some of the older statins (eg, lovastatin, pravastatin, simvastatin) showed reductions of 25%–39% in LDL and 8%–12% in triglycerides, as well as a 6%–8% increase in HDL. More potent agents (eg, atorvastatin, rosuvastatin) were later developed, making it possible to achieve even more stringent target lipid goals (up to 55% reduction in LDL, up to 20% lowering in triglycerides, and up to 10% increase in HDL).[11,12]
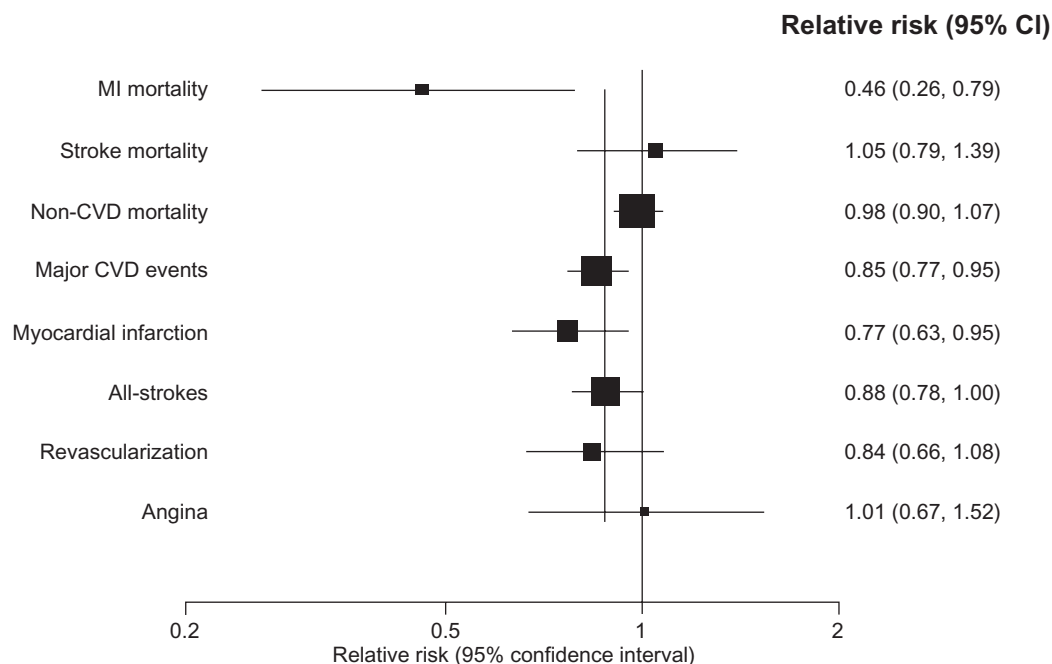
Statins in the primary prevention of CHD

Because atherogenic lipoproteins are involved very early in the atherosclerotic process, it is conceivable that treatment with statins could potentially obviate the first onset of CHD events in individuals who are at risk but have not had a previous coronary event. Indeed, analysis of data from primary prevention studies[13] showed that statin therapy, on average, reduces the risk of overall mortality by 7% and MI by 27% (see Figure 1).

In patients with elevated cholesterol levels but without prior history of MI or stroke, the benefit of treatment with statins in the primary prevention of CHD was assessed by the West of Scotland Coronary Prevention Study (WOSCOPS)[14] and the more recent Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)[15] trial. With an aggregate sample size of over 14,500 people, in both studies it was demonstrated that pravastatin was associated with reductions in MI (31% in WOSCOPS, 48% in MEGA) and mortality (32% in WOSCOPS, 28% in MEGA) after 5 years of follow-up.

In individuals who have moderate cholesterol levels and are free of overt CVD, statin therapy using lovastatin was associated with reductions in major CHD events by 64% in the Asymptomatic Carotid Artery Progression Study (ACAPS)[16] and 37% in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Similarly, in over 10,300 patients with average cholesterol profile and moderate CVD risk, the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)[17] found that low-dose atorvastatin therapy resulted in a 36% reduction in fatal CHD and nonfatal MI.

In a primary prevention study of nearly 18,000 healthy participants with normal cholesterol profiles but elevated C-reactive protein levels, the Justification for the Use of

Relative risk (95% CI)

MI mortality	0.46 (0.26, 0.79)
Stroke mortality	1.05 (0.79, 1.39)
Non-CVD mortality	0.98 (0.90, 1.07)
Major CVD events	0.85 (0.77, 0.95)
Myocardial infarction	0.77 (0.63, 0.95)
All-strokes	0.88 (0.78, 1.00)
Revascularization	0.84 (0.66, 1.08)
Angina	1.01 (0.67, 1.52)

Relative risk (95% confidence interval)

Figure 1 Plotted estimates of outcomes pooled from primary prevention trials on statin therapy. Pooled relative risk with bars representing 95% confidence intervals (CIs).
Notes: Adapted with permission from Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol*. 2008;52(22):1769–1781.

Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[18] found that treatment with the agent rosuvastatin led to a 54% reduction in MI and 20% mortality reduction in this group of low-risk individuals. How the results of the JUPITER trial impact the current and future standards of clinical preventive therapy remains to be seen.

Lipid-lowering guidelines published before the completion of the JUPITER trial recommend that for primary prevention of CHD in low-risk patients, statin therapy should be started if LDL is above 190 mg/dL, and is only optional if LDL > 160 mg/dL. Pharmacologic treatment is otherwise not advocated for healthy individuals with LDL < 160 mg/dL, unless two or more CVD risk factors are present.[19] To date, there remains no consensus as to the clinical benefit of starting maintenance statin treatment in low-risk, normocholesterolemic individuals.

Statins in the secondary prevention of CHD

While the debate continues as to whether or not healthy individuals should be treated with statins as a primary preventative measure, the role of statin therapy in the secondary prevention of further CHD events is unquestioned, and has, in fact, revolutionized the medical management of patients with preexisting CVD. The Scandinavian Simvastatin Survival Study (4S)[20] was the first large clinical trial to demonstrate

such benefit. In this study of 4,444 patients with established CHD, long-term treatment with simvastatin was shown to significantly reduce rates of mortality by 30% and coronary events by 34%. This was followed by the Cholesterol and Recurrent Events (CARE) trial, in which a 24% decrease in CHD events with pravastatin was found in over 4,000 patients with prior MI.[21]

The mortality benefit of statin therapy was unclear in the CARE trial, but this was definitively established by the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)[22] study of over 9,000 patients with unstable CHD. In this trial, pravastatin lowered the overall mortality by 14% and cardiovascular mortality by 24%, along with a 29% reduction in MI. The survival advantage of statin therapy was consistent, irrespective of baseline cholesterol level, as illustrated by the Heart Protection Study[23] involving over 20,500 high-risk patients with CVD. In this trial, simvastatin was associated with significant reductions in all-cause mortality by 13% and in cardiovascular mortality by 18%, across a wide range of initial LDL levels.

High-dose statin therapy is associated with significantly greater reduction in the rate of progression of atherosclerosis compared to a moderate-intensity regimen in patients with CHD and elevated LDL.[24] The benefits conferred by intensive statin therapy extends even to those with normal LDL levels, as seen in the Treat to New Targets (TNT) trial, where in over 10,000 patients with CHD and LDL < 130 mg/dL, high-dose

atorvastatin therapy was superior to low-dose treatment in preventing recurrent CHD events.[25]

In patients with acute coronary syndrome (ACS), the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)[26] study showed that statin therapy using high-dose atorvastatin significantly lowered early recurrent ischemic events by 24%. Also, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22)[27] trial it was found that intensive therapy using high-dose atorvastatin was superior to moderate-intensity treatment using pravastatin in preventing subsequent CHD events in this high-risk group of patients with ACS.

A meta-analysis of 25 trials involving nearly 70,000 patients with CHD found that statin therapy, on average, reduces CVD events by 25% and overall mortality by 16%,

irrespective of pretreatment lipid levels, including those with baseline LDL below 100 mg/dL (see Figure 2).[28]

The prevailing secondary prevention guidelines for patients with established CHD recommend prompt initiation of statin therapy to achieve a goal LDL < 100 mg/dL, using an intensity sufficient enough to achieve a 30%–40% LDL reduction in high-risk individuals. A target LDL goal <70 mg/dL using high-dose statin treatment is also considered desirable.[29] Additionally, in patients with ACS, including those who underwent revascularization, it is strongly advocated that statin therapy be started regardless of baseline LDL levels.[30]

Statins and cerebrovascular disease

In addition to the significant reduction in CHD risk, there is also evidence pointing to the advantages of statin therapy
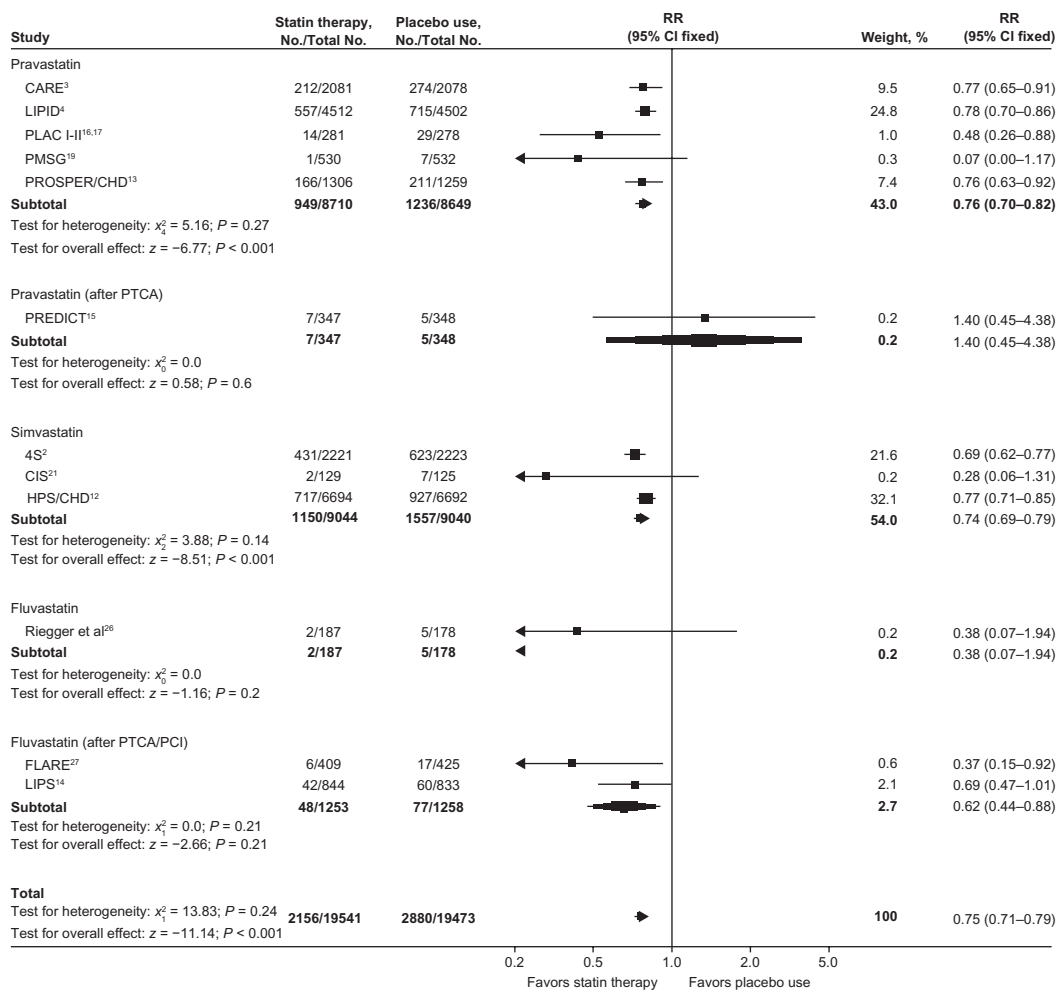
Figure 2 Comparison of relative risks for coronary heart disease mortality and nonfatal myocardial infarction between statin therapy and placebo from the different secondary prevention trials.
Notes: Adapted with permission from Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med.* 2004;164(13):1427–1436.

in the primary prevention of stroke. Statin treatment was associated with a 27% reduction in stroke in high-risk patients enrolled in the ASCOT-LLA primary prevention study. Among low risk patients, on the other hand, statin therapy was associated with a 51% reduction in ischemic stroke in the JUPITER primary prevention trial.[31]

There are ample data supporting the benefit of statin therapy in the secondary prevention of cerebrovascular events as well. In over 4,700 patients with recent stroke or transient ischemic attack (TIA), in the prospective, randomized Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[32] it was found that treatment with high-dose atorvastatin was associated with significant reductions in the incidence of recurrent stroke by 16% and CVD events by 20%. In a large registry of patients with ischemic stroke, pretreatment with statins was associated with a 40% reduction in the odds of poor outcome after stroke in Whites. The same effect, however, was not demonstrated in Blacks.[33] In elderly individuals with CVD, statin therapy reduced the incidence of TIA by 25% in the PROSPER trial, although the overall stroke risk was unaffected.

Pooled data from the LIPID, CARE, and WOSCOPS trials, involving nearly 20,000 patients with CHD, showed that pravastatin therapy reduced the total stroke risk by 22% across a wide range of lipid values.[34] More recently, the TNT trial demonstrated a 25% reduction in fatal and nonfatal strokes in CHD patients treated with high-dose compared to low-dose atorvastatin. Also, in patients with ACS, a substudy of the MIRACL trial found that short-term treatment with atorvastatin was associated with a significant 50% reduction in fatal and nonfatal strokes.[35]

Recommendations on specific target lipid goals and initiation of statin therapy in the primary prevention of cerebrovascular events are the same as that of CHD.[36] Statins are strongly recommended in patients with stroke or TIA and co-morbid CHD to achieve a target LDL goal < 100 mg/dL, and LDL < 70 mg/dL for very high-risk individuals with multiple risk factors. In stroke or TIA patients without concomitant CHD or hyperlipidemia, initiation of statin therapy is considered reasonable for prevention of subsequent CVD events.[37]

Statins and heart failure

Retrospective analyses of landmark clinical trials on lipid-lowering therapy have pointed to the potential beneficial effect of statins in the setting of HF. The earliest clinical data suggesting such effect came from the post-hoc analysis of the 4S trial, in which in patients with CHD but without symptomatic HF, simvastatin therapy was associated with a lower incidence of subsequent development of symptomatic HF compared to placebo. In patients with preexisting HF, statin therapy was also linked to a 19% reduction in mortality.[38] Similarly, a substudy of the Treating to New Targets (TNT) trial which enrolled 10,000 patients with stable CHD demonstrated that high-dose statin therapy (atorvastatin 80 mg daily) resulted in a 26% risk reduction in hospitalization for HF compared to low-dose atorvastatin (10 mg daily). This effect was even more prominent (41% risk reduction) in people who had history of HF.[39]

In patients with known CHD and ischemic HF, analysis of data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) showed that those who used statin ≥ 90% of the time had a 35% lower incidence of ventricular arrhythmias or cardiac death compared to participants who took statins less often.[40] In patients with nonischemic cardiomyopathy, on the other hand, a substudy of the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial found a 22% decrease in appropriate defibrillator shocks and an 84% reduction in arrhythmic sudden death in participants treated with a statin.[41]

However, large, prospective, randomized trials failed to corroborate these findings. For instance, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) involving over 5,000 elderly patients with ischemic HF, found no significant beneficial effect of statin treatment with rosuvastatin on risk reduction of CVD events.[42] Likewise, rosuvastatin treatment had a similar influence as placebo in terms of CVD outcomes in over 4,500 patients with ischemic and non-ischemic HF enrolled in the GISSI-HF trial.[43]

Given the lack of definitive evidence, existing heart failure guidelines do not specifically address the role of statins in heart failure therapy. However, these guidelines do recommend that patients with other concomitant CVD (eg, hyperlipidemia, diabetes or CHD) be treated according to current standards of care.[44] In this context, statin therapy should be utilized in patients with HF if there are any comorbid conditions requiring its use.

Statins and peripheral vascular disease

Post-hoc analysis of the Heart Protection Study provided one of the earliest reliable data sets for the beneficial effects of statin therapy in PVD. In over 6,700 patients with known PVD enrolled in the trial, statin therapy using simvastatin was found to be associated with a 22% reduction in CVD events and a 20% decrease in noncoronary revascularization, effects

which appeared to be independent of baseline cholesterol levels.[45] Small, non-randomized studies also showed that statin use in patients with PVD was linked to significant improvements in walk performance and overall leg function.[46,47] Pleitrophic effects of statins have been postulated to be responsible for these effects, as the findings appeared to be independent of cholesterol-lowering.

Randomized trials in which a small number of patients with PVD and intermittent claudication were enrolled also demonstrated improvements in overall walking performance, ankle-brachial pressure indexes, and symptoms of claudication with statin therapy. Short-term (6 months) treatment with statins, on average, increased pain-free walking distance by 90 meters and symptom-free exercise time by nearly 1 minute.[48–50]

Still lacking, however, are large, multicenter, randomized trials that are adequately powered to confirm the therapeutic advantage of statins on both CVD outcomes as well as symptom/quality-of-life measures. Since this condition is considered a CHD-equivalent, existing guidelines recommend the use of statin therapy to prevent CVD events in all patients with PVD to achieve a target LDL < 100 mg/dL, or lower (<70 mg/dL) in those with lower extremity PVD at very high risk for ischemic events.[51] The role of lipid-lowering therapies for treatment of claudication symptoms, however, has yet to be established.

Use of statins in diabetes mellitus

Early studies on lipid-lowering therapy raised the possibility of a beneficial effect of statins on CVD events in patients with diabetes. Meta-analysis of the LIPID, CARE, and 4S trials found that in diabetic patients, statin therapy was associated with a 28% reduction in coronary events and a 32% reduction in stroke, across a wide range of baseline cholesterol levels. The protection from CVD events seen with statins was greater for patients with diabetes than the non-diabetics.[52]

The Heart Protection Study provided the first direct evidence that statin therapy produces reductions in CVD events among people with diabetes.[53] It was found that among nearly 6,000 patients with known diabetes, treatment with simvastatin was associated with a 22% reduction in coronary events and strokes, irrespective of comorbid CVD conditions and baseline LDL levels.

The effectiveness of statin therapy in the primary prevention of CVD in patients with diabetes was subsequently established by the Collaborative Atorvastatin Diabetes Study (CARDS).[54] In this trial of over 2,800 diabetic patients with average cholesterol levels and without preexisting CVD, treatment with atorvastatin led to reductions in CHD events by 36%, stroke by 48%, and mortality by 27%.

Current clinical practice standards recommend statin therapy to achieve an LDL goal < 100 mg/dL in most patients with diabetes. In those with overt CVD, statin therapy is encouraged regardless of baseline lipid levels, with LDL < 70 mg/dL listed as a reasonable goal in these patients.[55]

Statins and chronic kidney disease

In over 1,700 CHD patients enrolled in the CARE trial with concomitant mild renal dysfunction, statin therapy using pravastatin was associated with a 28% reduction in coronary events.[56] In a similar subset of patients in the 4S trial, simvastatin treatment was associated with decreases in CHD events by 33% and in mortality by 31%.[57] Of particular note, statin therapy did not appear to reduce the incidence of stroke in these studies of patients with mild CKD.

Patients with moderate CKD were shown to have nearly 50% higher risk of CVD events compared to those with normal renal function or mild CKD. In a subgroup analysis of the MEGA study, reduction in the incidences of CHD by 48%, stroke by 73%, and mortality by 51% were seen with pravastatin therapy in patients with moderate CKD.[58]

A recent meta-analysis of 26 trials involving over 25,000 patients with CKD not requiring dialysis found a significant mortality reduction with statin therapy without an increase in adverse events.[59] However, this benefit did not appear to extend to those with end-stage CKD. The prospective German Diabetes and Dialysis Study (GDDS) randomized over 1,200 diabetic patients on maintenance dialysis to treatment with either atorvastatin or placebo. After 4 years of follow-up, no beneficial effect on CVD events or mortality was seen with atorvastatin therapy. Although statin therapy led to a modest 18% reduction in combined cardiac events, this was, however, negated by a 2-fold increase in the incidence of fatal stroke.[60] A similar conclusion was made by the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial, where rosuvastatin treatment showed no significant influence in terms of CHD, stroke, or mortality risk reduction in patients undergoing dialysis, despite a 43% lowering in LDL.[61] It is thought that the initiation of lipid-lowering therapy in patients who already have end-stage renal disease may be too late to translate into consistent improvement of outcomes.

The National Kidney Foundation guidelines classify all stages of CKD as CHD-equivalent, and recommend that all patients with CKD be treated to a target LDL < 100 mg/dL. Statin is the initial preferred agent if baseline LDL is above 130 mg/dL or in patients with Stage 5 CKD (kidney failure or clinical indication for dialysis or transplantation).[62]

Compliance to statins in the real world

Despite the well-established benefits and abundance of clinical management guidelines strongly advocating statin use in high-risk cardiac conditions, long-term adherence to statin regimens in patients who are appropriate candidates has generally been poor, and continued use of statins drops substantially over time. In the WOSCOPS trial, for example, less than 40% of patients in the original statin group were on a statin 5 years after the study ended.[63] In one series, the greatest decline occurred during the first 6 months, and only 25% of patients maintained an acceptable level of compliance to statins 5 years after initiation of therapy.[64]

In patients with CHD, in a recent survey a 26% rate of noncompliance to statins was found, which was in turn associated with an 85% increase in overall mortality.[65] Among those who had ACS, the continuation rate for statin drops to 44% after 3 years.[66] Similarly, the stroke survivors' adherence to recommended statin regimens rapidly declines after hospital discharge, and barely half of these patients remain on treatment after 2 years.[67] Diabetics are not faring any better, with less than half of patients maintaining a satisfactory degree of long-term statin adherence.[68]

The causes for noncompliance are multifactorial. One of the major reasons is the unfounded fear by patients and physicians alike regarding the toxicity of lipid-lowering agents. A major contributor to this anxiety is the glut of information on the Internet on the adverse effects of statins. Such safety concerns, however, are obviously not supported by recent large randomized trials (see Figure 3). Although myalgia without any CPK rise can occur in up to 5% of statin users, which might be perceived as a side effect, serious adverse events are rare, and statin-induced rhabdomyolysis occurs in less than 1 per 100,000 patients exposed.[69] Another explanation for the nonadherence of patients to statin therapy is the lack of education and awareness about the long-term benefits of treatment, especially since they do not feel better right away.

Younger age, female gender, black or hispanic ethnicity, higher comorbidity, and lower median income were some of the patient-related predictors of nonadherence to prescribed statin regimen.[70] Among physician-related factors, patients were more likely to comply if the statin was prescribed by a cardiologist or a primary care doctor.[71] All these factors need to be considered in devising approaches to enhance adherence to guideline-based therapies.

Interventions to increase adherence to statin regimen

It is now well-established that the use of statins is associated with lower mortality, and prolongs the lifespan by an average of 2 years, even if therapy is initiated at a more advanced age.[72] For patients to reap the full protective benefits of statin therapies, however, it is obvious that overall compliance to such regimen needs to be improved.

In individuals and patient groups who are more likely to discontinue treatment, perhaps a more intensive educational
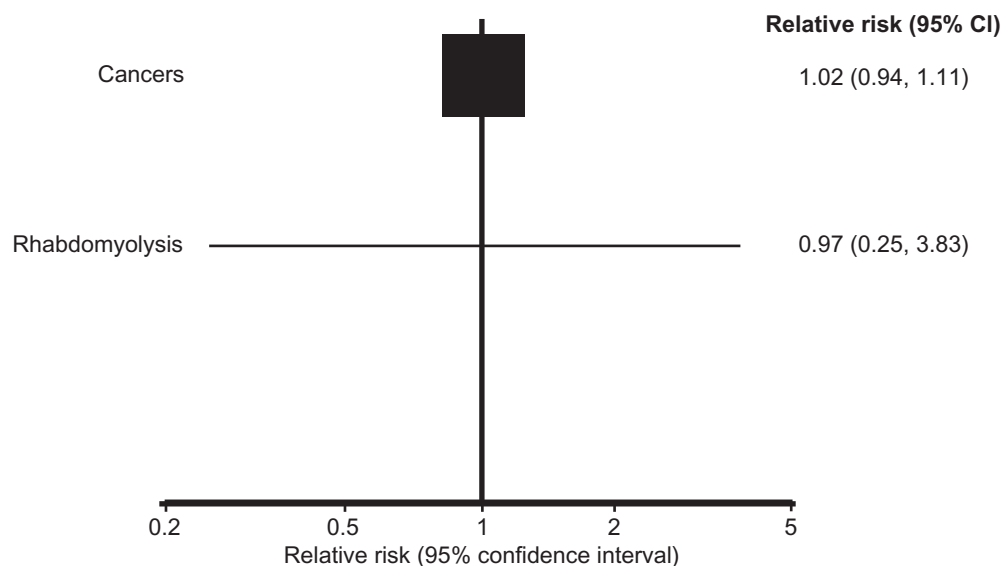
Figure 3 Plotted estimates of adverse events cancer and rhabdomyolysis pooled from primary prevention trials on statin therapy. Pooled relative risk with bars representing 95% confidence intervals (CIs).
Notes: Adapted with permission from Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol.* 2008;52(22):1769–1781.

program (highlighting the safety, and long-term benefits with achieved target LDL) and closer monitoring of compliance could be used to ensure sustained long-term statin use. The utilization of statins by patients has been shown to be dynamic, with over half of new statin users having periods of nonadherence lasting at least 90 days. Regular clinical follow-up visits and serial lipid testing appear to promote reinitiation of therapy in one study,[73] and can be one of the simpler interventions clinicians can employ to promote long-term statin adherence in most patients.

A multidisciplinary disease-management team approach to patient management has also been shown to improve compliance to statins and other guideline-based therapies. In a single-center interventional program for patients who underwent coronary artery bypass surgery, a quality improvement team consisting of thoracic surgeons, clinical pharmacists, dieticians, physical therapists, and nurse coordinators, implemented a goal-directed approach to postoperative care, which resulted in a significantly higher adherence to recommended therapies on hospital discharge.[74] This is important since it is known that prescription for statins at the time of hospital discharge enhances long-term statin compliance.[75] A similarly structured cardiac rehabilitation program may also exert a favorable impact on the sustained adherence to statins and other essential medications in the outpatient setting.[76]

Another possible reason for poor utilization of statins is that some healthcare providers may fail to prescribe them in appropriate patients. Hence, compliance to the recommended therapies by physicians needs to be addressed as well. National and institution-based initiatives to promote adherence to guideline-based therapies, including statin utilization, in high-risk CVD patients have been shown to be effective and have resulted in improved outcomes. Among those successfully implemented include the Get-With-The-Guidelines (GTWG) initiative, the Guidelines Applied in Practice (GAP) project, and the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP).

CHAMP, which was initiated at a large university hospital, implemented a simplified treatment algorithm that focused improving utilization of statins and other guideline-based therapies before hospital discharge in patients with CHD. Comparison of outcomes before and after the program started showed that CHAMP was associated with a significant increase in use of recommended medications, and an increase in the proportion of patients achieve target lipid goals, which subsequently led to significant reductions in recurrent MI and mortality.[77]

The GAP project was promoted by the American College of Cardiology and was adopted by 33 participating hospitals.

The program aimed to foster systems-based hospital care of ACS patients from admission to discharge, incorporating standard, evidence-based tools into practice and targeting patients, physicians, and nurses. In hospitalized patients with ACS, the improved adherence to statins and other guideline-based therapies associated with the project was demonstrated to result in significant lowering of short-term and long-term mortality.[78]

The GTWG quality improvement initiative, on the other hand, was implemented by the American Heart Association to optimize and standardize the hospital care for patients with CHD, stroke, and HF. In nearly 1,500 voluntarily-participating hospitals, this program has improved the compliance to recommended therapies in the inpatient setting, which translated to improvement in CVD outcomes.[79] In patients with high-risk CVD, adherence to GWTG quality measures has eliminated or at least diminished the age-, gender-, racial-, and ethnicity-related disparities in hospital care.[80–82] The benefits of participation in the GTWG program have also been shown to persist over time, independent of hospital characteristics.[83]

Initiatives like the GTWG are excellent models by which to pattern interventions to enhance statin compliance, especially if such programs are expanded to include the outpatient and general community setting. From a regulatory perspective, the core measures and the accreditation standards set forth by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) for MI, HF, stroke, and CKD are another powerful venue where utilization of guideline-based therapies can potentially be enhanced. Inclusion of the use of statins in the JCAHO quality measures for these patients with high-risk CVD would certainly improve adherence to such agents.

Higher drug prescription co-payment costs and insurance cost-sharing schemes adversely affect adherence to lipid-lowering therapies. In high-risk patients who need statins the most, full out-of-pocket spending for drug prescription nearly doubles the likelihood of stopping treatment.[84] On a broader economic perspective, elimination of out-of-pocket costs may be an appropriate, cost-effective public health strategy (by reducing the need for hospitalization and expensive procedures) to enhance long-term compliance to statin therapy. While an increase in statin utilization might increase drug-related expenditure in the short term, this is counterbalanced eventually by the expected benefits in terms of mortality and morbidity reduction. In a recent Medicare cost-effectiveness model analysis, it was projected that full drug coverage for secondary prevention therapies would result in greater functional life expectancy and less resource utilization, a move that appears highly cost-effective in the long term.[85]

Conclusion

An overwhelming amount of data that confirm the morbidity and mortality benefit of statin therapy in high-risk CVD conditions have been reported, both in the primary and secondary prevention settings. National and international clinical guidelines in the management of CHD, stroke, diabetes, CKD, CHF, and PVD all advocate the utilization of statin therapy in appropriate patients. However, overall compliance to statin therapy remains suboptimal. Patient-, physician-, and economic-related factors all play a role. These factors need to be considered in devising approaches to enhance adherence to guideline-based therapies. To fully benefit from the potential of these agents, interventions which improve long-term treatment compliance in real-world settings should be encouraged.

Disclosure

The authors report no conflicts of interest in this work.

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