

Formulary Considerations, Beyond Acquisition Cost, to Optimally Manage a Dyslipidemic Patient Population

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Summary

Aggressive management of cardiac risk factors with statins is beneficial and generally safe for the majority of patients. Statins do have some significant benefits, which are independent of lipid lowering. These benefits may be most significant for atorvastatin. Hospital-based regulatory requirements for improving quality and medication errors can be negatively affected by formulary policy. A fairly liberal approach when choosing statins for a managed care formulary is beneficial to both managed care and the hospital delivery side of the healthcare system.

Key Points

- The greater the LDL reduction, the greater the cardiovascular event reduction.
- Statins have significant effects beyond LDL lowering.
- High potency statins should be available to managed care organization patients in both inpatient and outpatient settings.
- Medication reconciliation is a new imperative for hospitals.
- Formulary restrictions of statins complicate the medication-reconciliation process and increase the likelihood of errors and noncompliance.

OPTIMAL MANAGEMENT OF CARDIAC RISK factors requires goal optimization and compliance with medications and non-drug measures. Drug selection should be based primarily on evidence of impact on morbidity and mortality outcomes, in addition to safety, cost and practical patient-related concerns. The evidence is clear that aggressive management of cardiac risk factors (early, sustained, goal optimization) is beneficial and generally safe for the majority of patients.

When looking at the four basic modifiable cardiac risk factors (hyperlipidemia, hypertension, smoking and diabetes), the majority of patients who have events have more than just one of these factors.¹ It is not enough to intervene on just one of the risk factors. Risk factor reduction must be done comprehensively.

Based on many large well designed studies, there is a direct linear relationship between low density lipoprotein (LDL) cholesterol and reduction in heart

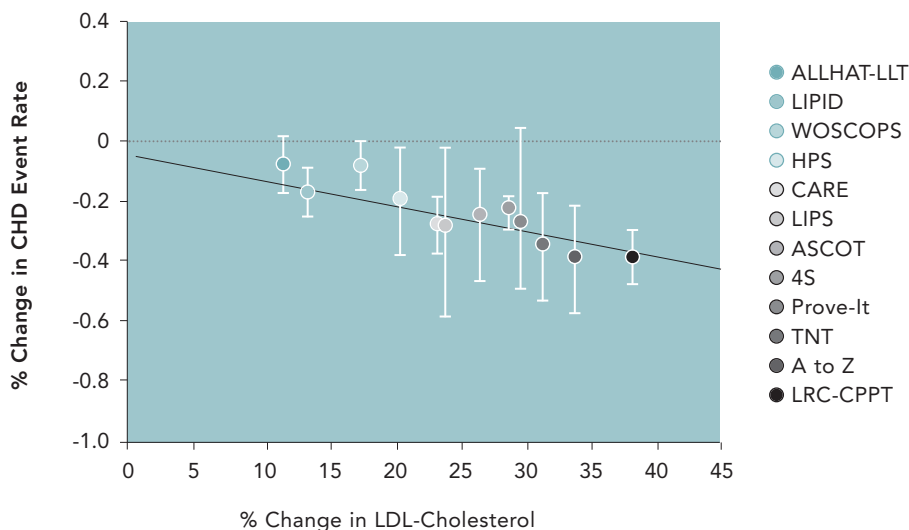
disease risk (Exhibit 1).^{2,3} To achieve the lowest LDL values and achieve the most risk reduction, preference should be given to more potent agents whenever possible.

The first set of landmark studies with statins demonstrated that for both primary and secondary prevention, there are definite reductions in morbidity and mortality compared to placebo (Exhibit 2). The second wave of trials examined statin use in specific groups of patients at risk for developing heart disease and also compared statins to each other. The most recently published trials have examined aggressive lipid lowering in patients with stable heart disease. An example of results comes from the Treating to New Targets (TNT) trial (Exhibit 3). This study demonstrated, using the same drug but in different doses, that more aggressive therapy with a higher dose produces a higher risk reduction.⁴ The Ideal Study, which compared simvastatin non-aggressive dosing with 20 mg versus atorvastatin 80 mg, also

demonstrated that aggressive dosing provides a benefit in risk reduction of 11 percent greater than that seen with standard dosing.⁵

In reducing cardiovascular disease morbidity and mortality, statins do much more than just lower LDL (Exhibit 4).⁶ The current evidence seems to indicate

Exhibit 1: The Reduction in CHD Risk is Proportional to the percent LDL-C Lowering



ALLHAT-LLT, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; WOSCOPS, West of Scotland Coronary Prevention Study; HPS, Heart Protection Study; CARE, Cholesterol and Recurrent Events; LIPS, Lescol Intervention Prevention Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; 4S, Scandinavian Simvastatin Survival Study; PROVE-IT, Atorvastatin Evaluation and Infection Therapy; TNT, Treating to New Targets; A to Z, Aggrastat to Zocor; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial

Exhibit 2: 11 Years of Landmark Statin Trials

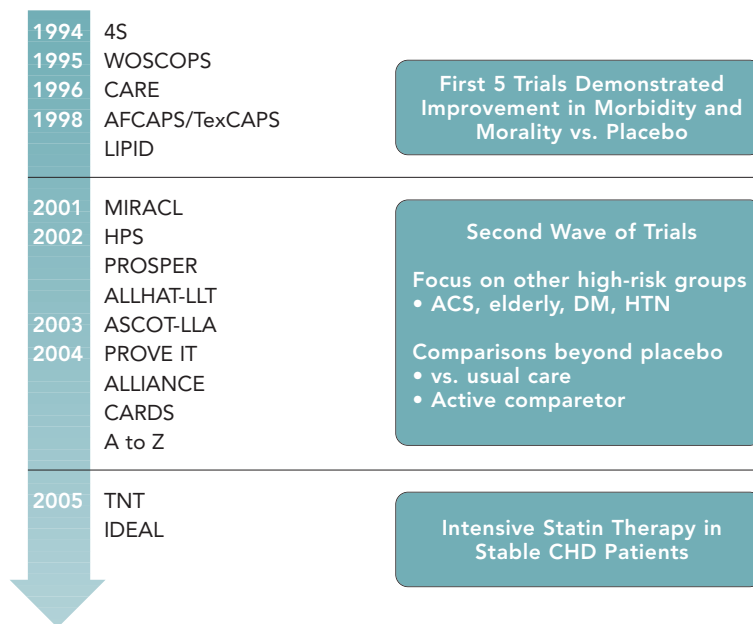
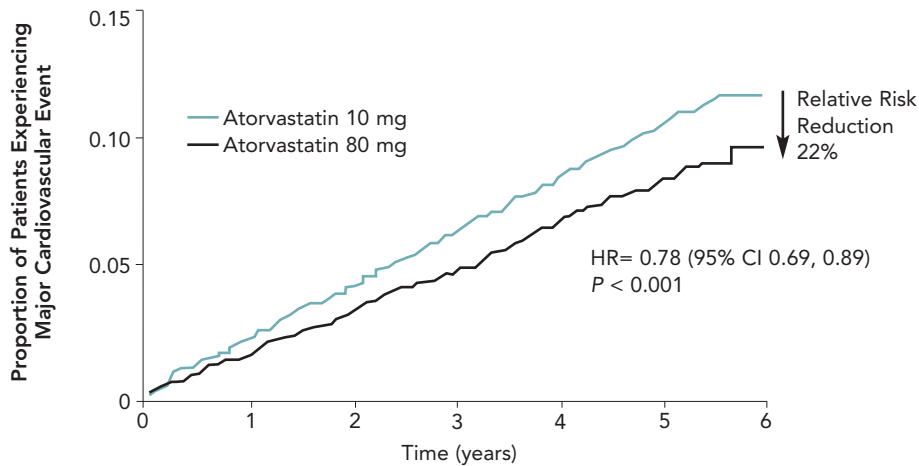
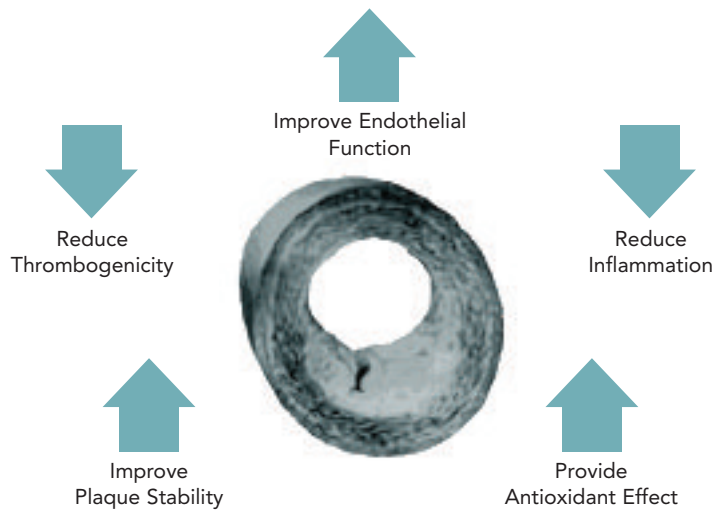


Exhibit 3: TNT: Primary Efficacy Outcome Measure First Major Cardiovascular Event*



*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

Exhibit 4: Proposed Non-LDL Effects of Statins in the Vascular Endothelium

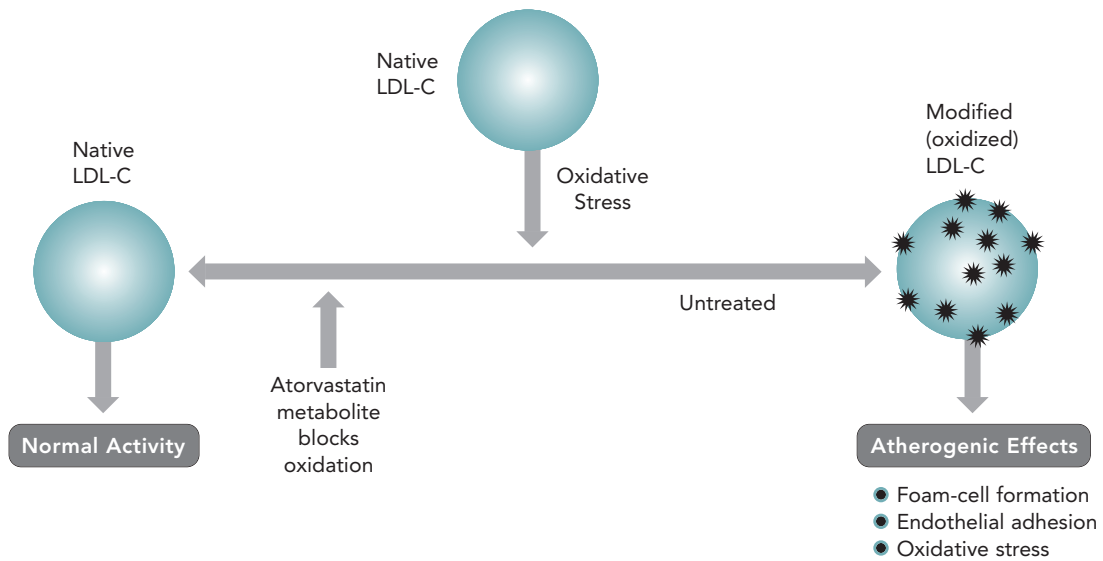


that higher doses of statins have more of these beneficial effects. Statins improve blood vessel wall (endothelial) function.^{7,8} If the endothelial cells are functioning effectively, the blood vessel is vasodilated, which is an environment where blood clots are unlikely to form and inflammation is reduced. Statins reduce thrombogenicity, improve and stabilize atherosclerotic plaques, provide a potent antioxidant effect, and significantly reduce vascular inflammation. Normal endothelia with healthy vascular tone provide an effective structural barrier to lipoproteins and other plasma components that might otherwise start to form plaques, limit platelet and leukocyte adhesion, and inhibit smooth muscle cell growth.

There is evidence to suggest that LDL cholesterol lowering itself may not be the primary mechanism of the statin-mediated improvement in endothelial function. At least one agent, atorvastatin, has been shown to produce greater effects on endothelial function in one study.⁸ However, further studies and clinical intervention trials are required to clarify the clinical importance of the endothelial effects in humans and their contribution to the well-established clinical benefits of statins.⁶

Inflammatory markers, such as C-reactive protein (CRP), may play a role in the development of atherosclerosis. CRP appears to be quite predictive of cardiovascular events, and there are multiple studies

Exhibit 5: Atorvastatin Metabolite Dramatically Slows the Rate of LDL Oxidation



demonstrating correlations of CRP with MI, coronary heart disease, and cardiovascular disease related death. There seems to be a correlation in some of the statin trials (A to Z, MIRACL, Prove-It) between the extent of CRP reduction and early event reduction.⁹ Much of the early (within the first or two years) benefit of statins appears related to rapid reduction in CRP levels. The greater CRP goes down, or the greater the extent of the anti-inflammatory effects of the drugs, the greater the early event reduction.

Statin also appear to have antioxidant effects. LDL needs to be oxidized before it becomes part of atherosclerotic plaques. Statins, particularly atorvastatin, appear to slow down this process of oxidation (Exhibit 5).¹⁰⁻¹²

As atherosclerosis progresses, the plaques can rupture, resulting in acute events, such as MI, unstable angina and stroke. A recently published trial (SPARCL) was specifically designed to examine the effect of a statin on stroke.¹³ This study included subjects with previously documented stroke or TIA without a history of coronary heart disease. Average LDL levels were between 100 and 160. There was a 16 percent relative risk reduction with statin compared to placebo (Exhibit 6).¹³ This trial demonstrated that history of stroke is an indication for a statin to reduce the risk of having a subsequent stroke. Also in the SPARCL Study, atorvastatin 80 mg substantially decreased the risk of major coronary and vascular events and revascularization procedures. Multiple previous clinical trials have demonstrated the effect of statins on reducing stroke risk in those without coronary heart disease or

with coronary heart disease with or without a prior stroke. No statin trial prior to SPARCL had demonstrated a reduction in the risk of recurrent stroke.

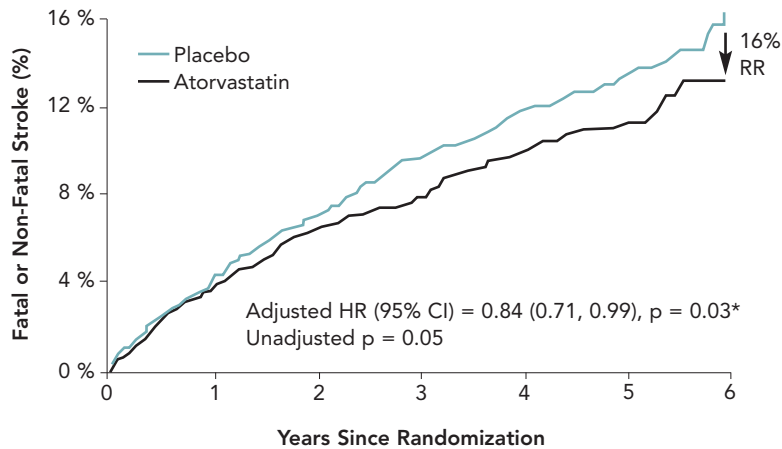
Achieving quality care means aggressive management, intervening early, and sustained and achieving appropriate targets. Drug selection to achieve quality of care should be based on the evidence of impact on long-term morbidity and mortality outcomes. There is abundant evidence out there that patients get started on statins and their dosing is sub-optimal or they stop treatment. Formulary management of statins should not interfere with achievement of quality of care goals. Formulary considerations may disrupt effective use of statins when hospitalizations occur and present safety, quality, and ultimately cost issues.

Up to 98,000 deaths a year are attributable to errors in hospitals.¹⁴ This is significantly above other causes of death in this country that are much higher profile. As can be seen in Exhibit 7, the reliability of inpatient medication administration is not ideal compared with other industries.

To place more emphasis on medication errors in the hospital setting and to begin to improve this problem, error reduction through medication reconciliation is a current quality improvement goal for hospitals. Medication reconciliation is included in the Joint Commission's National Patient Safety Goals.

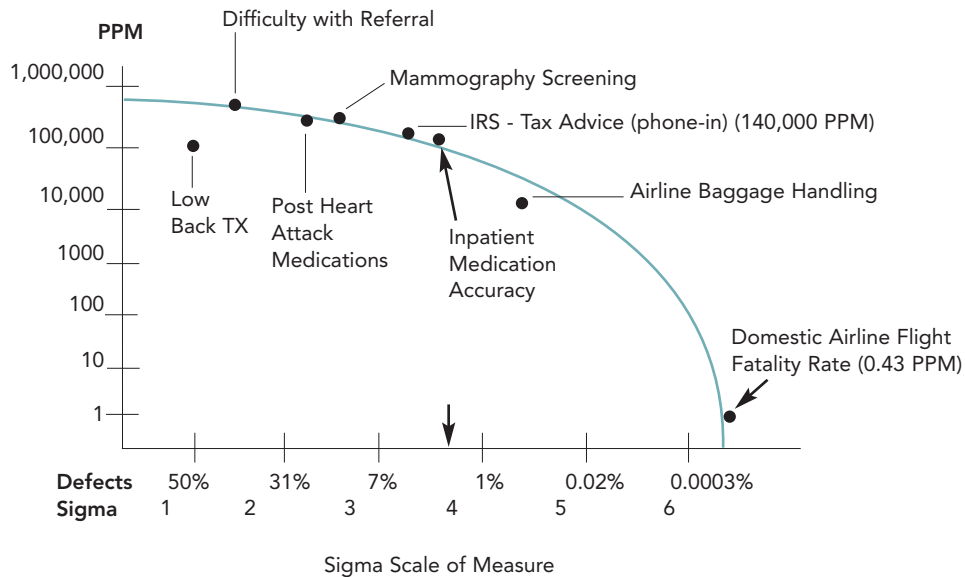
Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking—including drug name, dosage, frequency, and route. The list is compared against the physician's admission, transfer, and/or discharge orders for discrepancies.

Exhibit 6: SPARCL: Primary Endpoint Time to Fatal or Non-Fatal Stroke



*Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.

Exhibit 7: Comparative Reliability Between Industries



The goal is to provide correct medications to the patient at all transition points within the hospital with discharge probably being the most important.

Experience from hundreds of organizations has shown that poor communication of medical information at transition points is responsible for as many as 50 percent of all medication errors and up to 20 percent of adverse drug events in the hospital. If this process does not occur in a standardized manner that

is designed to ensure complete reconciliation, medication errors may lead to adverse events and harm. One example related to statins includes the patient taking multiple agents because a generic was prescribed before, and he or she leaves the hospital on a brand-name product.

Medication reconciliation should be a winning action for both hospitals and managed care organizations. By implementing this process, both sides

should see decreased lengths of stay, fewer complications, fewer re-hospitalizations, and reduced medication costs from elimination of redundancies and unnecessary prescriptions. Using statins as the example, discharging a patient on an effective regimen for aggressive lowering of LDL is a winning strategy for both the managed care organization and the hospital because greater lipid lowering leads to greater reduction in disease burden.

Formulary restrictions both in the hospital and in outpatient settings can complicate the medication reconciliation process. For example, a patient comes into the hospital on one statin, and that is switched to the hospital formulary agent. At the time of discharge, the patient may receive a new prescription of the hospital agent and yet still has a supply of the previous agent, which he or she continues to take. The possibility for taking two statins and suffering significant adverse effects is very real.

Formulary decision-makers should be aware of the potential clinical, safety and economic impact of formulary selections relative to medication reconciliation issues. For hospitals, the direct cost for statins is relatively minimal when compared to more commonly used agents such as antibiotics, chemotherapy, anesthetic agents, and when compared to the potential large indirect costs of switching patients to a less expensive, possibly less potent, statin agent. High potency, higher cost statins pose a potentially large direct cost for outpatients using them on a regular basis, but should save far more than their direct costs via event reduction and avoidance if used aggressively and appropriately.

There are potential compliance implications of switching formulary statins. Patients need to be compliant on therapy to benefit. When patients switch medications, their compliance could drop and they may not achieve the full benefit of therapy. Thiebaud and colleagues conducted a study to determine the effect of switching medications on the compliance and persistence of new statin users.¹⁵ They conducted a retrospective database analysis of pharmacy claims provided by a large PBM. The study sample consisted of 38,866 new statin users between the ages of 18 and 65 who were beginning treatment with atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. Compliance was measured by the medication possession ratio and persistence was measured by the time to discontinuation. Switching rates were derived from the proportions of patients filling a prescription other than the initial statin. They found that patients who switched statins were less compliant by 18.9 percent ($P<.001$).¹⁵ Statin switchers were less persistent by 20.9 percent to 48.3 percent ($P<.001$), depending

on the gap length used to define discontinuation.¹⁵ To ensure better compliance, the authors suggested that special care should be given to patients who change statins.¹⁵

Conclusion

From numerous studies over the years, statins have proved effective for reducing cardiovascular events. Maximization of risk reduction occurs with aggressive use of statins. Formulary decision-makers in both the hospital and outpatient setting need to consider the implications of making formulary decisions, which may limit access to the potent statins required to achieve aggressive goals. **JMCM**

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