Utilization of and Adherence to Guideline-Recommended Lipid-Lowering Therapy After Acute Coronary Syndrome
Opportunities for Improvement

Benjamin J. Hirsh, MD,* Nathaniel R. Smilowitz, MD, y Robert S. Rosenson, MD, z Valentin Fuster, MD, PhD,* Laurence S. Sperling, MD

ABSTRACT

In addition to aggressive lifestyle and nonlipid risk factor modification, statin therapy improves cardiovascular disease outcomes following acute coronary syndromes. Despite established benefits of treatment, contemporary registries reveal substantial underutilization of and nonadherence to statin therapy for secondary prevention. In randomized controlled trials investigating statin therapy, including moderate-intensity statin plus ezetimibe therapy, rates of nonadherence are reported in up to 40% of subjects. Durable strategies to address gaps in lipid lowering for secondary prevention are essential to maximize reduction in cardiovascular disease risk. (J Am Coll Cardiol 2015;66:184–92) © 2015 by the American College of Cardiology Foundation.

Lipid lowering with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor (statin) therapy is essential for secondary prevention after acute coronary syndromes (ACS) in combination with an antiplatelet agent, beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor antagonist, and intensive lifestyle and risk factor modifications, including weight reduction in overweight individuals, smoking cessation, and aerobic exercise. Statin therapy lowers concentrations of low-density lipoprotein-cholesterol (LDL-C) and other apolipoprotein-B-containing lipoproteins, reduces arterial inflammation, stabilizes the lipid core, and promotes regression of atherosclerosis (1,2). Randomized clinical trials (RCTs) have shown that statin therapy reduces cardiovascular disease (CVD) events by 25% to 40% and that these benefits accrue within the first 6 months after ACS (3,4). Consequently, high-intensity statin therapy before hospital discharge after ACS is a Class I, Level of Evidence: A guideline-recommendation, irrespective of baseline LDL-C level (5).

Despite these established benefits, contemporary registries reveal substantial underutilization of and nonadherence to statin prescriptions for secondary prevention after ACS. In RCTs investigating the efficacy of statin therapy on CVD outcomes after ACS, including the recently reported IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), up to 40% of patients...
discontinued the study medication prematurely (6). Clinical practice registries demonstrate even higher nonadherence rates. Other clinical trials and registries have reported higher mortality rates following discontinuation of statin therapy after ACS (2,7). Suboptimal pharmacologic LDL-C lowering after ACS can be attributed to statin underutilization (Table 1) and to medication nonadherence (Tables 2 and 3).

**UNDERUTILIZATION OF STATIN THERAPY AFTER ACS: CONTEMPORARY EVIDENCE**

In a recent issue of the Journal, Maddox et al. (8) used the National Cardiovascular Data Registry’s PINNACLE (Practice Innovation and Clinical Excellence) database to assess the effect of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines (5) on current cardiovascular practice in the United States. In the cohort of 1,174,545 patients age 18 years or older, 1,029,633 (91.2%) were eligible for statins on the basis of known atherosclerotic CVD. Among patients with atherosclerotic CVD, 506,009 (49.9%) received statin therapy only; 200,789 (20.0%) received both statin and nonstatin therapies; 28,887 (2.9%) received nonstatin therapy only; and 285,211 (27.9%) patients did not receive any lipid-lowering medications. These findings suggest that a large number of patients lack optimized lipid management. Similar findings were reported in a recent analysis of secondary prevention in patients with a history of myocardial infarction (MI) from the large National Health and Nutrition Examination Survey (9). Although statin use in the United States increased over the past decade from 36% in 1999 to nearly 73% in 2012 (p = 0.04), opportunities exist to improve risk reduction and lipid lowering for the 27% of patients who are not currently taking statin therapy after ACS.

The statin dose prescribed after ACS is also a concern. A separate publication in the Journal examined a sample of Medicare beneficiaries who were prescribed a statin at discharge following a hospitalization for ACS from 2007 to 2009 (10). Only 27.0% of prescriptions filled were for a high-intensity statin, which increased to only 35% within 365 days from the discharge date. Among patients not taking statins before admission, 23.1% were prescribed a high-intensity statin at discharge. Only 9.4% of patients treated with a low- to moderate-intensity statin before admission were prescribed a high-intensity statin at discharge. In contrast, 80.7% of patients treated with a high-intensity statin before admission were prescribed the high-intensity dose at discharge.

Other registries have reported similar findings. In the United States and Europe, 23% to 38% of patients hospitalized for MI are prescribed maximal-intensity statin therapy at discharge (11-13). An observational study of 6,748 patients at 31 U.S. hospitals enrolled in both the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) and the TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status) registries (11) found that although 88% of patients were prescribed a statin at discharge after ACS, only 1 in 3 were prescribed a statin at goal dose. The TRIUMPH registry defined the goal dose as achieving >75% of maximal statin potency (approximately a 50% to 60% reduction in LDL-C), which included: atorvastatin 40 to 80 mg, lovastatin 80 mg, pravastatin 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg daily.

These failures to prescribe statins or to maximize statin intensity suggest a lack of knowledge regarding the benefits of high-dose statin therapy over moderate- or low-dose statin therapy (14), as demonstrated in clinical trials of ACS patients (3,15). For example, the most important predictor of change to a high-intensity statin was the dosage the patient received before the ACS event (10), suggesting a continued treatment focus on LDL-C levels, lack of knowledge regarding the benefits of high-intensity statins, or clinical inertia. Underutilization of high-intensity statin diminished progressively in the year after the ACS event. Fragmented care in inpatient and ambulatory settings and poor communication between community-care providers and specialists may limit provider attention to starting statin therapy or dose optimization. To improve decision-making and statin utilization for older patients with multiple comorbidities on several medications, physicians may need alternative guidelines that address concerns for possible medication interactions with statins (16). Nurse-managed protocols may provide another useful approach in improving outpatient implementation of guideline-directed measures and promoting adherence of patients with multiple medical comorbidities (17).

Shorter hospitalizations for acute MI over the past decade permit less time for dose titration before discharge. Moreover, current performance measures credit providers for any dose of guideline-recommended medication, even a low/moderate-intensity statin (11). Although specific reasons for statin nonprescription, such as prior intolerance, may
account for some treatment gaps in quality of care metrics at discharge, further studies are required to understand and address deficiencies. Continued monitoring of practice patterns will facilitate health care delivery of optimal therapies for secondary prevention (18).

NONADHERENCE TO STATIN THERAPY FOR SECONDARY PREVENTION

IMPROVE-IT is the first clinical outcomes trial to show that statin therapy plus a nonstatin LDL-C-lowering treatment reduces CVD in patients who are at high risk of recurrent CVD events. Even in this well-designed trial, 42% of subjects prematurely discontinued the study therapy, likely reducing the treatment effect in both arms and leading to underestimation of the observed benefit. The average annualized rate of statin discontinuation in IMPROVE-IT is similar to that in other large RCTs of statin therapy for secondary prevention (Table 2). The highest annual rates of statin discontinuation were reported in the A to Z (Aggrastat to Zocor) (19) and PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) (14) trials, with >30% of patients discontinuing therapy over the course of follow-up. In the majority (55%) of cases in the A to Z trial, the study statin was discontinued due to physician or patient preference, with adverse experiences or events accounting for 28% of premature discontinuation (19). In the PROVE IT-TIMI 22 study, only 5.3% of patients discontinued the study atorvastatin dose due to laboratory abnormalities or side effects; the remainder stopped due to patient or physician preference (14). In-depth focus on the rationale for premature study drug discontinuation in clinical trials, commonly ascribed to patient or physician preference, may inform explanations for statin discontinuation in routine clinical practice. In large, real-world registries of patients with CHD, adherence to statin therapy is even lower than in clinical trials and can reach 50% at 1 year (Table 3). In addition to statin underutilization, nonadherence to lipid-lowering therapy for secondary prevention remains an important obstacle to CVD event reduction (Central Illustration).

Adherence refers to the extent to which a patient’s medication-taking practice coincides with prescribed medical recommendations (20). Although many patient characteristics can affect statin efficacy, nonadherence is among the most important determinants of outcome. Rasmussen et al. (21) demonstrated that increasing levels of statin adherence are inversely associated with LDL-C and mortality after ACS. Only 50% to 60% of patients remain adherent within 1 year of initiation, declining to 30% to 40% at 2 years (22,23). Nonadherence is multifactorial and is influenced by demographic and socioeconomic factors, lifestyle habits, time since last provider visit, adverse effects of therapy, and complex medication regimens (24). Nonadherence affects all guideline-directed medical therapy, including LDL-C-lowering therapy. A multimodality, systems-based, incentive approach may be necessary to overcome these barriers.

<table>
<thead>
<tr>
<th>Table 1 Underutilization of Statin Therapy for Secondary Prevention</th>
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<tbody>
<tr>
<td><strong>First Author (Ref. #)</strong></td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Rosdak et al. (10)</td>
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<tr>
<td>Maddox et al. (8)</td>
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<td>Arnold et al. (11)</td>
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<tr>
<td>Arnold et al. (12)</td>
</tr>
<tr>
<td>Javed et al. (13)</td>
</tr>
<tr>
<td>Ho et al. (32)</td>
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<tr>
<td>Ho et al. (51)</td>
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</tbody>
</table>

*Intensive lipid-lowering therapy with atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, simvastatin 80 mg, or statin of any dose + ezetimibe + any statin therapy. †Any statin therapy. ‡Maximally potent statin (rosuvastatin 20 to 40 mg or atorvastatin 80 mg) at hospital discharge. §Any statin therapy at hospital discharge. |(1) | Statin at ≥75% of the target dose at hospital discharge. |(12) | ACS = acute coronary syndrome(s); ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = congenital heart disease; CMS = Centers for Medicare and Medicaid Services; GWGT = Get With The Guidelines; KPCA = Kaiser-Permanente of Colorado; MI = myocardial infarction; PCI = percutaneous coronary intervention; PINNACLE = Practice Innovation And Clinical Excellence; PREMIER = Prospective Registry Evaluating Myocardial Infarction: Events and Recovery; TRIUMPH = Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status.

Table 2 Prescribed Inclusion Criteria

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Registry</th>
<th>Years</th>
<th>N</th>
<th>Statin Prescribed</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosdak et al. (10)</td>
<td>CMS</td>
<td>2006-2010</td>
<td>8,762</td>
<td>27%</td>
<td>Medicare beneficiaries 65-74 yrs of age who filled a statin prescription after a CHD event</td>
</tr>
<tr>
<td>Maddox et al. (8)</td>
<td>PINNACLE</td>
<td>2008-2012</td>
<td>1,029,633</td>
<td>72%</td>
<td>Adults with confirmed ASCVD</td>
</tr>
<tr>
<td>Arnold et al. (11)</td>
<td>TRIUMPH</td>
<td>2005-2008</td>
<td>4,271</td>
<td>91%/23%</td>
<td>Adults hospitalized with ACS, discharged alive, no contraindications to statin</td>
</tr>
<tr>
<td>Arnold et al. (12)</td>
<td>PREMIER</td>
<td>2003-2008</td>
<td>6,748</td>
<td>88%/33%</td>
<td>Adults hospitalized with ACS, discharged alive</td>
</tr>
<tr>
<td>Javed et al. (13)</td>
<td>GWGT</td>
<td>2005-2009</td>
<td>65,396</td>
<td>89%/38%</td>
<td>Adults hospitalized with ACS, prescribed lipid-lowering therapy at discharge</td>
</tr>
<tr>
<td>Ho et al. (32)</td>
<td>KPCA CAD Registry</td>
<td>2000-2005</td>
<td>15,767</td>
<td>86%</td>
<td>Patients in CAD registry with prior MI, PCI, or CABG</td>
</tr>
<tr>
<td>Ho et al. (51)</td>
<td>PREMIER</td>
<td>2003-2004</td>
<td>2,498</td>
<td>80%</td>
<td>Adults hospitalized with ACS, discharged alive</td>
</tr>
</tbody>
</table>

*Intensive lipid-lowering therapy with atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, simvastatin 80 mg, or statin of any dose + ezetimibe + any statin therapy. †Any statin therapy. ‡Maximally potent statin (rosuvastatin 20 to 40 mg or atorvastatin 80 mg) at hospital discharge. §Any statin therapy at hospital discharge. |(1) | Statin at ≥75% of the target dose at hospital discharge. |(12) | ACS = acute coronary syndrome(s); ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = congenital heart disease; CMS = Centers for Medicare and Medicaid Services; GWGT = Get With The Guidelines; KPCA = Kaiser-Permanente of Colorado; MI = myocardial infarction; PCI = percutaneous coronary intervention; PINNACLE = Practice Innovation And Clinical Excellence; PREMIER = Prospective Registry Evaluating Myocardial Infarction: Events and Recovery; TRIUMPH = Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status.
MEASURING ADHERENCE

Providers are currently not adept at recognizing nonadherence (25). In qualitative studies, providers did not inquire about adherence in one-third of patients with poor blood pressure control (26,27), suggesting a need for broader recognition of the importance of nonadherence to outcomes, which will be increasingly linked to provider payment, posing both new challenges and opportunities. Measuring nonadherence is challenging, requiring integration of health services at multiple levels. Currently, adherence is inferred on the basis of pill counts, blister packs, and patient questionnaires or self-reports, such as diaries. Questioning of patients during provider visits or through questionnaires can be susceptible to misrepresentation and tend to overestimate adherence (25,26). Pill counts, another common approach to assess medication adherence, appear to be simple and objective. However, patients can switch medicines between bottles and may have an insufficient or excess quantity of pills that can influence accuracy (26,27). Despite these biases, poorer adherence, as measured by these methods, has been associated with adverse CVD events (24,27).

Electronic monitoring devices and event monitors that record the timing and opening of bottles provide more reliable data on adherence dynamics over

### Table 2: Rates of Statin Discontinuation in RCTs With Statins Including Patients With Prior ACS

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Year</th>
<th>N</th>
<th>Statin Studied</th>
<th>Discontinuation of Statin Therapy</th>
<th>Follow-Up Duration</th>
<th>Average Annual % Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE-IT (6)</td>
<td>2014</td>
<td>18,144</td>
<td>Simvastatin</td>
<td>42%</td>
<td>72 months†</td>
<td>7.0%</td>
</tr>
<tr>
<td>SEARCH (52)</td>
<td>2010</td>
<td>12,064</td>
<td>Simvastatin</td>
<td>27%</td>
<td>80 months‡</td>
<td>4.1%</td>
</tr>
<tr>
<td>IDEAL (53)</td>
<td>2005</td>
<td>8,888</td>
<td>Atorvastatin</td>
<td>14%</td>
<td>58 months§</td>
<td>2.9%</td>
</tr>
<tr>
<td>TNT (54)</td>
<td>2005</td>
<td>10,001</td>
<td>Atorvastatin</td>
<td>7%§</td>
<td>59 months§</td>
<td>1%‡</td>
</tr>
<tr>
<td>A to Z (19)</td>
<td>2004</td>
<td>4,497</td>
<td>Simvastatin</td>
<td>34%</td>
<td>24 months§</td>
<td>17.2%</td>
</tr>
<tr>
<td>PROVE IT-TIMI 22 (14)</td>
<td>2004</td>
<td>4,162</td>
<td>Atorvastatin</td>
<td>30%</td>
<td>24 months‡</td>
<td>15.2%</td>
</tr>
<tr>
<td>HPS (55)</td>
<td>2002</td>
<td>20,536</td>
<td>Simvastatin</td>
<td>18%</td>
<td>60 months‡</td>
<td>3.6%</td>
</tr>
<tr>
<td>LIPID (56)</td>
<td>1998</td>
<td>9,014</td>
<td>Pravastatin</td>
<td>19%</td>
<td>73 months§</td>
<td>3.1%</td>
</tr>
<tr>
<td>CARE (57)</td>
<td>1996</td>
<td>4,159</td>
<td>Pravastatin</td>
<td>6%</td>
<td>60 months§</td>
<td>1.2%</td>
</tr>
<tr>
<td>4S (58)</td>
<td>1994</td>
<td>4,444</td>
<td>Simvastatin</td>
<td>10%</td>
<td>65 months§</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

†Median. †Mean. ‡Discontinuation due to treatment-related adverse events only. All-cause discontinuation was not reported. 4S = Scandinavian Simvastatin Survival Study; ACS = acute coronary syndrome(s); A to Z = Aggrastat to Zocor; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22; RCT = randomized controlled trial; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT = Treating to New Targets.

### Table 3: Adherence to Statin Therapy for Secondary Prevention of CAD in Registry Databases

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Registry</th>
<th>Years</th>
<th>N</th>
<th>Statin Adherence</th>
<th>Inclusion Criteria</th>
<th>Follow-Up (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al. (51)</td>
<td>PREMIER</td>
<td>2003-2004</td>
<td>2,498</td>
<td>78.5%*</td>
<td>Adults hospitalized with ACS, discharged alive, no contraindications to statin</td>
<td>1</td>
</tr>
<tr>
<td>Ho et al. (32)</td>
<td>KPCO</td>
<td>2000-2005</td>
<td>13,596</td>
<td>74%</td>
<td></td>
<td>Patients in Kaiser CAD registry with prior MI, PCI, or CABG</td>
</tr>
<tr>
<td>Muntner et al. (23)</td>
<td>CMS Chronic Condition Data Warehouse</td>
<td>2007-2009</td>
<td>2,695</td>
<td>63.8%‡</td>
<td>Medicare beneficiaries with CHD-related hospitalization, filled prescriptions for antihypertensive, initiation of statin therapy within 90 days of hospital discharge</td>
<td>1</td>
</tr>
<tr>
<td>Yang et al. (59)</td>
<td>Medicare Part D Enrollees</td>
<td>2005-2006</td>
<td>962,877</td>
<td>53.6%</td>
<td></td>
<td>Medicare Part D enrollees with diabetes</td>
</tr>
<tr>
<td>Foody et al. (60)</td>
<td>PharmMetrics Patient Centric Database</td>
<td>2003-2005</td>
<td>11,331</td>
<td>50%§</td>
<td>Statin naïve adults with a prior cardiac event and ≥1 prescription for atorvastatin or simvastatin</td>
<td>0.75</td>
</tr>
<tr>
<td>Ye et al. (61)</td>
<td>MedStat MarketScan Commercial Claims and Encounters Database + Medicare Supplemental and Coordination of Benefit Database</td>
<td>2000-2002</td>
<td>5,548</td>
<td>61.4%‡</td>
<td>Patients who initiated statin treatment within 6 months of hospitalization for cardiovascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

*Interview with medication review. †Proportion of days covered ≥80%. ‡Proportion of days covered ≥50%. §Continuation without ≥60-day gap. |Medication possession ratio ≥80%. Abbreviations as in Table 1.
time and, therefore, greater insight into patients’ medication-taking behavior (28). Electronic medication packaging devices are also being tested to improve monitoring of adherence. Although these methods are used widely in research settings, there is limited data supporting their validity in routine clinical practice, and variability in the quality of studies testing these devices complicates assessments of their efficacy (29). Other direct measures of adherence, including measurements of medication levels or metabolites, were effective in improving blood pressure control for patients with resistant hypertension (30); however, these methods are currently too inconvenient and costly for routine practice (24).

Clinical support tools may also be used to facilitate assessment of adherence. Other measures strongly associated with nonadherence include physiological markers, such as visit-to-visit variability in LDL-C (31). More recently, electronic pharmacy refill data have been utilized to monitor adherence; patients with prescriptions filled ≥80% of the time are categorized as adherent (32). This approach is gaining momentum, but requires that patients obtain prescriptions within a closed pharmacy system. Reliable measurements and implementation of interventions to improve adherence will require strong clinical care partnerships between multiple providers, pharmacies, caregivers, and patients.

**Sociodemographics and Health Systems**

Lower-income earners, black or Hispanic women, those without access to a caregiver, and patients with higher copayments are more likely to discontinue statin treatment after MI (33). Several interventions may improve adherence for these vulnerable patients. Health literacy interventions, including instructional checklists, educational drug fact pamphlets, and national campaigns promoting disease awareness, have illustrated the benefits of treatment. Providing information in the patient’s native language may lessen the burden of poor health literacy.

Policy changes designed to overcome barriers to care, such as elimination of out-of-pocket costs, the use of generic rather than brand-name medications, and full coverage for preventative medications after MI, are cost-neutral with respect to overall health care spending and have demonstrated improved...
adherence (34,35). Other health system barriers to optimal secondary prevention include access to provider appointments, continuity of care, prescription of limited numbers of medication refills, and providers’ competing priorities for patients with multiple medical comorbidities (18). Other patient-level barriers to care include belief systems, varying expectations of treatment, forgetfulness, and lack of noticeable benefits of taking medications with apparent side effects (36).

At an initial patient encounter, providers should gather data on drug insurance coverage, social support, and the role of the caregiver. The provider should assess the risk for medication nonadherence, evaluate reasons for forgetfulness (when applicable), and consider the expectation of the treatment outcome most valued by the patient. Because physician time constraints can make such conversations impractical, team-based approaches may be necessary. In addition to outpatient nurse-management protocols, pharmacy outreach programs are effective in providing further education on medications, monitoring, and reinforcing adherence (31,37).

LIFESTYLE AND COMORBID CONDITIONS

Obesity, smoking, alcohol consumption, and the presence of medical comorbidities are associated with nonadherence to statin therapy in secondary prevention (32). Providers, family caregivers, and health care systems must facilitate and support behavioral changes. Cardiac rehabilitation is an underutilized intervention that demonstrates a significant effect on morbidity and mortality after MI, percutaneous coronary intervention, or coronary artery bypass graft (38). In addition to improved health benefits through enhanced physical activity and nutritional counseling, participants demonstrate >30% improvement in adherence to statin therapy (39).

Depression is an underappreciated predictor of statin nonadherence in outpatients with CVD. Recognition of the signs and symptoms of depression and routine screening can provide important clinical information to physicians at both initial and subsequent visits (40). Psychosocial support and behavioral tools can be valuable for integrating medication adherence into daily life. Adherence may be improved by communication with open-ended questions and shared decision-making. Likewise, adherence to cardiovascular medications has been linked to faith in the provider, suggesting that the quality of the patient-provider relationship may be an important determinant (24).

RECOGNIZING TEMPORAL PATTERNS IN ADHERENCE

Patient adherence is greatest in the 5 days before and after an appointment with a provider, and diminishes significantly thereafter; this is termed “white coat adherence” (41). Adherence can be improved by applying individualized surveillance through interventions including electronic medical prescription-filling records and use of reminder trigger systems. Currently, over 90% of the U.S. population owns a mobile phone, and recent efforts have demonstrated successful utilization of text messaging to understand and improve adherence (42). Future trials that incorporate this technology in the study design are likely to improve adherence.

The transition from the inpatient to the outpatient setting is another crucial time period to monitor and ensure adherence. A multimodal approach has been effective. Ho et al. (43) randomized 253 patients discharged after ACS from 4 centers to either a multifaceted intervention to improve adherence or usual care. The intervention arm, combining education and counseling at discharge with post-discharge communication with pharmacists and automated voice messages, demonstrated a 15.4% increase in adherence (89.3% vs. 72.9%; p = 0.003) over the year following discharge. Another approach improved early adherence by programming an electronic medical record–linked automated voice call reminder to patients who did not fill a statin prescription 1 to 2 weeks post-discharge (44).

ADVERSE EFFECTS OF LIPID-LOWERING THERAPY

Statin intolerance and concerns regarding adverse effects of statin therapy contribute to nonadherence. Many patients may be reluctant to begin statin therapy due to concern for developing adverse events. In RCTs, statin therapy causes only a slight increase in side effects compared with placebo. Statin intolerance ranges from approximately 1% to 10% in RCTs, to as high as 10% to 25% in observational studies (33,45). Myalgia, the most common reason for discontinuation, occurs with similar frequency in both placebo and treatment arms (45,46). In a recent systematic analysis on myalgia prevalence reported by 26 statin clinical trials, Ganga et al. (45) found an average incidence of 12.7% in patients treated with statins compared with 12.4% in the placebo group (p = 0.06), suggesting that both patients and physicians overestimate the frequency of statin-associated myalgia. However, clinical trials included in this analysis did
not use a standard definition for statin-associated myalgia, and only 1 trial specifically queried patients regarding muscle problems.

Until large clinical trials incorporate uniform definitions and standardized assessment of myalgias, the incidence and prevalence of statin-induced myalgias remains uncertain. Furthermore, pre-statin assessments of myopathy, myalgias, and other constitutional symptoms, such as fatigue, should be performed to ensure that symptoms present at baseline are not erroneously attributed to statin therapy. Notwithstanding these controversies, simple strategies to overcome intolerance to statins have been successful. Rechallenging with the same or a different statin, reduced dosing, or alternate-day dosing have proven effective for 92.2% of patients who were initially intolerant of statins (46).

Misperceptions regarding the long-term safety and risk-benefit ratio of lipid lowering may also contribute to nonadherence. Although statins can increase the incidence of diabetes mellitus (1 additional case per 500 patients treated with intensive vs. moderate-intensity statin therapy), existing data suggests that the CVD benefits outweigh this risk (47). Patient counseling on these benefits and preemptively addressing concerns regarding adverse effects are important measures to improve adherence.

### PILL BURDEN AND FIXED-DOSE COMBINATION THERAPY

Guideline-recommended therapy for patients after ACS specifies the use of multiple agents, including a statin, aspirin, and often an (angiotensin-converting enzyme) inhibitor and beta-blocker. Although cost may affect adherence, in the MI-FREEE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation) trial (48), elimination of copayments resulted in only a 4% to 6% improvement in adherence. Overall rates of adherence to prescribed treatment were <50% (even in the group with full coverage) at a median follow-up of 394 days. Therefore, other factors, including pill burden, may have a greater effect on nonadherence than cost.

Adherence to medication is inversely related to the number of pills and doses required per day (21). Reduction of pill burden has demonstrated improvement in adherence, particularly in patients at high risk for CVD (20,49). Fixed-dose combination therapy (FDC), or the polypill, contains medications that address multiple CVD risk factors and is gaining momentum for its potential to facilitate application of guideline-recommended therapy (20). The polypill is now under investigation as a measure to improve adherence and outcomes in secondary prevention of CVD.

In the UMPIRE (Effects of a Fixed Dose Combination Strategy on Adherence and Risk Factors in Patients with or at High Risk of CVD) trial (49), use of a pill combining simvastatin with aspirin, lisinopril, and atenolol demonstrated a substantial improvement in self-reported adherence compared with usual care (86% in the FDC arm vs. 65% in the usual-care arm; p < 0.001). Among patients nonadherent before study enrollment, a marked improvement in adherence was noted (77.2% in the FDC arm vs. 23.1% in the standard-care arm; p < 0.01).

Most recently, the FOCUS (Fixed-Dose CoCombination Drug for Secondary Prevention PROJECT) trial (50) tested adherence to the polypill versus its 3 individual components (simvastatin 40 mg, aspirin 100 mg, and ramipril 2.5, 5, or 10 mg) in a randomly selected population of 695 patients from 4 countries following acute MI as part of phase 2 testing. After 9 months of follow-up, the polypill group demonstrated improved adherence compared with the group receiving 3 separate medications (50.8% compared with 41%; p = 0.019) without an increase in adverse effects, demonstrating the potential utility of this strategy in secondary prevention. Notably, the study was not designed to assess clinical outcomes.

From a global health perspective, the polypill’s potential to improve CVD event reduction in secondary prevention is appealing for patients in Western nations due to reduced complexity of treatment, convenience, and ease of distribution. In lower-income countries, where CVD is projected to constitute the leading cause of death by 2030, its potential to deliver medications at lower cost is particularly appealing (20). Detractors express concerns regarding efficacy and the possibility that side effects from 1 component could lead to discontinuation of treatment and loss of benefit from all drugs in the formulation. Therefore, caution is warranted, and larger clinical outcomes trials are needed.

### CONCLUSIONS AND OUTLOOK: THE PRESENT AND FUTURE

Despite great advances in optimizing medical management after ACS, fundamental challenges to achieving cardiovascular risk reduction remain. Within the optimal conditions of recent clinical trials, patients continue to demonstrate high rates of nonadherence after ACS. Multiple large database registries report even greater rates of nonadherence and
underutilization of high-intensity statin therapy. These failures have an enormous effect on achieving improved outcomes.

Guidelines, enhanced quality metrics, coordination of care, and outpatient outreach programs offer mechanisms to improve implementation of system-based approaches to optimal prescribing. Strategies that incorporate strong clinical care partnerships to address nonadherence to smoking cessation, hypertension control, exercise programs, and lipid management will result in improved outcomes after ACS. The polypill is a strategy that offers a viable, simple, and highly effective intervention to overcome nonadherence to antiplatelet, lipid, and blood pressure medication use in high-risk patients. Although a well-designed clinical outcomes trial supports combination therapy with a statin plus ezetimibe to reduce CVD events in ACS patients, increasing provider awareness of guideline-driven high-intensity statin utilization and patient adherence to all forms of therapy may be more important ways to improve clinical outcomes.

REFERENCES