Unblinded Title Page (include all contact information) and Word Count, number of figures, tables and number of text pages

This is a final peer-reviewed manuscript. For a published version, please go to http://journals.lww.com/lww-medicalcare/Abstract/2015/04000/Statin_Use_After_Acute_Myocardial_Infarction_by.6.asp.

Statin Use After Acute Myocardial Infarction by Patient Complexity: Are the Rates Right?

John M. Brooks, PhD*
Arnold School of Public Health, University of South Carolina
915 Greene Street 303D Discovery 1, Columbia, SC 29208
Phone: (803) 777-9224
Fax: (803) 777-1836
john-brooks@sc.edu

Elizabeth Cook, M.S.
Clinical Trials Statistical & Data Management Center, University of Iowa
2400 University Capitol Center
Iowa City, IA 52240-4034
Phone: (319) 384-3446
elizabeth-cook@uiowa.edu

Cole G. Chapman, PhD.
Arnold School of Public Health, University of South Carolina
915 Greene Street 303C Discovery 1, Columbia, SC 29208
Phone: (803) 777-9879
cole-chapman@sc.edu

Mary C. Schroeder, PhD
Department of Pharmacy Practice and Science, University of Iowa
115 S. Grand Ave. S525 PHAR
Iowa City, IA 52242
Phone: (319) 384-4516
mary-schroeder@uiowa.edu

Elizabeth Chrischilles, M.S., PhD
University of Iowa College of Public Health
105 River St., S424 CPHB, Iowa City, IA 52242
Phone: (319) 384-1575
e-chrischilles@uiowa.edu

Kathleen M. Schneider, PhD
Schneider Research Associates, LLC
121 - 30th Street, Des Moines, IA 50312
Phone: (515) 771-3981
schneidLLC@aol.com

Puttarin Kulchaitanaroaj, PhD
Health Economics Research Group, Brunel University London
Uxbridge, UB8 3PH, United Kingdom
Phone: 440 1895265460
puttarin.kulchaitanaroaj@brunel.ac.uk

Jennifer Robinson, M.D., M.P.H.
University of Iowa College of Public Health,
105 River St., S455 CPHB,Iowa City, IA 52242
Phone: (319) 384-1563
jennifer-robinson@uiowa.edu

*Corresponding Author

Funding Source: This project was supported by an Agency for Healthcare Research and Quality grant (1R21HS019574-01) under the American Recovery and Reinvestment Act of 2009.

Manuscript Word Count: 3,434
Number of Text Pages: 13
Number of Figures: 0
Number of Tables: 4

Brief Title: Statin Effectiveness by Patient Complexity

Statin Use After Acute Myocardial Infarction by Patient Complexity: Are the Rates Right?

Abstract

Background: Guidelines suggest statin use after acute myocardial infarction (AMI) should be close to universal in patients without safety concerns yet rates are much lower than recommended, decline with patient complexity, and display substantial geographic variation. Trial exclusions have resulted in little evidence to guide statin prescribing for complex patients.

Objective: Assess the benefits and risks associated with higher rates of statin use after AMI by baseline patient complexity.

Research Design: Sample includes Medicare fee-for-service patients with AMIs in 2008-2009. Instrumental variable estimators using variation in local area prescribing patterns by statin-intensity as instruments were used to assess the association of higher statin prescribing rates by statin-intensity on 1-year survival, adverse events, and cost by patient complexity.

Results: Providers appear to have individualized statin use across patients based on potential risks. Higher statin rates for non-complex AMI patients were associated with increased survival rates with little added adverse event risk. Higher statin rates for complex AMI patients were associated with tradeoffs between higher survival rates and higher rates of adverse events.

Conclusions: Higher rates of statin use for non-complex AMI patients are associated with outcome rate changes similar to existing evidence. For the complex patients in our study, who were least represented in existing trials, higher statin-use rates were associated with survival gains and higher adverse event risks not previously

documented. Policy interventions promoting higher statin-use rates for complex patients may need to be re-evaluated taking careful consideration of these tradeoffs.

Key Words: statins, effectiveness, survival, adverse events, costs, geographic variation, instrumental variables.

Introduction

Guidelines for statin use after acute myocardial infarction (AMI) have become more definitive over time as evidence has accumulated. Earlier guidelines focused on cholesterol reduction[1-3] and provided qualifications for statin use such as "absence of contra-indications"[3,4] and limited recommendations to "like study patients".[5] The latest European guideline however has no qualifications, stating, "Statins should be given to all patients with acute myocardial infarction, irrespective of cholesterol concentration… and given at high doses."[6] The US 2013 ACC/AHA Cholesterol Guideline recommends high-intensity statin therapy following AMI in individuals up to age 75 years without heart failure or end-stage renal disease for whom there are no safety concerns. Lower-intensity statins are recommended for patients >75 years or patients with safety concerns from high-intensity statins.[7] Yet, studies show statin-use rates after AMI are much lower than guidelines recommend, decline with patient complexity, and display substantial geographic variation.[8-11] In light of this, patient and provider interventions to encourage higher rates of statin use have been suggested.[12]

The source of this apparent underuse of statins does not appear to be insufficient evidence diffusion as an LDL-C of less than 100 mg/dl (defined as the goal of treatment in earlier US cholesterol guidelines[13]) was identified by 96% of US physicians as the treatment goal for high-risk patients.[14] Alternatively, non-universal statin prescribing after AMI may reflect provider beliefs that statin benefits and risks are heterogeneous across patients and that the statin prescribing in practice is being individualized to patient circumstances. Randomized controlled trial (RCT) evidence supports the idea that absolute risk reductions from statins are heterogeneous across patients with

respect to factors such as diabetes or heart failure.[15-18] In addition, although the rate of statin-related adverse events reported in RCTs were low, adverse events appear more often in practice and vary with statin intensity, patient age, gender, weight, health behaviors, comorbidities, and concomitant drug use.[19-25]

If providers are trying to limit statin prescribing to only those patients for whom they believe statin benefits outweigh risks, the relevant policy question then becomes whether statin-use rates after AMI represent an optimal sorting of statins across patients. Are existing rates "right"?[26] If present statin-use rates are less than optimal, higher rates should yield survival gains sufficient to outweigh additional adverse effect risks and treatment costs. Conversely, if statin-use rates after AMI are optimal, higher rates could result in higher healthcare costs and higher adverse effect rates with little added survival benefit. Estimates of the benefits and risks of statins for AMI patients on the "extensive margin"[27-29] are needed to address this question. AMI patients on the extensive margin can be thought of as those who would be next to receive a statin if use rates increased, or those first not to receive a statin if rates were lowered.

The objective of this paper is to use the variation in statin practice styles for Medicare AMI patients across local areas found in earlier research[11] to assess the benefits and risks of statins for patients on the extensive margin. We use instrumental variable (IV) estimation methods to assess the effects of higher use rates of both lower-intensity and high-intensity statins after AMI on survival rates, adverse event rates and healthcare costs. IV estimators yield estimates that are properly generalized to the subset of patients whose treatment choices were influenced by the instrument used in the study.[30,31] Here we use instruments derived from the variation in statin practice

styles across local areas so that our estimates can be interpreted tangibly as what might be expected from interventions targeted at changing statin-use rates. Separate IV analyses are performed for complex patient subgroups because statin rates have been observed to vary with complexity.

Methods

Data and Study Cohort

Medicare claims files and enrollment information for all Medicare beneficiaries with an AMI in 2008 and 2009 were obtained based on the Chronic Condition Data Warehouse (www.ccwdata.org) definition of AMI (an inpatient claim with the primary diagnosis code 410.x1). The study cohort contained all AMI Medicare patients with sufficient fee-for-service coverage to enable proper measurement of study variables. The online appendix contains a full description of the exclusion criteria used. The final corhort contained 124,813 patients. In addition, because statin use after AMI was found to vary substantially with patient complexity, we stratified the cohort based on prior heart failure (N = 66,644), prior chronic kidney disease (N = 43,690), prior diabetes (N = 54,125), and patients with none of these three conditions prior to AMI admission (N = 31,170).

Treatment Variables

Two binary statin treatment variables (lower-intensity and high-intensity) were specified for each patient to represent statin availability for use in the month after AMI discharge. High-intensity statins were defined as those that can lower LDL-C by 50% or more: atorvastatin 40,80mg; and rosuvastatin 20,40mg. Lower-

intensity statins were defined as those that lower LDL-C less than 50%: atorvastatin 10, 20mg; fluvastatin 20,40,80mg; lovastatin 10,20,40,80mg; rosuvastatin 5,10mg; pravastatin 10,20,40,80mg; and simvastatin 5, 10,20,40,80mg.[32] The online appendix provides the approach used to measure these binary variables using Medicare Part D event data.

Outcome Variables

This study focused on four separate outcomes: 1-year survival; 1-year cardiovascular-event-free survival; 1-year occurrence of any adverse event found to be associated with statins in previous population studies[25,33] (muscle-related inpatient and outpatient events; inpatient acute renal events, or inpatient acute hepatic events); and 1-year total healthcare cost from the perspective of the Medicare program. Secondarily, the 1-year occurrence of each distinct adverse event were analyzed. The online appendix describes the approaches used to measure study outcomes and the ICD-9 codes and Medicare claims files used.

Covariates

A list of the covariates specified in all estimation equations can be found in the online appendix. Full definitions of these variables can be also found in a previous publication.[11]

Instrumental Variable Strategy

A linear two-stage least squares (2SLS) instrumental variable estimator with robust standard errors was used to estimate the absolute effect of statins on each study outcome. STATA software was used. Linear 2SLS yields consistent estimates of absolute treatment effects on outcomes for the group of patients whose treatment choices were influenced by the instrument specified regardless of underlying error distributions. Further justification for this estimator can be found in the online appendixl.

The instruments used in this study were measures of local area statin practice styles for the AMI patients living around the residence ZIP codes of the patients in our sample. We postulated that patients did not choose their residence in a manner related to unmeasured confounders for a future acute condition and that patients with an acute condition living in a local area with physicians having stronger preferences for a particular treatment are more apt to receive that treatment. A full description of the local area practice style measurement approach used here is documented elsewhere.[11] Briefly, local areas were constructed for each patient ZIP code by consecutively adding AMI patients from the next closest ZIP codes based on driving times until at least 150 patients were found.[34] Robustness checks for alternative local area sizes were performed. For the patients in the local area around each ZIP code, *area treatment ratios* (ATRs) for “no statin”, “lower-intensity statins” and “high-intensity statins” were calculated as the ratio of the number of patients in the local area who received each respective statin intensity over the sum of the predicted probabilities across these patients of receiving that statin intensity. This approach to measure local area practice styles was found to explain a larger portion of treatment variation than other local area definitions and effectively balance measured covariates.[34-36]

Results

Table 1 provides average characteristics for our sample when patients are grouped by (1) post-AMI statin intensity and (2) the quintiles of the local area treatment ratio (ATR) for "no statins". Patients using either a high or lower-intensity statin after AMI relative to patients without a statin were more likely younger, male, and living in a ZIP code that was metropolitan with a higher than average income and a higher than average life expectancy. Statin users also had fewer comorbidities as measured by the Charlson Score,[37] had fewer prior conditions related to adverse events, were more likely to have used a statin previous to their AMI **and more likely to have been initially prescribed other drugs. Statin users** had characteristics suggestive of more serious AMIs (more likely arterial wall, ST-elevation, and received cardiac catheterization) than non-users. Statin users had higher unadjusted 1-year survival and cardiovascular-event-free survival rates, lower 1-year acute renal and 1-year muscle-related event rates, and lower 1-year Medicare costs than non-users. In addition, lower-intensity statin users had lower unadjusted 1-year hepatic event rates than non-users.

Comparisons across ATR quintiles provide some evidence as to whether our instruments provide a "natural experiment" in statin use. In the first quintile 32.4% of patients had no statin available for use within 30 days of AMI discharge (67.6% had a stain available) compared to 43.6% of patients in the fifth quintile (56.4% had a stain available). While trends in several measured covariates across quintiles reached statistical significance, for the most part these differences were modest compared to when patients were grouped by statin use. Exceptions were mainly for demographic and socioeconomic characteristics. Local areas with higher statin use (e.g. quintile 1) had

higher percentages of African Americans, patients who lived in a metropolitan area, and patients who lived in a ZIP code with a higher than average income than the other quintiles. No trends in unadjusted survival or Medicare cost were observed across quintiles. Unadjusted adverse event rates fell as statin-use rates fell moving from quintiles 1 to 5.

Table 2 contains average unadjusted 1-year outcomes for the full sample and by patient complexity. The adverse event rates for our population were much greater than what was reported for younger and less complex patients using statins.[24] Survival and cardiovascular-event-free survival rates were lower in the complex patient subsets compared to the non-complex subset while Medicare costs and adverse event rates were higher in these subsets.

Table 3 summarizes our IV results for the full sample and subsets based on complex conditions. **Alternative representations of Table 3 based on local areas using 100-patient and 200-patient thresholds around patient residence ZIP codes are available in the online appendix.** For each cohort, each row of Table 3 provides estimates by statin intensity. Column 1 shows the percentage of patients using statins by intensity level and the inter-quintile range of these percentages across local area practice style quintiles. Estimates of the absolute effect of statin use on each outcome should be interpreted in terms of statin rate changes only within these ranges. Column 2 contains the F-statistics testing whether the instruments had statistically significant impacts on lower-intensity and high-intensity statin use.[38] The instruments had statistically significant impacts on both lower and high-intensity statin use for the full sample and within each complexity subset. Columns 3-9 contain the absolute effect

estimates of statin use by intensity on each study outcome relative to no statin. For example, (.081) is the absolute effect estimate of lower-intensity statin use on 1-year survival for the marginal patients within the full sample relative to no statin. This result **can also be** interpreted as follows: a one percentage point increase in the use of lower-intensity statins within the range of 43% to 57% (e.g. increasing the lower-intensity percentage from 50 to 51) was associated with an .081 percentage point increase in 1-year survival (e.g. 85.4 to 85.481) relative to no statin. The same one percentage point increase in lower-intensity statin use within this range led to an average decrease in Medicare costs for marginal patients of $2,370. Across the full sample, higher statin-use rates were associated with higher 1-year survival and cardiovascular-event-free survival rates (columns 3-4) with high-intensity statins showing greater additional survival benefit from higher use rates than lower-intensity statins. Higher statin-use rates in the full sample were also associated with higher adverse event rates (columns 5-8) with high-intensity statin-use rates being positively associated with higher rates of all three adverse advents. Column 9 shows that average Medicare costs per marginal patient were reduced with greater statin-use rates but this association was only statistically significant for lower-intensity statins.

The statin treatment effect estimates stemming from rate differences across local areas varied with patient complexity. AMI patients with no prior heart failure, no chronic kidney disease, and no diabetes had the highest use rates of both lower- and high-intensity statins. For this subset higher rates of high-intensity statin use were associated with survival gains and the absolute effect of this association was about half of what was found for the full sample. No statistically significant associations with other

study outcomes were found for this patient subset. Statin-use rates were lower for complex patients as compared to non-complex patients. Complex patients had larger increases in 1-year survival and 1-year cardiovascular-event-free survival rates associated higher statin-use rates than non-complex patients. Conversely, higher statin-use rates for complex patients were associated with higher adverse event rates than for non-complex patients. Statin-use rates regardless of intensity were positively associated with acute hepatic events in each complex patient subset. Use rates of high-intensity statins were positively associated with acute renal event rates in each complex patient subset. Higher statin-use rates did not have statistically significant associations with muscle-related adverse effects in any patient subset, but the estimates for these conditions were generally higher for complex patients than non-complex patients. In addition, higher statin-use rates among complex patients were associated with larger reductions in 1-year Medicare costs than among non-complex patients. For patients with prior heart failure Medicare cost reductions of over $4,000 were found associated with greater statin-use rates for either statin intensity level.

Discussion

Our results provide strong evidence that providers were attempting to individualize statin prescribing to patients after AMI. Statin users after AMI were less complex, had higher rates of prior statin use, and lower rates of prior hepatic, renal and muscle-related events as compared to the patients without a statin after AMI. In addition, statin users had *lower unadjusted* 1-year post-AMI rates of acute renal events and muscle-related events than non-users. Lower-intensity statin users also had lower post-AMI 1-year rates of acute hepatic events than non-users. Because statins are not

considered protective with regard to these conditions, these unadjusted outcome comparisons suggest that providers purposely restricted statins from patients who were at higher risk of these adverse events.

Table 4 summarizes our results with regard to changes in statin-use rates after AMI. For the non-complex patients in our study high-intensity statin-use rates were positively associated with 1-year survival with no additional adverse event risk. These estimates are consistent with the 2013 ACC/AHA cholesterol guidelines in that patients should be on a high-intensity statin if safety concerns are not present.[7] These guidelines were based on randomized controlled trials (RCTS) and meta-analyses of RCTs that showed survival gains and cardiovascular event risk reductions from statins with few reported adverse events.[39,40] The non-complex patients in our sample were most closely aligned to the populations in these studies.

In contrast, outcome tradeoffs were associated with higher rates of statin use for the complex patients in our study. From initially lower statin-use rates as compared to non-complex patients, higher statin-use rates for complex patients were associated with larger survival and cardiovascular-event-free survival rate increases than what was observed for non-complex patients. These statin benefits were tempered by larger positive associations between statin-use rates and adverse event rates than what was observed for non-complex patients. Across the three complex patient subgroups, a one percentage point increase in statin-use rates was associated with between a .095 - .176 increase in the proportion of patients with acute hepatic events over the next year, depending on statin intensity. Likewise, a one percentage point increase in high-intensity statin-use rates was associated with a .138 - .178 increase in the proportion of

patients with acute renal events over the next year. While no estimate for muscle-related adverse events was statistically significant within any complex patient subset, a positive association between high-intensity statin availability and muscle-related events over the entire sample appears to emanate from the associations seen within the complex patient subsets. The 2013 ACC/AHA cholesterol guidelines are clear that safety concerns should be considered in the statin prescribing decision. The practice patterns we observed for complex patients may reflect provider attempts to incorporate safety concerns into practice in light of the limited RCT evidence available for complex patients. Indeed, the patients represented in the statin RCTs had far fewer complexities than the patients in our Medicare sample. Moreover, even the few statin RCTs that included more complex patients still had exclusions based on liver function, renal impairments, and muscular problems.[41,42] Our study provides important new evidence of the stain side effect risks for older complex patients.

It is important to understand that our estimates should be generalized only to patients within each complex subset whose statin use would have changed had they resided in a local area with different statin prescribing preferences. The inter-quartile ranges in statin-use rates in Table 3 are the ranges within which our results should be interpreted. Extrapolating our estimates outside these ranges is problematic if statin recommendations were individualized across patients based expected benefits and risks and our evidence suggests that providers were attempting to individualize statin use across patients. Consequently, our estimates only inform the discussion of whether existing statin-use rates should change within a window around the rates observed in

2008-2009 and not a discussion of whether statins should or should not be used generally within each patient subset defined by complexity.

It should also be emphasized that validity of our estimates is based on the assumption that local area statin practice styles are not associated with unmeasured factors related to study outcomes. This assumption is supported by previous research showing local area statin practice styles varying substantially across and within states[11] and that grouping patients by local area practice styles substantially reduced the imbalance in most measured clinical covariates as compared to grouping patients by actual statin use. However, grouping patient by local area practice styles did exacerbate the imbalance in some demographic and socioeconomic variables relative to grouping patients by statin use. While these factors were controlled for directly in our analysis, they could be symptomatic of other unmeasured differences across local areas that may confound our results. For example, if statin use and unmeasured healthcare access were positively correlated it is possible that higher adverse event rates in areas with higher statin use are partially attributable to reporting bias. Patients with greater access to healthcare may have greater opportunities to be diagnosed with adverse events. **It is also possible that local area statin rates could be positively correlated with local area use of other types of aggressive care we have not measured. Table 1 shows a slight positive relationship between local area statin rates and rates of beta blockers and renin-angiotensin system antagonists after AMI. While we controlled for the use of these drugs directly in our analysis, our results could be partially attributable to correlations with other unmeasured treatments.** However, if unmeasured confounders were the predominant source of our

estimates we would expect to find higher adverse event rates associated with statin use across all complex patient subsets, rather than the specificity of the association for complex subsets only.

Statins are advocated for use after AMI with a proviso for safety concerns. Randomized controlled trial (RCT) evidence suggests that statin safety concerns are minimal which has led some to believe that statin prescribing post AMI should be close to universal and behavioral interventions be used to increase statin initiation.[12] However, statin RCTs have generally excluded the most complex patients. Our study shows that most elderly AMI patients within Medicare are complex and would have been excluded from these trials and that providers have been individualizing statin use across Medicare patients based on perceived risks of adverse events that have not been observed in published evidence. Complex patients had lower statin-use rates than non-complex patients and the effects of higher statin-use rates on benefits and risks varied with patient complexity. Higher rates of high-intensity statin use for non-complex AMI patients was associated higher survival rates with no additional adverse event risk which is consistent with RCT evidence. In contrast, for complex patients who are unrepresented in the RCTs we showed that higher statin-use rates involves tradeoffs between survival benefits and adverse event risks. Because of these tradeoffs, the "right rate" of statin use by complex patients remains unclear. At a minimum our evidence suggests that promoting universal statin use among complex AMI patients over observed practice without consideration of the potential of safety issues may not be wise policy.

References

1. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. Journal of the American College of Cardiology 2000;36:970-1056.
2. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-2002: Summary article - A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation 2002;106:1893-900.
3. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk REduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 Update - A Guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458-73.
4. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. European Heart Journal 2008;29:2909-45.
5. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal 2003;24:28-66.
6. Steg G, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal 2012;33:2569-619.
7. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013.
8. Javed U, Deedwania PC, Bhatt DL, et al. Use of intensive lipid-lowering therapy in patients hospitalized with acute coronary syndrome: an analysis of 65,396 hospitalizations from 344 hospitals participating in Get With The Guidelines (GWTG). Am Heart J 2010;160:1130-6, 6 e1-3.
9. Lewis WR, Ellrodt G, Peterson E, et al. Trends in the Use of Evidence-Based Treatments for Coronary Artery Disease Among Women and the Elderly: Findings From the Get With the Guidelines Quality-Improvement Program. Circulation 2009;2:633-41.
10. Zuckerman IH, Yin X, Rattinger GB, et al. Effect of exposure to evidence-based pharmacotherapy on outcomes after acute myocardial infarction in older adults. J Am Geriatr Soc 2012;60:1854-61.
11. Brooks JM, Cook EA, Chapman CG, et al. Statin Use Following Acute Myocardial Infarction by Patient Complexity: Evidence of Effective Care? Medical Care 2014;52.
12. Grabowski DC, Lakdawalla DN, Goldman DP, et al. The Large Social Value Resulting From Use Of Statins Warrants Steps To Improve Adherence And Broaden Treatment. Health Affairs 2012;31:2276-85.
13. National Cholesterol Education Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3143-421.
14. Yan AT, Yan RT, Tan M, et al. Contemporary management of dyslipidemia in high-risk patients: Targets still not met. Am J Med 2006;119:676-83.
15. Robinson JG, Stone NJ. Identifying patients for aggressive cholesterol lowering: The risk curve concept. Am J Cardiol 2006;98:1405-8.

16. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005 - 16.
17. Shepherd J, Kastelein JJP, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: The TNT (Treating to New Targets) study. J Am Coll Cardiol 2008;51:1448-54.
18. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.
19. Mansi I, Frei CR, Pugh MJ, Makris U, Mortensen EM. Statins and Musculoskeletal Conditions, Arthropathies, and Injuries. JAMA Intern Med 2013;173:1308-17.
20. Zhang HB, Plutzky J, Skentzos S, et al. Discontinuation of Statins in Routine Care Settings A Cohort Study. Annals of Internal Medicine 2013;158:526-+.
21. Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. Expert Opin Drug Saf 2011;10:373-87.
22. Golomb BA, Evans MA. Statin adverse effects : a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008;8:373-418.
23. Florentin M, Elisaf MS. Simvastatin interactions with other drugs. Expert Opin Drug Saf 2012;11:439-44.
24. Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: An assessment using an administrative claims database. American Journal of Cardiology 2006;97:61C-8C.
25. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. British Medical Journal 2010;340:12.
26. Wennberg JE. Which Rate is Right? New England Journal of Medicine 1986;315:810-5.
27. Phelps CE. Health Economics. 2nd ed: Addison-Wesley; 1997.
28. Park TR, Brooks JM, Chrischilles EA, Bergus G. Estimating the effect of treatment rate changes when treatment benefits are heterogeneous: Antibiotics and otitis media. Value in Health 2008;11:304-14.
29. Brooks JM, McClellan M, Wong HS. The marginal benefits of invasive treatments for acute myocardial infarction: Does insurance coverage matter? Inquiry-J Health Car 2000;37:75-90.
30. Harris KM, Remler DK. Who Is the Marginal Patient? Understanding Instrumental Variables Estimates of Treatment Effects. Health Services Research 1998;33:1337-60.
31. McClellan M, Newhouse JP. Instrumental Variables Analysis Applications in Health Services Research -- A Special Supplement to HSR -- Overview of Supplement Issue. Health Services Research 2000;35:1061-9.
32. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. British Medical Journal 2003;326:1423-7.
33. Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. Am J Cardiol 2006;97:61C-8C.
34. Fang G, Brooks JM, Chrischilles EA. A New Method to Measure Geographic Variation in Prescription Use and Its Implications for Comparative Effectiveness Research. Medical Care 2010;40:710-7.
35. Fang G, Brooks JM, Chrischilles EA. Comparison of Instrumental Variable Analysis Using a New Instrument With Risk Adjustment Methods to Reduce Confounding by Indication. American Journal of Epidemiology 2012;175:1142-51.
36. Brooks JM, Chrischilles EA, Landrum MB, et al. Survival implications associated with variation in mastectomy rates for early-staged breast cancer. Int J Surg Oncol 2012;2012:127854.

37. Klabunde CN, Warren JL, Legler JM. Assessing Comorbidity Using Claims Data. Medical Care 2002;40:IV26-IV35.
38. Wooldridge J, M. Introductory Econometrics: A Modern Approach. Mason, Ohio: Thomson South-Western; 2003.
39. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
40. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
41. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.
42. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study C. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

Table 1

Table 1: Medicare AMI Patient Characteristics 2008-2009 by Initial Statin Intensity and Local Area No-Statin Prescribing Style											
	Total Population	Statin Use				Quintiles of Local Areas Based on "No-Statin" Use (Local areas with lower statin use →)					
		None	Lower Intensity	High Intensity	P-value	1st	2nd	3rd	4th	5th	P-value[h]
N	124,813	47,566	62,316	14,931		24,962	24,960	24,966	24,958	24,967	
No-Statin Area Treatment Ratio[a]	*	*	*	*		0.869	0.949	0.998	1.05	1.13	
Treatment					<0.0001*						
No Statin %	38.1	100.0	0.0	0.0		32.4	36.1	37.8	40.6	43.6	<0.0001*
Lower-Intensity Statin[b] %	49.9	0.0	100.0	0.0		52.4	51.0	50.2	49.0	47.1	<0.0001*
High-Intensity Statin[b] %	12.0	0.0	0.0	100.0		15.2	12.9	11.9	10.5	9.3	<0.0001*
Age											
66-75 %	40.7	33.1	43.9	51.8	<0.0001*	38.8	40.8	40.8	41.0	42.3	<0.0001*
76-85 %	38.6	38.7	39.0	36.6	0.0033*	39.2	38.4	38.9	38.2	38.1	0.0139*
86+ %	20.7	28.2	17.1	11.6	<0.0001*	22.0	20.7	20.3	20.8	19.6	<0.0001*
Sex					<0.0001*						0.0144*
Male %	43.2	39.7	44.6	48.5		42.6	43.4	43.0	42.9	44.1	
Female %	56.8	60.3	55.4	51.5		57.4	56.6	57.0	57.1	55.9	
Race											
White %	83.0	83.0	83.2	82.0	0.1135	78.4	84.2	83.7	85.5	83.2	<0.0001*
Black %	7.9	8.6	7.3	7.8	<0.0001*	10.2	7.9	8.1	7.1	6.1	<0.0001*
Other/Missing %	9.1	8.4	9.5	10.2	<0.0001*	11.4	8.0	8.3	7.4	10.7	0.0011*
Complex Conditions											
Heart Failure	53.4	60.9	49.3	46.7	<0.0001*	56.3	52.9	53.2	53.1	51.4	<0.0001*
Chronic Kidney Disease	35.0	39.3	32.6	31.4	<0.0001*	36.4	35.3	35.2	34.6	33.5	<0.0001*

Diabetes	43.4	43.9	43.0	43.4	0.0043*	44.6	42.5	43.4	43.6	42.7	0.0065*
Charlson Score[b]					<0.0001*						<0.0001*
0 %	33.4	28.3	36.2	38.3		32.2	33.6	33.3	33.7	34.3	
1+ %	66.6	71.7	63.8	61.7		67.8	66.4	66.7	66.3	65.7	
Arterial Wall AMI[d] %	6.1	4.4	6.8	8.7	<0.0001*	5.9	6.4	6.0	6.2	6.2	0.2987
NSTEMI AMI[e] %	75.9	79.7	74.4	69.7	<0.0001*	77.7	75.8	75.7	75.2	75.0	<0.0001*
Cardiac Catheterization During Index Stay %	58.9	43.5	66.9	74.9	<0.0001*	55.9	58.3	59.0	59.4	62.2	<0.0001*
Statin Rx in 180 Days Prior to Index AMI %	47.0	25.9	60.4	58.5	<0.0001*	49.5	47.5	47.3	46.2	44.7	<0.0001*
Prior Conditions Related to Statin Adverse-Effects											
Pre-Index AMI[f] %	22.7	26.3	20.7	19.3	<0.0001*	23.9	22.8	22.3	21.9	22.5	<0.0001*
During Index AMI[f] %	19.9	23.4	18.0	17.0	<0.0001*	21.2	20.5	20.0	19.5	18.6	<0.0001*
ZIP Code Characteristics											
Low Income[g] %	49.8	51.3	49.4	46.5	<0.0001*	43.3	47.7	47.8	51.9	58.3	<0.0001*
Metropolitan Area %	69.3	68.8	69.0	72.5	<0.0001*	76.6	69.3	69.4	63.5	67.7	
Life Expectancy Below Median %	50.0	51.9	48.9	48.7		48.2	48.7	50.5	52.8	49.7	
Additional Treatments after discharge											
beta blockers, %	**66.7**	**47.9**	**77.4**	**81.2**	**<0.0001***	**67.9**	**66.7**	**66.3**	**66.5**	**65.8**	**<0.0001***
renin-angiotensin system antagonists %	**48.4**	**33.2**	**56.8**	**61.7**	**<0.0001***	**49.5**	**48.2**	**48.5**	**47.7**	**48.0**	**<0.0001***
1-Year Outcomes											
Survival %	84.5	77.7	88.3	90.7	<0.0001*	84.5	84.6	84.6	84.3	84.7	0.8977
Cardiovascular-Event Free Survival %	75.9	69.3	79.8	80.5	<0.0001*	75.7	76.1	75.6	76.0	75.9	0.6744
Average Medicare Costs	$10,802	$11,119	$10,550	$10,842		$10,682	$10,738	$10,744	$10,989	$10,856	

Acute Renal Event %	15.6	18.5	13.9	13.7	<0.0001*	16.9	16.0	15.7	14.9	14.7	<0.0001*
Acute Hepatic Event %	3.8	3.9	3.6	4.1	0.0440*	4.8	3.7	3.7	3.4	3.4	<0.0001*
Muscle-Related Event %	17.6	18.5	17.0	17.1	<0.0001*	18.2	17.8	17.5	17.0	17.3	0.0004*

a. Based on Area Treatment Ratio (ATR) of actual "no statin" treatment rate over predicted "no-statin" treatment rate for the 150 AMI patients living closest to a patient residence ZIP code.
b. Based on highest statin intensity available to patients in 30 days after AMI discharge.
b. Klabunde CN et al. Development of a comorbidity index using physician claims data. Journal of Clinical Epidemiology, 200 Dec; 53(12) 1258-67.
c. HF: Heart Failure: CKD: Chronic Kidney Disease. See Appendix for CKD, HF, and diabetes ICD-9 codes
d. ICD-9 codes 410.0 410.1
e. ICD-9 410.7x
f See Appendix for CKD, HF, and diabetes ICD-9 codes acute renal failure/acute tubular necrosis ICD-9 584.xx; acute glomerulonephritis ICD-9 580.xx. Myopathy: ICD-9-CM 728.89, 729.1, 359.4,359.8, 359.9, 710.4, 728.9, 729.8X, E942.2; CPT codes 82550, 82552, 82554, 80012, 80016, 80018, or 80019. Acute/sub-acute necrosis of liver ICD-9 570.xx; hepatitis ICD-9 573.3x; other disorders of liver ICD-9 573.8x, 573.9x.
g. Percentage of low income residents was above median in 2000 for beneficiary ZIP code.
h. Cochran-Armitage two-sided test of trend in characteristic value across patients grouped into quintiles based on local area high-intensity practice style measure. For example, the p value for Age 76-85 tests whether a linear trend in the percentage of patients in this age group exists across quintiles of the high-intensity ATR-based patient groups
* $p < .05$

Table 2

Table 2: Unadjusted 1-Year Average Outcomes for Medicare AMI Patients 2008-2009 by Patient Complexity

1-Year Outcome	Full Sample (N=124,813)	Non-Complex Patients[a] (N=31,170)	Prior Heart Failure (N=66,644)	Prior Chronic Kidney Disease (N=43,690)	Prior Diabetes (N=54,125)
Survival %	84.5	93.6	78.0	77.4	82.9
Cardiovascular-event free survival (%)	75.9	87.1	68.4	67.3	72.4
Medicare costs	$10,802	$9,009	$12,046	$12,256	$11,715
Acute renal events (%)	15.6	4.1	22.1	30.1	20.6
Acute hepatic events (%)	3.8	2.7	4.4	4.9	4.3
Muscle-related events (%)	17.6	14.6	19.3	20.3	19.3

a. Patients with no heart failure, chronic kidney disease, or diabetes 1-year prior to AMI admission.

Table 3

Table 3: Instrumental Variable Estimates of Absolute Local Average Treatment Effects (LATEs) on 1-Year Outcomes by Statin Intensity Across Patient Subsets.

		1	2	3	4	5	6	7	8	9
Cohort	Statin intensity	Percentage using statins at this intensity (inter-quintile range)	1st-Stage Instrument F-Statistics[a]	1-Year Outcomes						
				Survival	Cardio-vascular Event Free Survival	Adverse Events				1-Year Medicare Costs
						Any Adverse Events[b]	Muscle-Related	Hepatic-Related	Renal-Related	
All (N=124,813)	Lower	50 (43-57)	84.5***	.081*[c] (.032)	.104** (.039)	.130** (.043)	.063 (.036)	.102*** (.018)	.034 (.032)	-2,370.31* (1067.71)
	High	12 (6-19)	198.8***	.145*** (.030)	.119*** (.036)	.124** (.040)	.067* (.033)	.074*** (.017)	.083** (.030)	-1,682.46 (994.76)
No HF, CKD or Diab (N=31,170)	Lower	56 (47-64)	48.00***	.057 (.039)	-.086 (.055)	.050 (.066)	.056 (.059)	-.009 (.028)	-.012 (.033)	-101.43 (1428.13)
	High	14 (7-24)	86.89***	.075* (.038)	-.017 (.054)	-.020 (.064)	-.010 (.057)	-.015 (.027)	-.011 (.033)	1184.25 (1374.29)
Any HF (N=66,644)	Lower	46 (41-52)	31.3***	.090* (.053)	.161*** (.060)	.137* (.063)	.029 (.052)	.151*** (.029)	.061 (.053)	-4477.90** (1719.17)
	High	10 (6-16)	77.7***	.176*** (.073)	.134* (.056)	.176** (.058)	.092 (.049)	.095*** (.027)	.141** (.049)	-4053.38* (1599.06)
Any CKD (N=43,690)	Lower	46 (41-52)	20.3***	.083 (.069)	.133 (.079)	.197* (.087)	.104 (.070)	.141*** (.039)	.051 (.079)	-4,406.27 (2396.34)
	High	11 (6-17)	52.0***	.141* (.062)	.093 (.071)	.212** (.077)	.106 (.063)	.102** (.035)	.170* (.070)	-3333.98 (2146.44)
Any Diab (N=54,125)	Lower	49 (44-55)	26.2***	.036 (.060)	.231** (.074)	.099 (.079)	.027 (.067)	.176*** (.036)	-.006 (.065)	-4432.83* (2139.99)
	High	12 (7-18)	63.2***	.147** (.055)	.195** (.067)	.225** (.072)	.107 (.061)	.143*** (.033)	.138* (.059)	-1528.33 (1956.33)

* p < 0.05; ** p < .01; *** p < .001

HF: Heart Failure; CKD: Chronic Kidney Disease; Diab: Diabetes

a. F-statistic used to test the exclusion restrictions on the instruments in the first-stage equations. See Wooldridge J, M. Introductory Econometrics: A Modern Approach. Mason, Ohio: Thomson South-Western; 2003, Chapter 4.

b. Any of the three adverse events.

c. This is the absolute local average treatment effect (LATE) estimate of lower-intensity statin availability on 1-year survival for the marginal patients within the full study cohort relative to not having a statin available. For example, a one percentage point increase in the availability of lower-intensity statins within the range of 43% to 57% (e.g. increasing the lower-intensity percentage from 50 to 51) is associated with an .081 percentage point increase in 1-year survival (e.g. 85.4 to 85.481).

Table 4

Table 4: Summary of Effects Statin Rate Differences on Outcomes by Patient Complexity

Complexity	Lower-intensity statins			High-intensity statins		
	Rate range[a]	Estimated effects associated with higher rate[b]		Rate range[a]	Estimated effects associated with higher rate[b]	
		Benefit increase[c]	Risk increase[d]		Benefit increase[c]	Risk increase[d]
All Patients	43-57	yes	yes	9-16	yes	yes
Non-Complex	47-64	no	no	7-24	yes	no
Heart Failure	41-52	yes	no	6-16	yes	yes
CKD	41-52	no	yes	6-17	yes	yes
Diabetes	44-55	yes	no	7-18	yes	yes

a. quintile range of statin utilization rates across local areas for respective complexity and age group.
b. relative to no statin based on statin rates in 2008-2009
c. “yes” if statistically significant increase in 1-year survival or 1-year cardiovascular event free survival rates is associated with a statin rate increase.
d. “yes” if statistically significant increase in 1-year muscle-related adverse events, renal-related adverse events or hepatic-related adverse event rates is associated with a statin rate increase.