Appendix

A. Coding Definitions for Clinical Conditions.

Variable	Definition/Source
Acute Myocardial Infarction (AMI)	Inpatient claim with ICD-9 codes 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 as the first or second diagnosis code on the claim.[1]
Heart failure	At least 1 inpatient, hospital outpatient or carrier claim with ICD-9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9.[1]
Chronic Kidney Disease (CKD)	At least 1 inpatient, skilled nursing facility or home health claim or 2 outpatient or carrier claims with ICD-9 codes: 016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4.[1]
Diabetes	At least 1 inpatient, skilled nursing facility or home health claim or 2 outpatient or carrier claims with ICD-9 codes 249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 366.41.[1]
Stroke	At least 1 inpatient claim or 2 hospital outpatient or carrier claims with ICD-9 codes 430, 431, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02. If any of the qualifying claims have: 800 <= ICD-9 Code <= 804.9, 850 <= ICD-9 Code <= 854.1 in any ICD-9 position OR ICD-9 V57xx as the principal ICD-9 code, then exclude.[1]
Unstable Angina	ICD-9 411 in any DX position on an inpatient claim.[1]
Muscle-related events	ICD-9 791.3x, 729.1x, 359.4x, 359.8x, 359.9x, 710.4x, 728.9x, 729.8x on any inpatient, carrier, outpatient, or skilled nursing facility claim or 728.89 or E9422 on an inpatient claim. For inpatient claims, for all codes except 791.3x if the code is not the first DX code on the claim then a BETOS code NOT in D1A, D1B, D1C, D1D, D1E, D1F, D1G, or O1A is required. ICD-9 code 791.3x can be on either of the first two listed DX codes without using the BETOs requirement.[2]

Acute hepatic events	ICD-9 570.xx, 573.3x, 573.8x, 573,9x in any DX position on an inpatient claim.[3]
Acute renal events	ICD-9 584.xx, 580.xx in any DX position on an inpatient claim.[3,4]

B. Cohort Exclusion Criteria

For each patient the AMI institutional episode of care was defined as the period from the acute hospital AMI admission date to the date the patient was discharged home. Thus, the episode period included all Medicare institutional days (acute, critical-access hospital, long term care hospital, inpatient rehabilitation facility, and short-term skilled nursing facility) with overlapping discharge and admission dates that followed the initial acute hospital AMI admission. We excluded AMIs from our analysis if the patient (1) did not survive the AMI institutional episode of care; (2) had an AMI within 12 months prior to the admission date; (3) was less than 66 years old at admission to ensure at least one year of Medicare eligibility prior to admission; (4) did not have continuous Medicare Parts A and B fee-for-service enrollment during the 12 months prior to admission; (5) was not continuously enrolled in Medicare Part D during the 6 months prior to admission; (6) did not have continuous Medicare Parts A, B fee-for-service and Part D enrollment during the period from the discharge date to the minimum of the patient death month or 12 months after discharge; (7) used hospice; and (8) were either readmitted to inpatient care, admitted to a skilled nursing facility, or died during the 30 days after the institutional stay discharge date to ensure a consistent statin measurement period after discharge. Finally, because our instrument is based on driving times around ZIP codes, our cohort was restricted to patients living in the continental U.S. at AMI admission.

C. Measurement of Treatment Variables

Medicare Part D event data before and after AMI discharge were used to measure statin use during the 30 days after the AMI discharge date. If a patient did not fill a statin prescription in the 30 days after AMI discharge and the patient did not have sufficient statins at home prior to discharge to cover the 30 days after discharge, then both treatment variables were set to zero (lower-intensity = 0; high-intensity = 0). If a patient's first statin prescription after discharge was a high-intensity statin, a patient filled two or more lower-intensity statin prescriptions of the same drug within 2 days of the first statin prescription with doses summing to high-intensity (e.g. two atorvastatin 20mg prescriptions), or the patient had no statin prescriptions in the 30 days after discharge but had at least 30 days of a high-intensity statin at home at AMI discharge, the treatment variables were assigned as lower-intensity = 0 and high-intensity = 1. If the patient had any other statin prescription combination during the 30 days after AMI discharge, or the patient had no statin prescriptions in the 30 days after discharge but had at least 30 days of a lower-intensity statin at home at discharge, the treatment variables were assigned as lower-intensity = 1 and high-intensity = 0.

D. Measurement of Outcome Variables

One-year patient survival after discharge was measured based on the CCW Beneficiary Summary File. This measure equaled 1 if the patient survived 1-year after AMI discharge, 0

otherwise. One-year cardiovascular-event-free survival was measured by adding event information from the CCW Inpatient Claims File to the survival data. This measure equaled 1 if the patient survived 1-year after AMI discharge without a cardiovascular-related inpatient hospitalization (AMI, unstable angina, or stroke), 0 otherwise. We also measured the adverse events found to be associated with statins in previous population studies[5,6] (muscle-related inpatient and outpatient events; inpatient acute renal events, and inpatient acute hepatic events) using Medicare claims files during the twelve months after AMI discharge. An aggregate adverse event measure equaled 1 if any of these conditions occurred during this period, 0 otherwise. Similar measures were created for each adverse event. Total 1-year healthcare cost was calculated for each patient from the perspective of the Medicare program by summing all Medicare reimbursements for each service across providers in the one year after AMI discharge. Medicare reimbursements were standardized across geography using a published algorithm.[7]

E. Measurement of Covariates

All models specified measures for patient demographics; patient comobidities and conditions associated with statin adverse events in the year prior to AMI admission and during the institutional AMI stay; medications used during the 180 days prior to the AMI admission; AMI diagnosis-type on admission; surgical procedures during the AMI stay; complications during the AMI stay; the number days during the AMI institutional stay that were spent in intensive care and critical care; other medications filled post discharge (beta blockers, renin-angiotensin system antagonists); Part D variables including premium levels, benefit phase at AMI admission and beneficiary accumulated total and out-of-pocket drug costs at AMI admission; Medicaid dual-eligibility in AMI admission month; patient low-income status, and socioeconomic characteristics for patient residence ZIP code (per capita income, poverty rate, education level, English-speaking percentage, rural/urban, life expectancy).

F. Linear Two-Stage Least Squares (2SLS) Justification

Methodological research has demonstrated that instrumental variable (IV) estimators yield an estimated effect of an independent variable (X) on a dependent variable (Y) that is an average over the subset of individuals in an empirical sample whose values of X *were affected by the specified instrumental variable or "instrument"*.[8] This estimate has been coined a local average treatment effect (LATE).[8] In the healthcare literature patients whose treatment choices were affected by the instruments specified have been called "marginal patients".[9] IV estimators yield a consistent estimate of LATE if the instrument (Z) used in the analysis has no direct effect on Y and is unrelated to other unmeasured factors that affect Y. This instrument property cannot be validated with measured information and must be assumed based on a plausible theoretical justification. If this assumption is true, Z provides a natural experiment in X for those in the sample whose X was affected by Z.[10] Because IV estimators use only the subset of X variation

related to Z, the standard errors associated with IV estimates are often an order of magnitude larger than those produced by other estimators.[11] Consequently, a strong relationship between Z and X and large sample sizes are often required to reject the null hypothesis that X has no effect on Y. We used the linear two-stage least squares (2SLS) instrumental variable estimator in this study with robust standard errors using STATA software. 2SLS has been used in several previous IV studies to estimate LATE.[12-14] Linear 2SLS yields consistent estimates of an absolute LATE on outcomes. Linear 2SLS is robust to underlying error distributions which compares favorably to other estimators that use stronger distributional assumptions and yield inconsistent estimates if the assumptions are wrong.[15] In addition, unlike linear 2SLS, non-linear two-stage IV estimators can only produce an estimate of an absolute LATE if the patients whose treatment choices were affected by the instruments can be identified ex post, which is not possible.

Table 3: Instrumental Variable Estimates of Absolute Local Average Treatment Effects (LATEs) on 1-Year Outcomes by Statin Intensity Across Patient Subsets – 100 Patient Local Areas.

		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)	108.46	0.059*[c] (0.028)	0.088** (0.033)	0.101** (0.037)	0.030 (0.031)	0.082*** (0.016)	0.054 (0.028)	-1303.53 (930.60)
	High	12 (6-20)	233.98	0.121*** (0.027)	0.102** (0.033)	0.083* (0.036)	0.040 (0.031)	0.061*** (0.015)	0.074** (0.028)	-795.97 (919.13)
No HF, CKD or Diab (N=31,170)	Lower	56 (46-65)	47.3944	0.018 (0.034)	-0.073 (0.047)	0.108 (0.057)	0.066 (0.050)	0.020 (0.023)	0.020 (0.029)	-53.12 (1215.93)
	High	14 (6-24)	87.3351	0.045 (0.034)	-0.024 (0.048)	0.023 (0.058)	-0.006 (0.051)	0.016 (0.024)	0.003 (0.029)	1052.73 (1239.64)
Any HF (N=66,644)	Lower	46 (39-55)	41.6527	0.048 (0.046)	0.115* (0.053)	0.064 (0.055)	-0.039 (0.046)	0.110*** (0.024)	0.086 (0.047)	-2064.89 (1515.36)
	High	10 (5-17)	94.8915	0.149** (0.046)	0.107* (0.052)	0.122* (0.055)	0.057 (0.046)	0.079*** (0.024)	0.130** (0.046)	-2161.47 (1508.34)
Any CKD (N=43,690)	Lower	46 (40-53)	26.6667	0.042 (0.059)	0.087 (0.067)	0.160* (0.073)	0.054 (0.059)	0.090** (0.031)	0.110 (0.066)	-2961.37 (2005.24)
	High	10 (5-17)	63.35	0.118* (0.057)	0.079 (0.064)	0.169* (0.070)	0.092 (0.057)	0.080** (0.030)	0.160* (0.064)	-2128.45 (1941.60)
Any Diab (N=54,125)	Lower	49 (43-55)	34.8514	0.043 (0.053)	0.218*** (0.065)	0.031 (0.069)	0.004 (0.059)	0.136*** (0.030)	-0.034 (0.057)	-2492.05 (1879.17)
	High	12 (7-19)	78.6702	0.118* (0.051)	0.176** (0.062)	0.157* (0.066)	0.092 (0.056)	0.115*** (0.029)	0.094 (0.055)	79.64 (1802.01)

* 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.

Table 3: Instrumental Variable Estimates of Absolute Local Average Treatment Effects (LATEs) on 1-Year Outcomes by Statin Intensity Across Patient Subsets – 200 Patient Local Areas.

		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 (44-56)	77.8213	0.066[c] (0.034)	0.103* (0.041)	0.125** (0.045)	0.050 (0.038)	0.096*** (0.019)	0.048 (0.035)	-2848.81* (1146.75)
	High	12 (7-19)	194.175	0.154*** (0.031)	0.134*** (0.038)	0.099* (0.042)	0.056 (0.035)	0.068*** (0.018)	0.070* (0.032)	-2459.65* (1052.71)
No HF, CKD or Diab (N=31,170)	Lower	56 (47-64)	37.4874	-0.001 (0.040)	-0.066 (0.056)	0.016 (0.067)	0.028 (0.060)	-0.011 (0.028)	-0.015 (0.034)	-16.69 (1451.27)
	High	14 (7-23)	74.3892	0.056 (0.039)	0.016 (0.055)	-0.040 (0.066)	-0.030 (0.059)	-0.016 (0.027)	-0.010 (0.034)	760.22 (1425.01)
Any HF (N=66,644)	Lower	46 (42-53)	26.8084	0.080 (0.059)	0.157* (0.067)	0.157* (0.070)	0.027 (0.058)	0.159*** (0.031)	0.096 (0.059)	-6679.38*** (1946.824)
	High	10 (5-17)	78.9217	0.189*** (0.051)	0.133* (0.058)	0.156* (0.061)	0.080 (0.051)	0.105*** (0.027)	0.120* (0.052)	-5203.06** (1704.52)
Any CKD (N=43,690)	Lower	46 (40-51)	18.0989	0.035 (0.076)	0.114 (0.086)	0.165 (0.094)	0.078 (0.077)	0.115** (0.041)	0.025 (0.085)	-5835.53* (2612.51)
	High	10 (6-17)	53.1064	0.145* (0.066)	0.111 (0.075)	0.180* (0.082)	0.092 (0.067)	0.090* (0.036)	0.127 (0.074)	-3959.14 (2275.61)
Any Diab (N=54,125)	Lower	49 (44-54)	24.6488	0.060 (0.064)	0.222** (0.078)	0.111 (0.084)	0.074 (0.071)	0.179*** (0.038)	-0.029 (0.069)	-3009.46 (2275.39)
	High	12 (8-18)	63.0119	0.179** (0.058)	0.216** (0.071)	0.197** (0.076)	0.147* (0.064)	0.142*** (0.034)	0.078 (0.062)	-1371.56 (2049.15)

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

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).

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