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Effect of guideline and formulary changes on statin prescribing in the VA

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Abstract

Objective. To compare the effects of two sequential policy changes – the addition of a high-potency statin to the Department of Veterans Affairs (VA) formulary and the release of the American College of Cardiology/ American Heart Association (ACC/ AHA) cholesterol guidelines – on VA provider prescribing.

Data Sources/Study Setting. Retrospective analysis of 1,100,682 VA patients 2011-2016.

Study Design. Interrupted time-series analysis of changes in prescribing of moderate-to-high-intensity statins among high-risk patients and across high-risk subgroups. We also assessed changes in prescribing of atorvastatin and other statin drugs. We

estimated marginal effects (ME) of formulary and guideline changes by comparing predicted and observed statin use.

Data Collection/Extraction Methods. Data from VA Corporate Data Warehouse.

Principal Findings. Use of moderate-to-high-intensity statins increased by two percentage-points following the formulary change (ME, 2.4, 95% confidence interval [CI], 2.2 to 2.6) and less than one percentage-point following the guideline change (ME, 0.8, 95% CI, 0.6 to 0.9). The formulary change led to approximately a twelve percentage-point increase in use of moderate-to-high-intensity atorvastatin (ME, 11.5, 95% CI, 11.3 to 11.6). The relatively greater provider response to the formulary change occurred across all patient subgroups.

Conclusions. Addition of a high-potency statin to formulary affected provider prescribing more than the ACC/ AHA guidelines.

Key Words. VA, quality of care, cardiovascular disease, provider interventions, pharmaceuticals

Introduction

Cholesterol-lowering statin drugs are among the most important tools in medicine for lowering the rates of cardiovascular disease. In spite of this, the quality and effectiveness of statin prescribing is uneven (Arnold et al. 2011; Kuklina, Yoon, and Keenan 2009; Maddox et al. 2014; Mozaffarian et al. 2016). Developing health system-level interventions to improve prescribing has been a primary goal of the movement to improve quality of care for decades (Institute of Medicine 2001). Because of the central role played by providers in prescribing medications, many of these interventions have targeted providers prescribing behaviors, including formulary restrictions, prescribing targets, and clinical practice guidelines. Yet evidence on the effectiveness of interventions targeting provider prescribing is mixed (Rashidian et al. 2015; O'Malley et

al. 2006; Lee et al. 2015; Francke et al. 2008). Previous investigations suggest that clinical practice guidelines are variably effective (Francke et al. 2008; Hysong, Best, and Pugh 2007; Fischer and Avorn 2004; Cabana et al. 1999). Some suggest that administrative or regulatory policies such as formulary restrictions or Food and Drug Administration (FDA) guidance may have greater influence on providers (Dorsey et al. 2010; Huskamp, Epstein, and Blumenthal 2003; Dusetzina et al. 2012). Nonetheless, there is little data that allows for any kind of direct comparison of these policies.

The release of the 2013 American Heart Association/ American College of Cardiology (ACC/ AHA) cholesterol treatment guidelines (Stone et al. 2014a) provides an ideal opportunity to examine the potential effects of clinical practice guidelines on provider behavior. The ACC/ AHA guideline fundamentally reshaped cholesterol treatment and simplified the task of managing cardiovascular risk. The new guideline shifted focus away from the previous 2004 guideline "treat-to-target" cholesterol approach (i.e., where statin intensities are altered until a specific cholesterol goal is reached) and instead recommended prescribing moderate- to high-intensity statin drugs to all patients with high cardiovascular risk. The ACC/ AHA guideline generated an unusually intense degree of media coverage by abandoning cholesterol targets, long an emphasis of providers and patients, and shifting focus to cardiovascular risk (Herper 2013; Ridker and Cook 2013; Kolata 2013b; a). Given the authoritative nature of the ACC/ AHA guideline, its relative simplicity and the considerable attention it captured, the ACC/ AHA guideline likely represents a "best case" scenario in the potential influence of guideline changes on provider behavior.

However, other changes that could influence statin prescribing occurred in the years prior to the ACC/ AHA guideline. The entry of generic atorvastatin, a higher-potency statin than the previously recommended simvastatin, in November 2011, promised to extend powerful cholesterol treatment throughout the US (Jackevicius et al. 2012). Generic atorvastatin was introduced soon after a June 2011 Food and Drug Administration (FDA) "black box" warning about the increased risk of muscle injury posed by high-dose simvastatin (Food and Drug Administration 2011). By October 2012, the Department of Veterans Affairs (VA), alongside other large health systems and

insurers, had added generic atorvastatin to formulary lists of approved drugs (Veterans Health Administration 2012).

Despite the wide publicity of both the ACC/ AHA cholesterol guideline and the entry of generic atorvastatin, we know very little about how these policies affected statin provider behavior. We attempt to fill this gap by exploiting the sequential introduction of two policies – the addition of atorvastatin to the VA's formulary in 2012 and the release of the ACC/ AHA cholesterol guidelines in 2013 – to compare the effects of formularies and guidelines on prescribing behavior. We do so by performing interrupted time series analyses on national VA prescribing data, examining changes in the use of moderate- to high-intensity statins among high-risk patients. We also examine changes in the use of specific statin drugs to further delineate the effects of the formulary and guideline changes.

Methods

Data. We constructed the study population using the VA Corporate Data Warehouse, a comprehensive database that contains data on all patients seen in the VA.

Study population. We performed a retrospective open cohort study. Our sample consisted of all of active VA primary care patients between ages 40 and 75 who sought care between July 1, 2011 and June 30, 2016 and were statutorily exempt from copayments due to meeting the VA Priority Group 1 Designation (Department of Veterans Affairs 2017). Priority Group 1 patients have severe service-connected disabilities. Most other VA patients paid $8 a month for each cholesterol medication they received during our study period. We restricted our sample to patients not liable for a VA copayment for two reasons. First, by excluding patients who faced VA copayments, we were better able isolate the effect on provider behavior of the formulary change. Second, because we could not account for medications prescribed outside the VA, this exclusion minimized any bias introduced by increases in patients seeking prescriptions from low-cost generic programs (e.g., $4 generic medications at some pharmacies) or other non-VA pharmacies. We also excluded patients under 40 years of age and over 75

years of age in each month because most risk calculators are not valid for these groups. Finally, we excluded any patients with a record of pregnancy, end-stage renal disease, or documented muscle weakness in the 2 years prior to start of each month. Further details regarding cohort creation are described in section A1 of the Appendix.

Outcomes. Our main outcome of interest, which was directly based on the ACC/AHA guidelines (Stone et al. 2014), was prescription of a moderate- to high-intensity statin among high-risk patients. Table S1 of the Appendix provides additional details on how we defined low-, moderate-, and high-intensity statins by active ingredient and dosage. We defined high-risk as belonging to one of four high-risk groups: (1) atherosclerotic cardiovascular disease (ASCVD); (2) hyperlipidemia; (3) diabetes; or (4) 10-year calculated ASCVD risk ≥ 7.5%. Because the VA allows a maximum 90-day prescription for statins and most (78%) patients receive a 90-day prescription, we defined a patient as being on a statin if we observed a prescription in the 90 days prior to the end of the month of interest (i.e., 90-day look-back). We categorized patient risk groups according to the ACC/AHA guidelines and in the following hierarchical, mutually exclusive manner. The ASCVD group comprised patients with history of myocardial infraction, coronary artery bypass grafting, percutaneous coronary intervention, or ischemic vascular disease. The hyperlipidemia group included patients with no ASCVD and low-density lipoprotein cholesterol (LDL) ≥ 190 mg/dL. The diabetes group included patients with no ASCVD, LDL between 70 and 189 mg/dL, and diabetes mellitus. The group with 10-year calculated ASCVD risk ≥ 7.5% included patients with no ASCVD, no diabetes, LDL between 70 and 189 mg/dL, and a 10-year ASCVD risk ≥ 7.5% as defined by the ACC/AHA ASCVD risk calculator (available at http://tools.acc.org/ASCVD-Risk-Estimator/). The ASCVD risk score is a function of age, gender, race (black vs. non-black), diabetes status, smoking status, systolic blood pressure, treatment for hypertension, LDL and total cholesterol levels. Any patient that did not fall into one of four high-risk groups was considered low-risk. The ACC/AHA guidelines did not specify whether or not low-risk patients should be on a statin and instead called for shared decision-making based on factors such as family history of ASCVD. Section A3 of the Appendix provides further details on how we defined the four high-risk groups.

To better understand the effects of changes to formulary and guideline policies, we assessed outcomes specific to each policy as well as those shared by the policies. First, we evaluated monthly changes in the prescription of statin drugs that were added to (atorvastatin), always on (simvastatin, pravastatin), or never on (rosuvastatin) the VA formulary during our study period (Veterans Health Administration 2012). Second, we evaluated changes in the prescription of nonstatin lipid-lowering drugs (listed in Section A2 of the Appendix), as these were not directly affected by the formulary change but were reduced in importance by the ACC/ AHA guideline. The new guideline shifted from recommending lowering LDL levels to specified goals (regardless of whether statins or nonstatins were used to lower LDL levels) and toward recommending lowering cardiovascular risk through the use of evidence-based statin drugs. Third, we evaluated monthly changes in the prescription of specific moderate- to high-intensity statins as defined by dosage (Table A3 in the Appendix) that were either added to (atorvastatin), always on (simvastatin, pravastatin), or never on (rosuvastatin) the VA formulary during our study period, as prescription of these drugs capture the joint effects of the formulary and guideline changes. Although we included all moderate- to high-intensity statin drugs in our main analysis, we only analyzed changes to specific statin drugs that were prescribed to at least five percent of patients over the study period, on average. This excluded fluvastatin (3%), lovastatin (1%), and pitavastatin (<1%).

Exposure. We used an interrupted time series approach, which estimates the effects of an *interruption* that occurs at a specific moment in time, or, in our analysis, two moments – October 12, 2012, when atorvastatin was added to the VA formulary, and November 12, 2013, when the new ACC/ AHA cholesterol guidelines were published online in the journals *Circulation* and *Journal of the American College of Cardiology* (Stone et al. 2014a; b). We divided our study into three periods: pre-formulary (July 2011-September 2012); post-formulary (October 2012-October 2013); and post-guideline (November 2013-June 2016). We defined the post-formulary and post-guideline periods as beginning in October 2012 and November 2013, respectively, so as to capture any immediate responses that occurred. We validated our choice of the post-formulary period through analysis of historical VA documents (Veterans Health

Administration 2012). We validated our choice of the post-guideline period by a series of Google trend analytics searches, all of which demonstrated an immediate, sharp increase in query volume between November 10 through November 23, 2013, for the terms "cholesterol guideline," "statin," "statin cholesterol," and "cholesterol risk calculator" (Figure S1 Panels A-D in the Appendix). Interest in the cholesterol guidelines was partially sustained (Figure S1 Panel A in the Appendix). This was in the setting of already increased interest in simvastatin after the FDA issued a June 2011 black-box warning that simvastatin might cause an increased rate of myopathy (see "simvastatin" query results in Figure S1 Panel E in the Appendix).

Statistical analysis. We first compared the characteristics of patients in the final months of the pre-formulary (September 2012), post-formulary (October 2013) and post-guideline (June 2016) periods. We then performed interrupted time series analyses to assess the sequential impact of the 2012 formulary change and 2013 ACC/AHA guideline change. We used patient-level generalized estimating equation (GEE) models and included a binomial distribution and a log link function to account for the binary nature of our outcomes (Ballinger 2004). We estimated GEE models for the following outcomes: (1) use of any moderate- to high-intensity statin among high-risk patients; (2) use of nonstatin lipid-lowering drugs among all patients; and (3) use of specific moderate- to high-intensity statin drugs, including atorvastatin, simvastatin, pravastatin, and rosuvastatin, among all patients.

We modeled changes in statin prescribing across the two policy changes using a linear term for time as well as linear splines for the pre-formulary, post-formulary, and post-guideline periods. This allowed us to estimate how trends in statin prescribing changed after the formulary change and after the guideline change (Kontopantelis et al. 2015). In all analyses, we accounted for possible changes in the composition of VA patients over time by adjusting for patient-level covariates. These included patient age, gender, race, diabetes status, and comorbidity (Charlson score). We also included indicators for each month to account for possible seasonal changes in statin prescribing patterns (Bhaskaran et al. 2013).

Next, we conducted counterfactual analyses for each model to compare the predicted use of statins with the observed use of statin in both the post-formulary and post-guideline periods. We calculated the effect of the formulary change on statin prescribing in the following three steps: (1) estimated trends in statin prescribing in the pre-formulary period (July 2011-September 2012); (2) used pre-formulary trends to estimate the expected percentage of patients using statins at the end of the post-formulary period (October 2013), had the formulary change not occurred; (3) estimated the difference between the predicted and observed percentage of patients using statins, i.e., the marginal effect of the formulary change. We performed a similar counterfactual analysis to calculate the effect of the guideline change on statin prescribing, now using trends estimated in the post-formulary period (October 2012-October 2013) rather than pre-formulary period to estimate expected versus observed statin prescribing, i.e., the marginal effect of the guideline change. Because the post-guideline period was nearly two years longer than the post-formulary period, we estimated expected use of statins at the midway point rather than endpoint of the post-guideline period (i.e., February 2015) to compare more fairly the effects of the formulary and guideline change (Kontopantelis et al. 2015).

We next assessed changes in prescribing of specific statin drugs (i.e., atorvastatin, simvastatin, rosuvastatin, pravastatin) graphically. We plotted unadjusted trends in the use of specific statin drugs across all patients as well as stratified by the five patient groups (i.e., ASCVD, hyperlipidemia, diabetes, 10-year calculated ASCVD risk ≥7.5%, and low-risk). We described changes for prescribing of specific statins at any intensity as well as across low-, moderate-, and high-intensities.

Sensitivity analyses. We performed sensitivity analyses to examine whether the effects of the two policy changes varied across important patient sup-groups. Because the 2013 ACC/ AHA guidelines recommend statins to certain patient populations that would not have required statins under the 2004 guidelines (i.e., patients with high 10-year calculated ASCVD risk), we hypothesized that the effect of the guidelines on statin prescribing might vary across the four ACC/ AHA high-risk groups (ASCVD,

hyperlipidemia, diabetes, 10-yr calculated ASCVD risk ≥ 7.5%). To evaluate this, we evaluated variation in the effects of the formulary and guideline changes on use of moderate- to high-intensity statins by estimating a GEE model in which we fully interacted indicators for the three time periods (pre-formulary, post-formulary, post-guideline) with indicators for the four risk groups.

Finally, we assessed whether prescribing responses to the formulary changes and the guideline changes varied across newly high-risk patients ("incident") versus those who had been already been high-risk for at least six months ("prevalent"). We defined incident patients as those with at least one diagnostic code for either ASCVD or diabetes within the six months prior to the month of interest, but none prior to that six-month period. We defined prevalent patients as those with at least one diagnostic code for either ASCVD or diabetes prior to that six-month period. To ensure that we captured disease incidence prior to the start of the study (July 1, 2011), we began our look-back for all patients in July 1, 2009. We performed this analysis for two reasons. First, we hypothesized that providers may be more responsive to formulary or guideline changes for incident patients than for prevalent patients, for whom clinical decisions have already been made. Second, we hypothesized that the two policies' specific sequence – namely, that the guideline change followed the formulary change – might affect our estimates of the guideline's effect on statin prescribing (i.e., "order effects"), since providers may have already changed care in response to the formulary change before the guidelines change occurred. If this were the case, these effects should be minimized in incident high-risk patients who should have not been affected by the formulary change. To test this, we estimated interaction models that examined whether the effects of the guideline or formulary changes differed across incident vs. prevalent patients.

We considered *P* values of less than 0.05 to be significant. We specified GEE models to include an exchangeable working correlation matrix and robust standard errors to account for within-patient correlation over time. All analyses were conducted in Stata, version 14.1. This study was supported as an internal, non-research activity under a Memorandum of Understanding with the VA Office of Reporting, Analytics,

Performance Improvement and Deployment (RAPID) in order to improve quality of care at the VA.

Results

We identified 1,100,682 active primary care patients (representing 36,818,121 patient-months or 33.5 months per patient), ages 40 to 75, who sought care in the VA from July 1, 2011 to June 30, 2016 and were in priority group 1 and thus exempt from drug copayments. Table 1 summarizes changes in patient characteristics over the study period. The mean age (SD) was 60.5 (8.0) in the pre-formulary period and 61.7 (9.2) in the post-guideline period (P<0.001). The share of patients belonging to one of four high-risk groups fell from 89.3% in the pre-formulary period to 86.9% in the post-guideline period (P<0.001). This was driven by a decline in the share of patients with history of ASCVD (from 47.1% to 43.1% in the pre-formulary and post-guideline periods, respectively; P<0.001).

Figure 1 displays estimated trends in prescribing of moderate- to high-intensity statins among high-risk patients, i.e., those with ASCVD, diabetes, hyperlipidemia, or a 10-year calculated ASCVD risk ≥ 7.5%. Prescribing of moderate- to high-intensity statin fell in the pre-formulary period (change in percentage of patients on a statin per month, -0.2 percentage point [pp] per month, 95% confidence interval [CI], -0.2 to -0.2; P<0.001), leveled off in the post-formulary period (0.0 pp per month, 95% CI, 0.0 to 0.0; P<0.001), and remained relatively flat in the post-guideline period (0.0 pp per month, 95% CI, 0.0 to 0.0; P<0.001; Figure 1 and Table 2).

The formulary change was associated with approximately a two percentage-point increase in use of moderate- to high-intensity statins (marginal effect [ME], 2.4 pp, 95% CI, 2.1 to 2.6; P<0.001) compared to what would have been expected from trends prior to the change. The guideline change was associated with a less than one percentage-point increase in use of moderate- to high-intensity statins (ME, 0.8 pp, 95% CI, 0.6 to 0.9; P<0.001).

We next assessed the prescribing behaviors we considered directly relevant to the formulary change (use of specific statin drugs), the guideline change (use of nonstatin lipid-lowering drugs), or both (use of specific moderate- to high-intensity statins).

Figure 2 demonstrates trends in the use of specific statin drugs that were added to (atorvastatin), always on (simvastatin, pravastatin), or never on (rosuvastatin) the VA formulary during our study period. We observed a large substitution away from prescribing simvastatin and rosuvastatin and toward prescribing atorvastatin. The substitution in prescribing occurred across all subgroups but was greatest for patients with ASCVD and least for low-risk patients. The proportion of VA patients prescribed atorvastatin increased from 0.5% in the pre-formulary period (July 2011) to 13.5% in the post-formulary period (October 2013), and then to 22.5% in the post-guideline period (June 2016). Conversely, simvastatin prescribing declined steadily throughout the study period, falling from 32.2% (July 2011) to 12.8% (June 2016). Finally, both rosuvastatin and pravastatin increased in the pre-formulary period, fell in the post-formulary period, and stabilized in the post-guideline period. In supplemental analyses, we found that substitution away from simvastatin and rosuvastatin and toward atorvastatin was greatest for high-intensity statins and least for low-intensity statins (Figure S2 in the Appendix).

We then assessed the joint influence of the formulary and guideline changes by modeling changes in the use of specific moderate- to high-intensity statin drugs (Table 2). These estimates confirmed our graphical analyses in Figure 2 and Figure S2 in the Appendix: the addition of atorvastatin to the formulary was associated with a nearly twelve percentage-point increase in the use of moderate- to high-intensity atorvastatin (ME, 11.5 pp, 95% CI, 11.3 to 11.6; $P<0.001$; Table 2). Conversely, the use of moderate- to high-intensity rosuvastatin fell by nearly nine percentage-points following the formulary change (ME, -8.8 pp, 95% CI, -8.8 to -8.9; $P<0.001$; Table 2). Meanwhile, the secular decrease in the use of moderate- to high-intensity simvastatin that predated the formulary change was not substantially affected by either the formulary or guideline change (Table 2).

Prescribing of nonstatin lipid-lowering drugs, the use of which the ACC/ AHA guidelines deemphasized, was not substantially affected by either the formulary or guideline change (Table 2). Prescribing of nonstatin lipid-lowering drugs fell in the pre-formulary period (change in percentage of patients on a statin per month, -0.2 pp per month, 95% CI, -0.2 to -0.2; *P*<0.001), fell more slowly in the post-formulary period (-0.1 pp per month, 95% CI, -0.1 to -0.1; *P*<0.001), and then again fell more quickly in the post-guideline period (-0.2 pp per month, 95% CI, -0.2 to -0.2; *P*<0.001). In counterfactual analyses, neither the formulary nor the guideline change was associated with substantial changes in the prescription of nonstatin lipid-lowering drugs (ME, 0.4 pp, 95% CI, 0.3 to 0.5; *P*<0.001 and ME, -0.8 pp, 95% CI, -0.8 to -0.7; *P*<0.001, respectively).

Changes in prescribing of moderate- to high-intensity statins were similar across the four patient risk groups (Table 2). The formulary change was associated with approximately a two percentage-point increase in the use of moderate- to high-intensity statins for patients with either ASCVD (ME, 2.4 pp, 95% CI, 2.1 to 2.6; *P*<0.001) or 10-year calculated ASCVD risk ≥ 7.5% (ME, 2.3 pp, 95% CI, 2.0 to 2.6; *P*<0.001) and a three percentage-point increase for patients with diabetes (ME, 3.0 pp, 95% CI, 2.6 to 3.4; *P*<0.001). The guideline change was associated with a slightly less than one percentage-point increase in the use of moderate- to high-intensity statins for patients with ASCVD, hyperlipidemia, diabetes, or 10-year calculated ASCVD risk ≥ 7.5%.

Finally, we found that the effects of the formulary and guideline changes had similar effects across incident and prevalent high-risk patients (Table 2). Following the formulary change, the use of moderate- to high-intensity statins increased by approximately three versus two percentage-points in incident versus prevalent patients (ME, 3.4 pp, 95% CI, 2.7 to 4.2; *P*<0.001 and ME, 2.4 pp, 95% CI, 2.2 to 3.4; *P*<0.001, respectively). As in our main analysis, we observed little change in the use of moderate-to high-intensity statins among either incident or prevalent high-risk patients following the guideline change (ME, -0.6, 95% CI, -1.3 to 0.1; *P*=0.090 and ME, 0.8, 95% CI, 0.6 to 0.9; *P*<0.001, respectively).

Discussion

We studied the sequential effects of two policy changes – the addition of a high-potency statin to the VA formulary in 2012 and the release of the national cholesterol treatment guidelines in 2013 – on provider prescribing behavior in the VA health care system. We found that the formulary change dramatically altered statin prescribing, increasing the use of atorvastatin and decreasing the use of statins that were either lower-potency or off-formulary. Conversely, we found that the use of moderate- to high-intensity statins among high-risk patients, the primary goal of the new ACC/ AHA guidelines, was not substantially affected by either the formulary or guideline change. In fact, the change in the VA formulary was associated with slightly larger effects than the guideline change, despite predating it, a finding likely driven by the increased availability of higher-potency atorvastatin. We observed these patterns across all high-risk groups and among both incident and prevalent high-risk patients. Collectively, our findings suggest that an administrative change to the VA formulary, simply by making a more potent statin readily available, had a greater effect on moderate- to high-intensity prescribing than the release of a guideline specifically intended to extend such prescribing across high-risk patients.

The effects of formulary changes and other administrative policies are often difficult to assess due to the fragmented nature of health care financing and delivery (Shrank et al. 2004). Previous studies of formulary restrictions, particularly those in which patients faced "tiered" copayments that vary according to formulary coverage, found that formularies significantly affected provider prescribing and patient adherence (for example, Shrank and Hoang 2006; Leibowitz, Manning, and Newhouse 1985). By performing this analysis in a setting with no tiered copayments and among patients who have no medication copayment, we isolated formularies' effects on providers specifically. Thus, the very large substitutions that we observed toward atorvastatin and away from simvastatin and rosuvastatin presumably resulted from the fact that providers could now prescribe atorvastatin – a more potent drug than what was previously available on formulary – with greater ease and without needing to request it

through non-formulary consultations. Our results are consistent with some previous studies showing that the VA's formulary system has the potential to significantly affect prescription drug use (Huskamp, Epstein, and Blumenthal 2003; Gellad et al. 2013). Similarly, the large decline in use of simvastatin during the pre-formulary period, though not a central focus of our analysis, is temporally associated with the FDA's June 2011 "black box" warning regarding use of high-dose simvastatin (Food and Drug Administration 2011), a finding consistent with some studies of previous drug-specific FDA regulatory warnings (Dorsey et al. 2010; Dusetzina et al. 2012).

The modest effect of the ACC/ AHA guideline change on statin prescribing we observed is consistent with some recent reports that the ACC/ AHA guideline change was associated with either a negligible (Tran et al. 2016) or small (Pokharel et al. 2017; Rodriguez et al. 2016) change in the use of statins and nonstatin lipid-lowering drugs. A study in the VA found somewhat larger changes in statin use but did not include patients in all four risk groups, was limited to six months of post-guideline data, and did not adjust for underlying trends in statin use (Rodriguez et al. 2016). In a large national cardiology outpatient registry, the guideline change was associated with a modest increase in the use of moderate- to high-intensity statins among high-risk patients (Pokharel et al. 2017). We extend and contextualize these prior results, finding that an administrative change designed to substitute one statin for another had a greater incidental effect on guideline-concordant prescribing of moderate- to high-intensity statins than the release of the ACC/ AHA guideline itself.

Nonetheless, overall use of moderate to high dose statins remains substantially lower than recommended by the guidelines, and there is no evidence of increased use in the ASCVD group for whom the benefits are felt to be the largest. Furthermore, our finding that the guideline's effect was similar between incident and prevalent high-risk patients suggests that its minimal impact held true among patients for whom clinical decisions had not yet been made and was not entirely due to the fact that the guideline change occurred after the formulary change. These low levels of statin use appear similarly unresponsive to changes in performance measurement, with little change in statin use among high-risk patients following the VA's FY2016 transition from HEDIS measures

focused on cholesterol levels (i.e., annual hyperlipidemia screening among patients with cardiovascular disease) to measures focused on treating cardiovascular risk (e.g., use of statins among patients with diabetes or cardiovascular disease).

There are several limitations to consider. First, the quasi-experimental design of our study makes it difficult to be sure that changes in prescribing behavior were caused by changes to the VA formulary or ACC/ AHA guideline. While the speed with which atorvastatin replaced simvastatin and rosuvastatin strongly suggests that the formulary change is the primary cause of that change, we cannot verify that the use moderate- to high-intensity statins would have continued to decline in the post-formulary period in absence of the formulary change. Likewise, the finding that the guideline change led to a large decrease in atorvastatin prescribing is contingent on the assumption that the dramatic post-formulary atorvastatin increase would have continued unabated in the post-guideline period. Second, we do not have information about patient refusal to take statins or whether patients experienced muscle pain or other side effects of treatment that might explain why some patients eligible for treatment are not getting it. Third, our 90-day look-back approach may miss some statin refills for patients with imperfect adherence or who have accumulated medicine beyond the maximum 90-day statin prescription length. However, most VA patients receive 90-day statin prescriptions, and a longer look-back period would have captured patients who had actually stopped statin use and made it more difficult to precisely detect monthly changes in prescribing behavior.

Fourth, because we could not account for medications prescribed outside the VA, we limited our sample to Priority Group 1 patients who are statutorily copayment-exempt in the VA and thus less likely to purchase statins outside the VA. Although we developed and chose this method to limit the bias that would be induced by an increase in the use of very low cost generic medicines and other non-VA pharmacies over time, our results may not generalize to patients with higher incomes or lower levels of disability (i.e., priority groups 2-8). Finally, the effect of formularies and other administrative policies is likely context specific and may not generalize outside of a large, integrated system such as the VA. At the same time, using data from the VA, the

largest integrated health care system in the US, offered a rare opportunity to examine how provider behavior is affected by administrative policies that are typically fragmented across payers and otherwise difficult to observe.

Overall, our study provides new evidence on the influence of guidelines and administrative policies on provider behavior. Relevant to payers and health care systems, our results suggest that lowering administrative barriers to substitute drugs that providers perceive as superior can have substantial effects on quality of care. For guideline developers, our results suggest that even a "best case" clinical practice guideline – that comes from a particularly prominent group, simplifies treatment, and generates widespread attention – may nonetheless exert limited influence on providers. This reflects, in part, the fact that guidelines are intended to shape and not compel provider behavior. And for both policymakers and health services researchers, we demonstrate that subtle changes to pervasive administrative policies may have large incidental consequences that should be both anticipated and searched for when evaluating other, seemingly unrelated health policies.

Our collective findings suggest that certain formulary policies may influence provider prescribing behavior more than clinical practice guidelines. Moving forward, research in this area should focus on how formularies and other administrative policies can be used to support adherence to clinical practice guidelines and complement other policies intended to promote the quality and efficiency of prescribing behavior.

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Table 1. Characteristics of patients in the VA before and after formulary and guideline changes (2011 to 2016; N=1,100,682)

	Across the three study periods			
Characteristic	**Pre-formulary** *September 2012*	**Post-formulary** *October 2013*	**Post-guideline** *June 2016*	***P* value**
Age, mean (SD)	60.5 (8.0)	61.1 (8.3)	61.7 (9.2)	<0.001
Female	7.0	7.4	8.6	<0.001
Black	22.2	22.5	23.4	<0.001
Smoker	26.5	25.9	23.3	<0.001
Diabetes	41.0	40.7	39.3	<0.001
Charlson score, mean (SD)	1.0 (1.5)	1.0 (1.5)	1.1 (1.6)	<0.001
ACC/AHA risk group				<0.001
High-risk	89.3	88.9	86.9	
ASCVD	47.1	46.0	43.1	
Hyperlipidemia	3.1	3.4	3.4	
Diabetes	18.6	18.8	18.8	
10-yr calculated risk ≥ 7.5%	20.4	20.7	21.6	
Low-risk (10-yr calculated risk < 7.5%)	10.7	11.1	13.1	
10-year calculated ASCVD risk				<0.001
< 7.5%	18.0	18.1	20.0	
7.5% to < 12%	13.7	12.5	10.9	

≥ 12%	68.3	69.4	69.1	
Most recent LDL in past year (mg/dL)				<0.001
< 100	48.7	48.8	45.6	
100-129	20.9	21.0	21.1	
130-189	12.8	12.8	14.3	
≥ 190	1.1	1.0	1.3	
No LDL measurement	16.5	16.3	17.7	

Notes. All estimates are reported in percent unless otherwise indicated. Characteristics as defined in text and Appendix. SD is standard deviation. ASCVD is atherosclerotic cardiovascular disease. LDL is low-density lipoprotein.

Figure 1. Changes in prescribing of moderate- to high-intensity statins among high-risk patients in the VA (2011-2016)

Table 2. Changes in prescribing of moderate- to high-intensity statins and nonstatin lipid-lowering drugs in the VA (2011-2016; N=1,100,682 patients and 36,818,121 patient-months)

	Pre-formulary	Post-formulary period			Post-guideline period		
Outcome	**Trend**	**Trend**	**Trend change**	**Marginal effect Φ**	**Trend**	**Trend change**	**Marginal effect Φ**
Unit	*Percentage change per month*	*Percentage change per month*	*Net change in percentage change per month*	*Percentage change from expected*	*Percentage change per month*	*Net change in percentage change per month*	*Percentage change from expected*
Use of moderate- to high-intensity statins χ							
Among high-risk patients	-0.2 (-0.2,-0.2)	0.0 (0.0,0.0)	0.2 (0.2,0.2)	2.4 (2.2,2.6)	0.0 (0.0,0.0)	0.1 (0.0,0.1)	0.8 (0.6,0.9)
By specific statins							
Atorvastatin γ	0.1 (0.1,0.1)	1.0 (1.0,1.0)	0.9 (0.9,0.9)	11.5 (11.3,11.6)	0.3 (0.3,0.3)	-0.7 (-0.8,-0.7)	-11.2 (-11.3,-11.0)
Rosuvastatin	0.1 (0.1,0.1)	-1.0 (-1.0,-1.0)	-1.1 (-1.1,-1.1)	-8.8 (-8.8,-8.9)	0.0 (0.0,0.0)	1.0 (1.0,1.0)	1.6 (1.6,1.7)
Simvastatin	-0.6 (-0.6,-0.6)	-0.3 (-0.3,-0.3)	0.3 (0.2,0.3)	1.4 (1.3,1.5)	-0.2 (-0.2,-0.2)	0.1 (0.1,0.1)	0.3 (0.2,0.4)
By ACC/AHA risk group							
ASCVD	-0.3 (-0.3,-0.3)	-0.1 (-0.1,-0.1)	0.2 (0.2,0.2)	2.4 (2.1,2.6)	0.0 (0.0,0.0)	0.1 (0.0,0.1)	0.8 (0.6,1.0)
Hyperlipidemia	-0.1 (-0.1,0.0)*	0.0 (0.0,0.1)*	0.1 (0.0,0.2)*	1.1 (-0.1,2.4)*	0.0 (0.0,0.1)	0.0 (0.0,0.1)*	0.6 (-0.4,1.6)*

Diabetes	-0.2 (-0.3,-0.2)	0.0 (0.0,0.0)*	0.2 (0.2,0.3)	3.0 (2.6,3.4)	0.1 (0.1,0.1)	0.1 (0.0,0.1)	0.9 (0.6,1.2)
10-yr calculated risk ≥ 7.5%	-0.1 (-0.2,-0.1)	0.0 (0.0,0.0)	0.2 (0.2,0.2)	2.3 (2.0,2.6)	0.1 (0.1,0.1)	0.0 (0.0,0.1)	0.6 (0.4,0.9)
By incident vs. prevalent high-risk Ω							
Incident high-risk	-0.1 (-0.2,-.1)	0.1 (0.1,0.2)	0.3 (0.2,0.3)	3.4 (2.7,4.2)	0.1 (0.1,0.1)	0.0 (-0.1,0.0)*	-0.6 (-1.3,0.1)*
Prevalent high-risk	-0.2 (-0.2,-0.2)	0.0 (-0.1,0.0)	0.2 (0.2,0.2)	2.4 (2.2,2.6)	0.0 (0.0,0.0)*	0.1 (0.0,0.1)	0.8 (0.6,0.9)
Use of nonstatin lipid-lowering drugs κ							
Use among all patients	-0.2 (-0.2,-0.2)	-0.1 (-0.1,-0.1)	0.1 (0.1,0.1)	0.4 (0.3,0.5)	-0.2 (-0.2,-0.2)	-0.1 (-0.1,0.0)	-0.8 (-0.8,-0.7)

Notes. Confidence intervals are in parentheses. All estimates are statistically significant at $P < 0.001$ unless otherwise noted, with * $P > 0.001$). Characteristics as defined in text and Appendix.

χ Analyses of use of moderate- to high-intensity statins among high-risk patients were based on 926,637 patients (representing 29,150,385 patient-months) that belonged to one of four high-risk groups.

Ω Analyses of use of moderate- to high-intensity statins among incident versus prevalent high-risk patients were based on 713,114 patients (representing 1,606,422 incident high-risk patient-months and 24,849,684 prevalent high-risk patients-months).

Φ We calculated the marginal effect of the formulary change by (1) using pre-formulary trends to estimate the expected percent of patients on a statin at the end of the post-formulary period (October 2013) had the formulary change not occurred and (2) estimating the linear combination of the predicted and observed statin use to calculate the marginal effect of the formulary change.

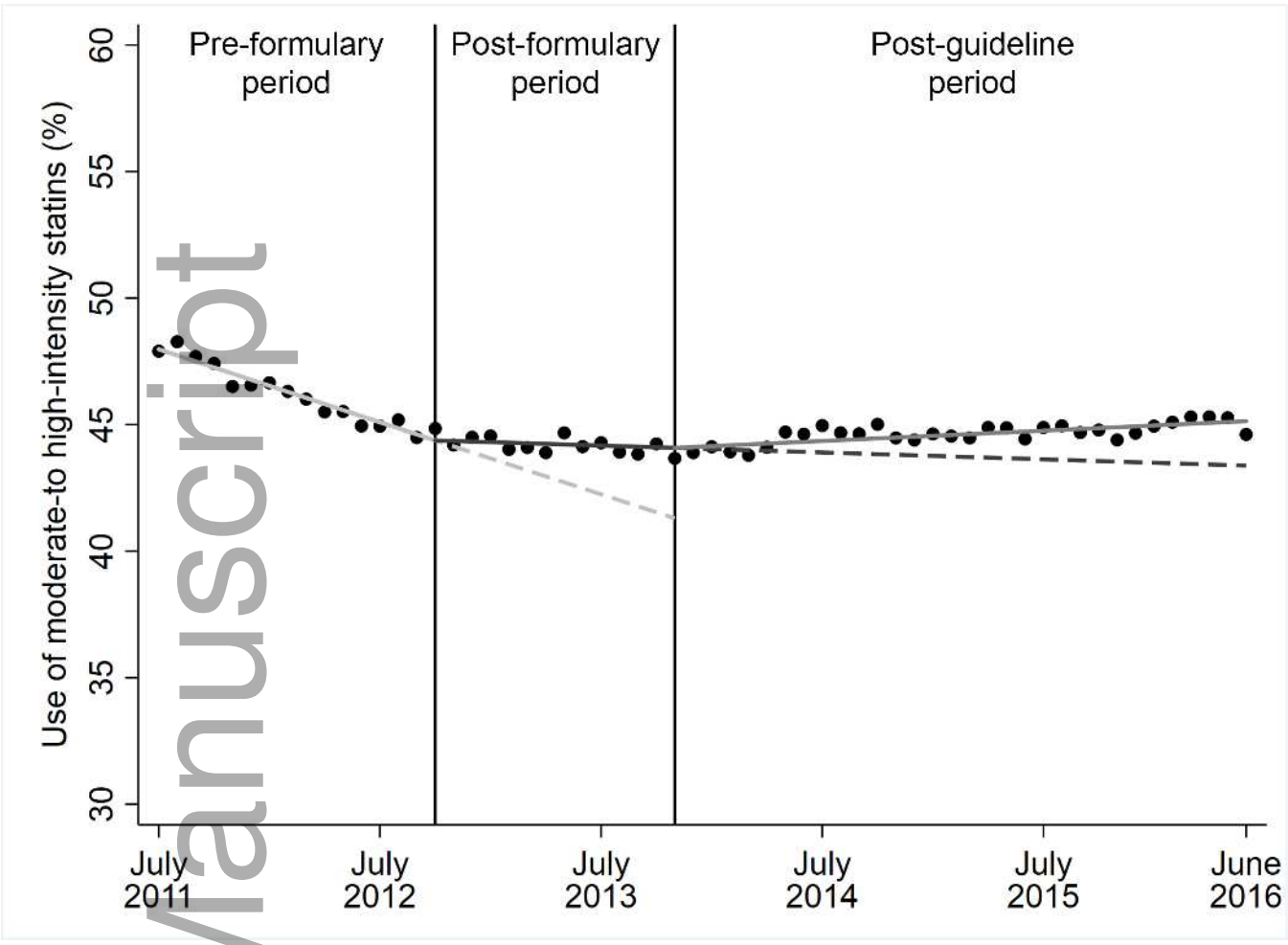
δ We calculated marginal effects of the guideline change as described above, now using post-formulary trends to estimate expected statin use at the midpoint of the post-guideline period (February 2015).

f We estimated models of overall use of moderate- to high-intensity statins only on those patients considered high-risk by the ACC/ AHA guidelines, as the guidelines did not specify whether providers should prescribe statins to low-risk patients. We estimated models of specific statin use (e.g., atorvastatin) on the entire cohort because the formulary change did not pertain to high- versus low-risk patients. We estimated models of nonstatin lipid lowering drugs on the entire cohort because the ACC/ AHA guidelines deemphasized use of nonstatins among all patients.

γ We used a Gaussian distribution in the atorvastatin generalized estimating equation model because the model with a binomial distribution did not converge.

κ Nonstatin lipid-lowering drugs included Niacin, Gemfibrozil, Fenofibric Acid, Clofibrate, Colesevelam, Colestipol, Cholestyramine, and Cholestyramine/ Sorbitol.

Figure 2. Trends in prescribing of specific statin drugs in the VA, by ACC/AHA risk group (2011-2016)



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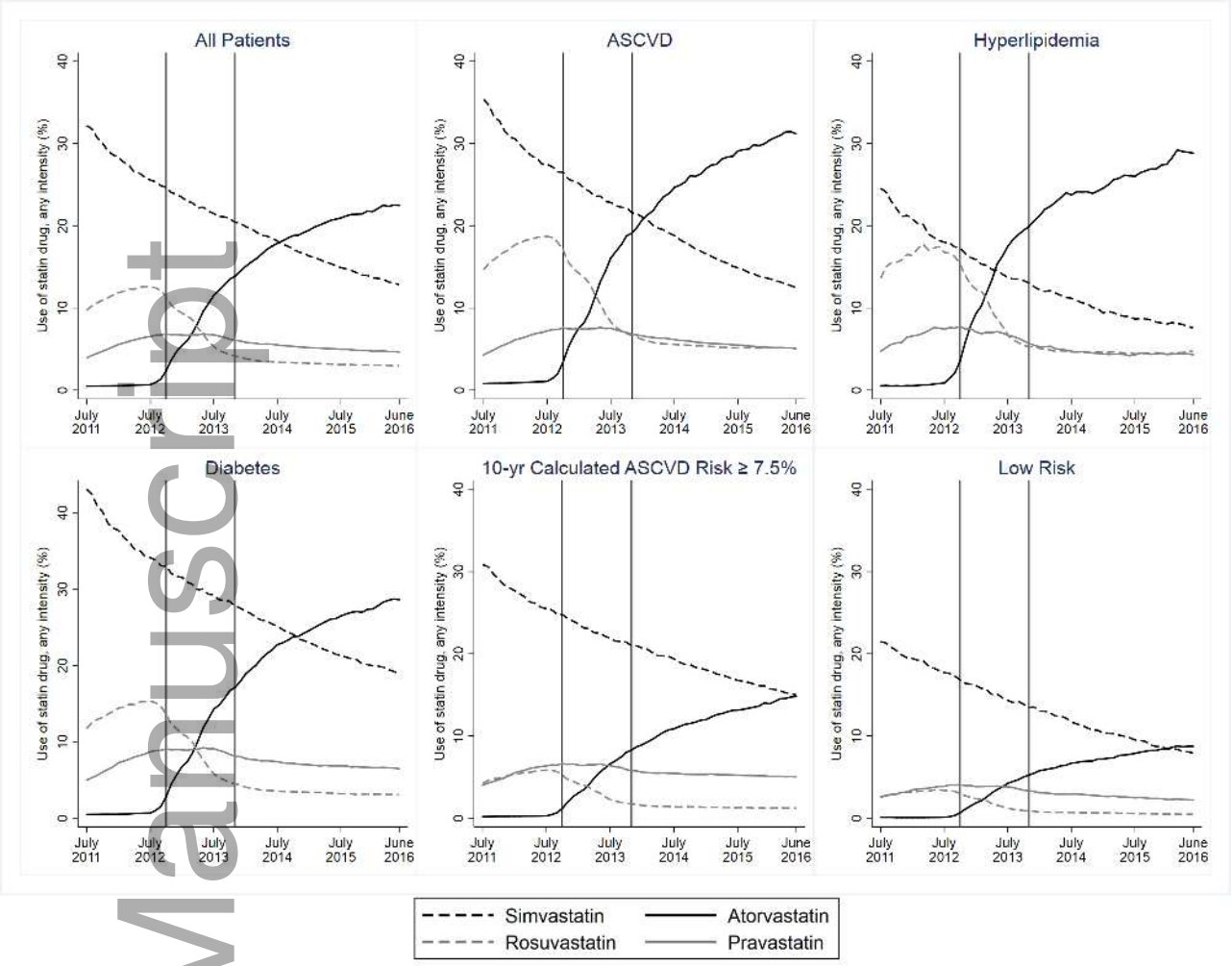

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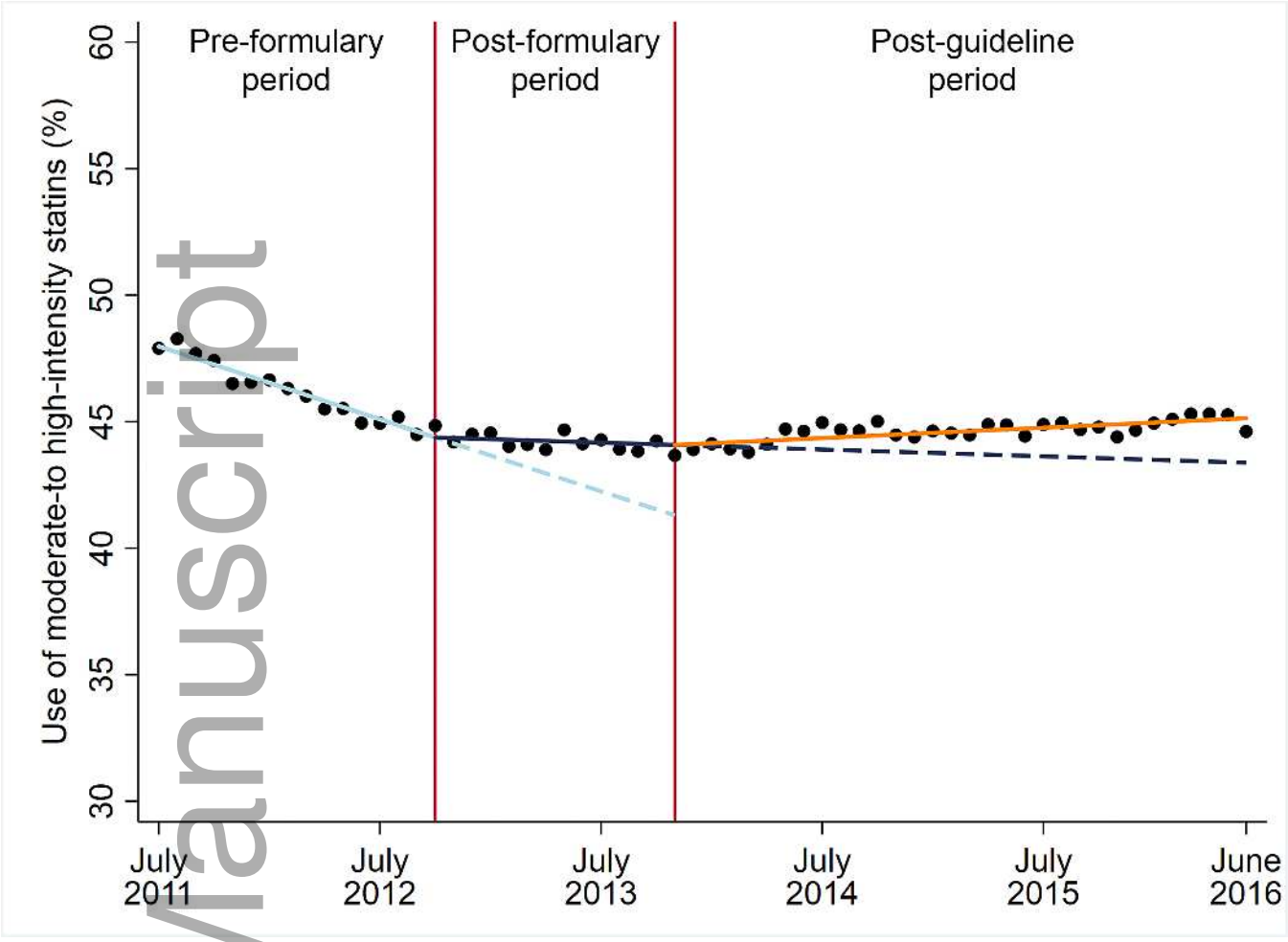

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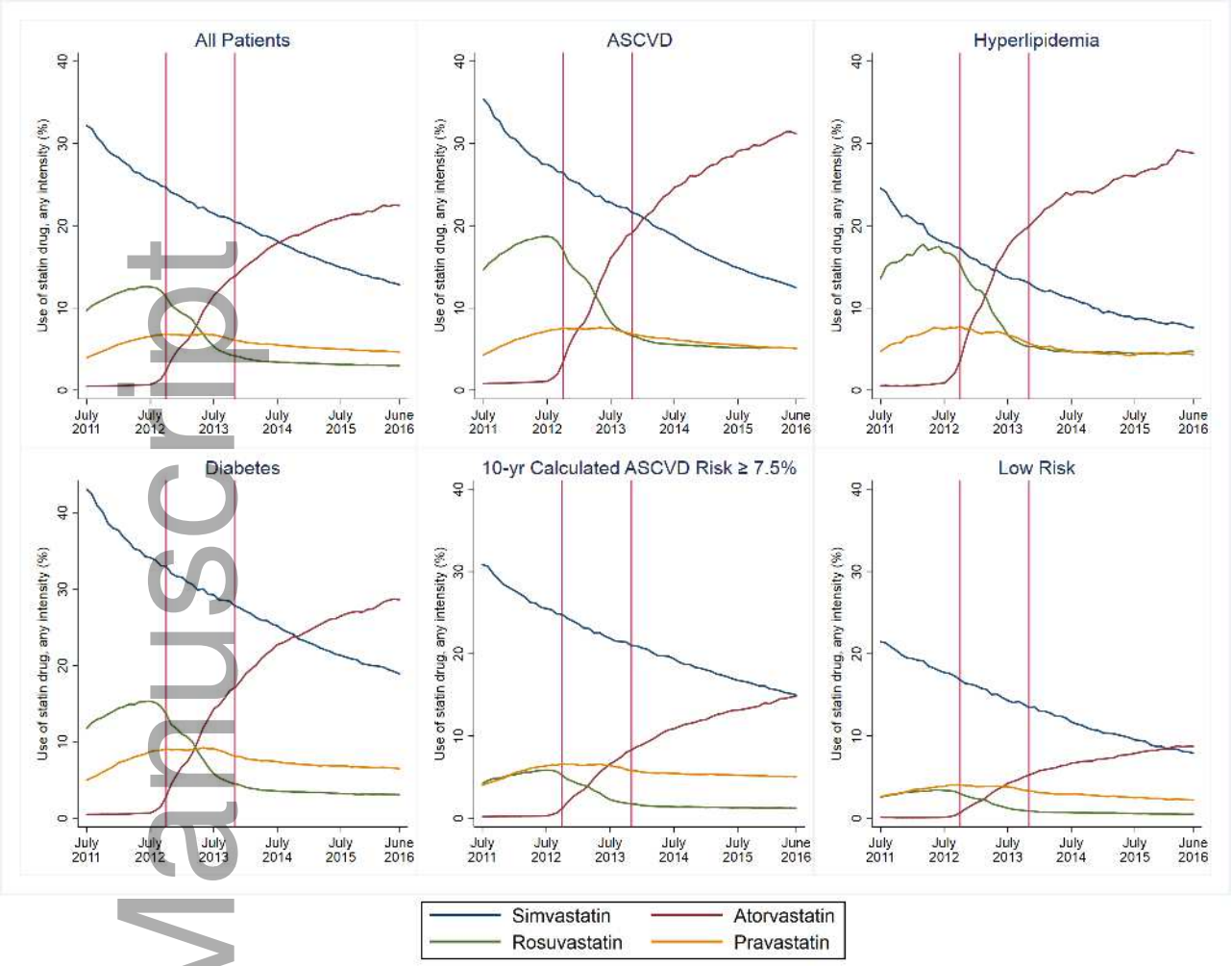

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