

Efficacy, Safety, Cost, and Clinical Outcomes After the Switch to Generic Rosuvastatin Compared with Consistent Brand-Name Atorvastatin Treatment.

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1 **Title**

2 Efficacy, safety, cost, and clinical outcomes after the switch to generic rosuvastatin
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4
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1 **Abstract**

2 **Background:**

3 The efficacy, safety, and clinical outcomes for patients switch to generic rosuvastatin,
4 compared with patients taking other brand-name atorvastatin, is unclear.

5 **Method:**

6 We retrospectively collected electronic medical records from January 1, 2013, to
7 December 31, 2020, of patients who switched medication, because of hospital policy, from
8 brand-name to generic rosuvastatin after March 14, 2018. we only considered patients who
9 had taken the medication at least 1 year prior to and 1 year after that date. We also
0 collected records of patients who consistently used brand-name atorvastatin during the
1 same period. The efficacy of lipid control, potential adverse effects, clinical outcomes of
2 major cardiovascular events (MACE), and medical expenses were compared between the 2
3 groups. Propensity score matching (PSM) was conducted to balance potential cofounders.

4 **Result:**

5 After 1:1 PSM, 592 patients were enrolled in the rosuvastatin and atorvastatin groups,
6 and no significant difference was observed in their total cholesterol (TC) level difference
7 (-4.38 ± 23.0 vs. -3.72 ± 26.95 mg/dL, $P = 0.702$), low-density lipoprotein (LDL-C) (-2.38
8 ± 19.89 vs. -2.42 ± 23.63 mg/dL, $P = 0.976$), or glycated hemoglobin ($-0.05\% \pm 0.7\%$ vs.
9 $-0.08\% \pm 0.76\%$, $P = 0.543$). No significant differences were noted in their cumulative
0 MACE (2.70% vs. 3.89%, log-rank $P = 0.265$) after the switch date, and each person in the

1 generic group had a 16% average reduction in their medical expenses.

2 **Conclusion:**

3 Switching to generic rosuvastatin led to comparable lipid-lowering efficacy, safety, and
4 clinical outcomes and fewer medical expenses compared with consistently using brand-name
5 atorvastatin.

6 **Keyword:** statin, cholesterol, generic, hyperlipidemia, HMG-CoA reductase

7

1 Introduction

2 HMG-CoA reductase, frequently referred to as statin, is currently the first-line
3 medication used to treat patients with hyperlipidemia for both primary and secondary
4 prevention, according to their individual risks with regard to underlying comorbidities,
5 family histories, age, and their calculated 10-year risk of fatal CVD ^{1,2}. Both rosuvastatin and
6 atorvastatin are categorized as high-potency lipid-lowering agents, and for each 1 mmol/L
7 (38.67 mg/dL) reduction of LDL-C by statin, they may reduce major vascular events by 22%².

8 Generic medication represents opportunities for patients who cannot afford essential
9 brand-name medications and to reduce public health expenses. Generic medications must
0 have identical active ingredients that produce the same or acceptable pharmaceutical
1 results as the referenced brand-name medication, with respect to pharmacokinetic and
2 pharmacodynamic properties. According to a report by Warraich et al., from 2012 to 2014,
3 the availability of generic atorvastatin led to a 28% reduction in atorvastatin-associated
4 expenditure in the United States³. Manzoli et al. performed a meta-analysis of studies
5 comparing generic and brand-name atorvastatin and simvastatin, and they demonstrated a
6 similar aggregated effect size of clinical efficacy in terms of soft outcomes (0.04, 95% CI:
7 -0.10 to 0.18) and safety in mild to moderate adverse events (-0.06, 95% CI: -0.40 to 0.27)
8 ⁽⁴⁾. Using data from a large retrospective cohort, Gao et al. also reported that major adverse
9 cardiovascular events (MACE) did not differ significantly between generic and brand-name
0 statin (pitavastatin, atorvastatin, pravastatin, simvastatin, or fluvastatin) users⁵. However,

1 another study indicated a lower rate of LDL-C target achievement (0.87, 95% CI: 0.80–0.95)
2 among patients who used generic atorvastatin or simvastatin that may be translated to an
3 increased rate of cardiovascular incidents (HR: 1.31, 95% CI: 1.15–1.50)⁶.

4 Nevertheless, evidence gaps persist. First, in real-world practice, government policies
5 rather than physicians may mandate the switch from brand-name to generic medication.
6 Therefore, patients are concerned whether the switch leads to poorer clinical outcomes
7 compared with other medications not being changed. Second, to our knowledge, clinical
8 evidence remains unavailable on generic rosuvastatin usage. Therefore, this study provides
9 clinical evidence comparing the efficacy, safety, clinical outcomes, and medical expenses
0 between a switch to generic rosuvastatin and consistent brand-name statin.

1

1 **Methods**

2 Ethical statement

3 This study was conducted in accordance with the Declaration of Helsinki, waives the
4 requirement to obtain informed consent, and approved by the Institutional Review Board of
5 National Cheng Kung University Hospital (B-ER-110-134).

6 Study design

7 We retrospectively collected data from January 1, 2013, to December 31, 2020, from
8 the cardiovascular databank of National Cheng Kung University Hospital. Because of
9 medicine contract, all brand-name rosuvastatin (Crestor 10 mg, Shionogi & Co., Ltd.) was
0 switched to generic medication (Roty 10 mg, China Chemical & Pharmaceutical Co., Ltd.)
1 after 14 March 2018, the switch index date in this study. We enrolled patients who had
2 received brand-name rosuvastatin for more than 1 year before and after the switch index
3 date. Patients who used brand-name atorvastatin (Lipitor 40 mg, Pfizer) within the same
4 timeframe served as the control group.

5 Data collection

6 From the cardiovascular electronic medical record databank, we collected information
7 on all patients' clinical diagnoses, underlying comorbidities, and medication histories. We
8 also collected their laboratory data, including total cholesterol (TC), LDL-C, HDL-C,
9 triglyceride (TG); alanine aminotransferase (ALT) and glycated hemoglobin (HbA1c) levels;
0 and estimated glomerulus filtration rates (eGFR) in the 1 year both before and after the
1 index date. Blood sampling frequency and timing were determined by the clinical physician.

1 This databank was created according to the study protocol of Artificial Intelligence with
2 Deep Learning and Genes on Cardiovascular Disease, with ClinicalTrials.gov Identifier
3 NCT03877614. Two cardiovascular physicians validated the database by manually reviewing
4 records highlighting 4 random traits, such as baseline characteristics, comorbidities, or
5 medications, for each of 200 randomly-selected patients. The accuracy rate for all traits was
6 99.12% (793/800)⁷. The primary endpoint of this study was MACE, defined as a composite
7 endpoint of all-cause mortality, acute myocardial infarction, and ischemic stroke. The
8 secondary endpoints were each individual event. The expense of medications was
9 calculated based on public price announced by National Health Insurance Administration
0 Ministry of Health.

1 Statistics

2 Patients were divided into 2 groups: generic-shift rosuvastatin and brand-name
3 atorvastatin, and 1: 1 propensity score matching (PSM) was performed to adjust for
4 confounders including age, sex and underlying comorbidities. Continuous variables are
5 presented as the mean \pm SD, the Student's *t* test was performed to examine the difference
6 between groups, and the paired *t* test was performed before and after the medication
7 switch. Dichotomous data are presented as numbers (percentages), and the chi-square test
8 was performed to examine differences. Kaplan–Meier survival analysis was employed to
9 compare cumulative endpoints between groups, and the log-rank test was used to examine
0 statistical significance. We performed PSM with MatchIt (version 4.2.0), and all other

1 analyses were conducted with R (version 4.0.1).

2

1 **Results**

2 Population

3 From January 2013 to December 2020, 12 969 patients received brand-name
4 atorvastatin, and 2926 patients received brand-name rosuvastatin in a switch from the
5 generic brands. Of those patients, 3094 and 1015 had already been using brand-name
6 atorvastatin and rosuvastatin respectively, for more than 1 year prior to the index date. The
7 brand-name atorvastatin group consisted of 2129 (57.8% male, mean age 68.5 ± 11.8 years)
8 patients, and the generic group consisted of 600 patients (52.7% male, mean age 65.2 ± 11.8
9 years) who had been using medication consistently for more than 1 year after the index date.
0 After 1:1 PSM, 592 (53.7% male, mean age 65.4 ± 12.1 years) patients remained in the
1 brand-name atorvastatin group, and 592 (53.4% male, mean age 65.2 ± 11.8 years) patients
2 were in the generic-switch rosuvastatin group. (Table 1 and Figure 1)

3 Efficacy and safety

4 After PSM, for efficacy in lipid-lowering effects, both generic-switch rosuvastatin and
5 brand-name atorvastatin groups exhibited comparable lower TC (-4.38 ± 23.00 mg/dL vs.
6 -3.72 ± 26.95 mg/dL, $P = 0.702$), LDL-c (-2.38 ± 19.89 mg/dL vs. -2.42 ± 23.63 mg/dL, P
7 $= 0.976$), and HDL-c (-1.23 ± 7.93 mg/dL vs. -1.60 ± 7.62 mg/dL, $P = 0.559$) levels after
8 the medication switch index date. Patients exhibited similar differences in HbA1c ($-0.05\% \pm$
9 0.7% , vs. $-0.08\% \pm 0.76\%$, $P = 0.543$), ALT (-0.58 ± 19.87 U/L vs. -0.14 ± 44.92 U/L, $P =$
0 0.841), and eGFR (-1.36 ± 6.95 mL/min/1.73 m² versus -1.37 ± 8.14 mL/min/1.73 m², $P =$

1 0.988) levels before and after the switch index date (Table 2 and Figure 3).

2 Outcome

3 Between the generic-switch rosuvastatin and brand-name atorvastatin groups, no
4 significant differences were observed in the primary endpoint (2.70% vs. 3.89%, $P = 0.265$)
5 after the switch index date with a median follow-up time of 820 and 822.5 days, respectively,
6 or after the medication initialization date (4.56% vs. 6.59%, $P = 0.664$) with a median
7 follow-up time of 1803.5 and 2359 days, respectively. No significant differences were noted
8 in any of the individual secondary endpoints (Table 3 and Figure 2).

9 Expenses

0 In 2019, the average cost for generic rosuvastatin and brand-name atorvastatin was
1 NT\$452.50 and NT\$539.30 per person. The annual expenditure for all patients was
2 NT\$9,350,854.90 and NT\$29,159,591.40, respectively. (Figure 4)

4 **Discussion**

5 Results revealed that compared with the brand-name atorvastatin group, the group that
6 transitioned from brand-name to generic rosuvastatin had a comparable lipid-lowering
7 efficacy, no increase in hepatic toxicity or averaged HbA1c, and comparable clinical
8 outcomes. The generic-switch group exhibited lower medication expenses per person;
9 however, this group had lower persistence in the use of medication. To our knowledge, our
0 study is the first to obtain data on the switch to generic rosuvastatin.

1 Efficacy and safety

1 In a previous study, Loch et al. observed no significant differences between LDL-c (2.64
2 vs. 2.64 mmol/L, $P = 0.923$) and TC (4.71 vs. 4.68 mmol/L, $P = 0.583$) levels and slightly
3 lower HDL-c levels (1.29 vs. 1.26 mmol/L, $P = 0.009$) before and after the switch to generic
4 atorvastatin⁸. Our results are comparable to these findings because, although both groups
5 exhibited significantly lower levels of LDL-c, TC, and HDL-c, the differences were similar
6 and more likely to have resulted from cholesterol management goals and stricter monitoring.
7 This highlights the value of our study design: only when simultaneous ongoing treatments
8 are compared could we verify that medication was not the only factor to affect cholesterol
9 levels; in this manner, people are not misled to believe that the improved efficacy was a
0 result of generic medications (Table 2 and Figure 3).

1 No significant differences were noted in potential side effects of statin, such as new
2 onset diabetes mellitus and hepatotoxicity. In meta-analysis studies by Kesselheim and
3 Manzoli et al., 6 comparison studies between generic and brand-name medications were
4 enrolled. These studies mostly employed cross-over designs examining simvastatin and
5 atorvastatin and revealed no significant differences in the clinical efficacy of LDL control
6 (effect size: 0.04, 95% CI: -0.10 to 0.18) or any mild or moderate adverse events (effect
7 size: -0.06, 95% CI: -0.40 to 0.27)^{4,9}. Although these studies provided no data on generic
8 rosuvastatin, they support our results.

9 Clinical outcomes

0 Numerous studies have reported clinical outcome comparisons between initial

1 treatments with generic and brand-name statins. Corrao et al. examined 13 799 newly treated
2 patients with generic or brand-name simvastatin from Italy's health care system, and
3 discovered no difference in the risk of cardiovascular outcomes (HR: 1.06; 95% CI: 0.83–
4 1.34)¹⁰. Gagne et al. examined the electronic data of American patients who were initially
5 treated with generic or brand-name statin (lovastatin, pravastatin, or simvastatin), with 6380
6 patients in each group. They discovered an 8% reduction in the rate of adverse clinical
7 outcomes in the generic group (HR: 0.92; 95% CI: 0.86–0.99)¹¹. Moreover, Gao et al.
8 conducted a Japanese cohort study with 14 313 patients (post 1:1 PPM) in each group who
9 took generic or brand-name statin (atorvastatin, pravastatin, pitavastatin, simvastatin, or
0 fluvastatin), and found no significant differences in MACE outcomes (HR: 1.04; 95% CI:
1 0.93–1.17). Additionally, Sicras-Mainar et al. examined a total of 13 244 records of patients
2 from Spain who were initially treated with generic or brand-name statin (atorvastatin and
3 simvastatin). This study revealed a higher occurrence of major cardiovascular incidents in
4 generic group (HR: 1.31; 95% CI: 1.15–1.50), and the authors stated a possible explanation
5 may be a lower (14% reduction) medication consistency rate among the generic group⁶.

6 Despite the relatively heterogeneous results of previous studies, our results are
7 comparable to most of the results, with no significant differences in clinical outcomes from
8 the medication start and switch dates. Moreover, because studies have investigated the
9 effects of initial medication, rather than those that resulted from a switch, and lacked
0 rosuvastatin data, our study provided more evidence regarding the switch to generic

1 rosuvastatin (Table 3 and Figure 2).

2 Medication persistence

3 In a comparison of 1-year persistence rates, Romanelli et al. reported lower persistence
4 in the generic than in the brand-name groups (61.3% and 66.2%, $P = 0.021$, respectively),
5 and our study revealed similar results [59.1% (600/1015) vs. 68.8% (2129/3094), $P < 0.001$,
6 respectively]¹². The lower persistence rate in the generic-switch group may be attributed to
7 the medication switch having driven patients to search for facilities that provided their
8 original medication. Nevertheless, we conducted an analysis on patients with persistent
9 medication use, which was expected to have no influence on the interpretation. Notably,
0 studies have also revealed that the switch to other types of statin was frequently to less
1 potent medications that may also affect clinical outcomes^{12,13}.

2 Medical expense

3 Although the efficacy of achieving controlled lipid levels was comparable between the
4 generic-switch and brand-name groups, the expense of statin use per person was
5 approximately 16.1% lower in the generic group than in the brand-name group (NT\$452.50
6 vs. NT\$539.30). This is consistent with the results obtained by Warraich et al., indicating a
7 23% reduction (from NT\$7.0 to NT\$5.4 billion). Given the comparable efficacy and clinical
8 outcomes, they recommended using a generic substitute to reduce costs³. (Figure 4)

9 Limitations

0 Our study has several limitations. First, this was a single-center retrospective study

1 enrolling people of primarily east-Asian ethnicities. Therefore, although our results are
2 comparable to those of global studies, their generalizability may be limited. Second, no
3 routine medical records were available regarding potential adverse effects of muscle pain or
4 creatine kinase levels that we could use for comparison. Third, longer follow-up periods after
5 the switch date may be required to measure cardiovascular outcomes. Although we analyzed
6 outcomes after the medication initiation and switch dates, long-term prognoses after the
7 switch date may require further investigation. Fourth, the medications in our study were
8 Crestor, Roty, and Lipitor, and the result may not be generalizable to other medications.

0 **Conclusion**

1 Patients who switched to generic rosuvastatin had comparable lipid-lowering efficacy,
2 safety, and clinical outcomes and lower medical expenses than patients who consistently
3 used brand-name atorvastatin.

1 **Declarations**

2 **Availability of data and materials**

3 The datasets used and/or analysed during the current study are available from the
4 corresponding author on reasonable request.

5 **Competing interests**

6 The authors declare that they have no competing interests

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3 **Authors' contributions**

4 MSH conducted data collection, analyzing, tables and figures drafting; CIW did
5 manuscript writing; PFS supervised data analyzing; PYL provide the concept and source of
6 data.

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9
0

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1 **Figure Legends**

2 **Figure 1.** Data flow diagram.

3 **Figure 2.** Kaplan–Meier survival analysis of primary endpoint of 2 groups, after propensity
4 score matching. Upper panel started from medication switch date, and lower panel from
5 medication initialization date. *P*: log-rank test.

6 **Figure 3.** Laboratory patient-paired difference before and after medication switch date. *P*:
7 Student’s t test.

8 **Figure 4.** Prescription amount (upper panel) and expense per person (lower panel) of statin
9 use to time for generic rosuvastatin, brand-name rosuvastatin, and brand-name
0 atorvastatin. The red vertical dash line indicates medication switch date: March 3, 2018.

1

2

1 Table 1 Clinical matching characteristics for current patient cohort with switch effect of
 2 brand-name atorvastatin and generic rosuvastatin use

	Before Matching					After Matching				
	Rosuvastatin (n=600)		Atorvastatin (n=2,125)		p	Rosuvastatin (n=592)		Atorvastatin (n=592)		p
	mean (count)	SD (percentage)	mean (count)	SD (percentage)		mean (count)	SD (percentage)	mean (count)	SD (percentage)	
Age (year)	65.15	11.82	68.54	11.79	<0.001	65.15	11.82	65.38	12.08	0.735
Body mass index (kg/m ²)	26.33	5.01	25.93	5.62	0.143	26.33	5.01	25.94	4.47	0.198
Median follow up duration (days)	820		827			820		822.5		
Gender (Male)	316	52.67%	1228	57.79%	0.04	316	53.38%	318	53.72%	0.907
Diabetes mellitus	363	60.5%	1144	53.84%	0.002	363	61.32%	368	62.16%	0.765
Hypertension	419	69.83%	1727	81.27%	<0.001	419	70.78%	408	68.92%	0.486
Chronic kidney disease	163	27.17%	813	38.26%	<0.001	163	27.53%	159	26.86%	0.794
Atrial fibrillation	58	9.67%	339	15.95%	<0.001	58	9.8%	62	10.47%	0.7
Coronary artery disease	125	20.83%	853	40.14%	<0.001	125	21.11%	133	22.47%	0.573
Beta-blocker	176	29.33%	708	33.32%	0.066	176	29.73%	184	31.08%	0.613
Renin-Angiotensin- Aldosterone System inhibitor	234	39.0%	1016	47.81%	<0.001	234	39.53%	246	41.55%	0.478
Antiplatelet	237	39.5%	1286	60.52%	<0.001	237	40.03%	305	51.52%	<0.001
Anticoagulation	55	9.17%	269	12.66%	0.02	55	9.29%	60	10.14%	0.624
Laboratory										
Total Cholesterol (mg/dL)	152.5	35.88	159	42.02	<0.001	152.1	35.76	160.7	38.23	<0.001
Low density lipoprotein (mg/dL)	86.07	29.39	92.29	34.16	<0.001	85.94	29.39	93.45	31.46	<0.001
High density lipoprotein (mg/dL)	51.32	14.91	51.65	15.46	0.613	51.36	14.95	53.66	16.14	0.007
Triglyceride (mg/dL)	139.6	78.52	137.6	95.14	0.512	138.4	77.11	137.4	98.65	0.788
HbA1c (%)	7.45	1.32	7.14	1.35	<0.001	7.45	1.3	7.22	1.32	<0.001
eGFR (mL/min/1.73m ²)	53.22	22.35	47.94	24.97	<0.001	53.34	22.28	51.65	25.8	0.082
ALT (U/L)	31.69	23.52	33.35	50.59	0.174	31.73	23.6	34.32	50.51	0.052

3

1 Table 2. Clinical characteristics before and after matching for current patient cohort with
 2 switch effect of brand-name atorvastatin and generic rosuvastatin use

	Before matching							P
	Rosuvastatin (n=600)			Atorvastatin (n=2,125)				
	Before	After	Patient-paired difference	Before	After	Patient-paired difference		
Total Cholesterol (mg/dL)	152.53 ± 35.88	146.58 ± 32.99	-4.44 ± 22.92	159.04 ± 42.02	154.34 ± 37.65	-2.64 ± 25.27	0.171	
Low density lipoprotein (mg/dL)	86.07 ± 29.39	83.08 ± 27.88	-2.35 ± 19.81	92.29 ± 34.16	89.9 ± 31.88	-1.57 ± 21.77	0.471	
High density lipoprotein (mg/dL)	51.32 ± 14.91	49.59 ± 13.22	-1.2 ± 7.9	51.65 ± 15.46	49.38 ± 14.18	-2.31 ± 7.36	0.017	
Triglyceride (mg/dL)	139.61 ± 78.52	136.13 ± 76.58	-5.66 ± 49.04	137.56 ± 95.14	135.05 ± 82.81	-1.37 ± 54.99	0.133	
HbA1c (%)	7.45 ± 1.32	7.39 ± 1.33	-0.05 ± 0.7	7.14 ± 1.35	7.07 ± 1.35	-0.05 ± 0.68	0.955	
eGFR (mL/min/1.73m ²)	53.22 ± 22.35	51.55 ± 23.27	-1.34 ± 6.94	47.94 ± 24.97	46.21 ± 25.81	-1.28 ± 7.31	0.891	
ALT (U/L)	31.69 ± 23.52	31.83 ± 40.0	-0.48 ± 20.03	33.35 ± 50.59	32.22 ± 73.87	-1.05 ± 28.22	0.672	
	After matching							P
	Rosuvastatin (n=592)			Atorvastatin (n=592)				
	Before	After	Patient-paired difference	Before	After	Patient-paired difference		
Total Cholesterol (mg/dL)	152.14 ± 35.76	146.35 ± 32.99	-4.38 ± 23.0	158.19 ± 43.03	154.45 ± 38.55	-3.72 ± 26.95	0.702	
Low density lipoprotein (mg/dL)	85.94 ± 29.39	82.94 ± 27.9	-2.38 ± 19.89	90.2 ± 33.95	88.91 ± 32.35	-2.42 ± 23.63	0.976	
High density lipoprotein (mg/dL)	51.36 ± 14.95	49.62 ± 13.25	-1.23 ± 7.93	49.94 ± 15.3	49.07 ± 14.38	-1.6 ± 7.62	0.559	
Triglyceride (mg/dL)	138.41 ± 77.11	134.93 ± 75.63	-5.36 ± 49.02	142.78 ± 84.98	136.68 ± 74.73	-5.06 ± 51.6	0.930	
HbA1c (%)	7.45 ± 1.3	7.37 ± 1.29	-0.05 ± 0.7	7.31 ± 1.44	7.24 ± 1.49	-0.08 ± 0.76	0.543	
eGFR (mL/min/1.73m ²)	53.34 ± 22.28	51.65 ± 23.25	-1.36 ± 6.95	50.6 ± 24.51	48.66 ± 26.07	-1.37 ± 8.14	0.988	
ALT (U/L)	31.73 ± 23.6	31.34 ± 37.05	-0.58 ± 19.87	34.75 ± 56.08	36.27 ± 118.68	-0.14 ± 44.92	0.841	

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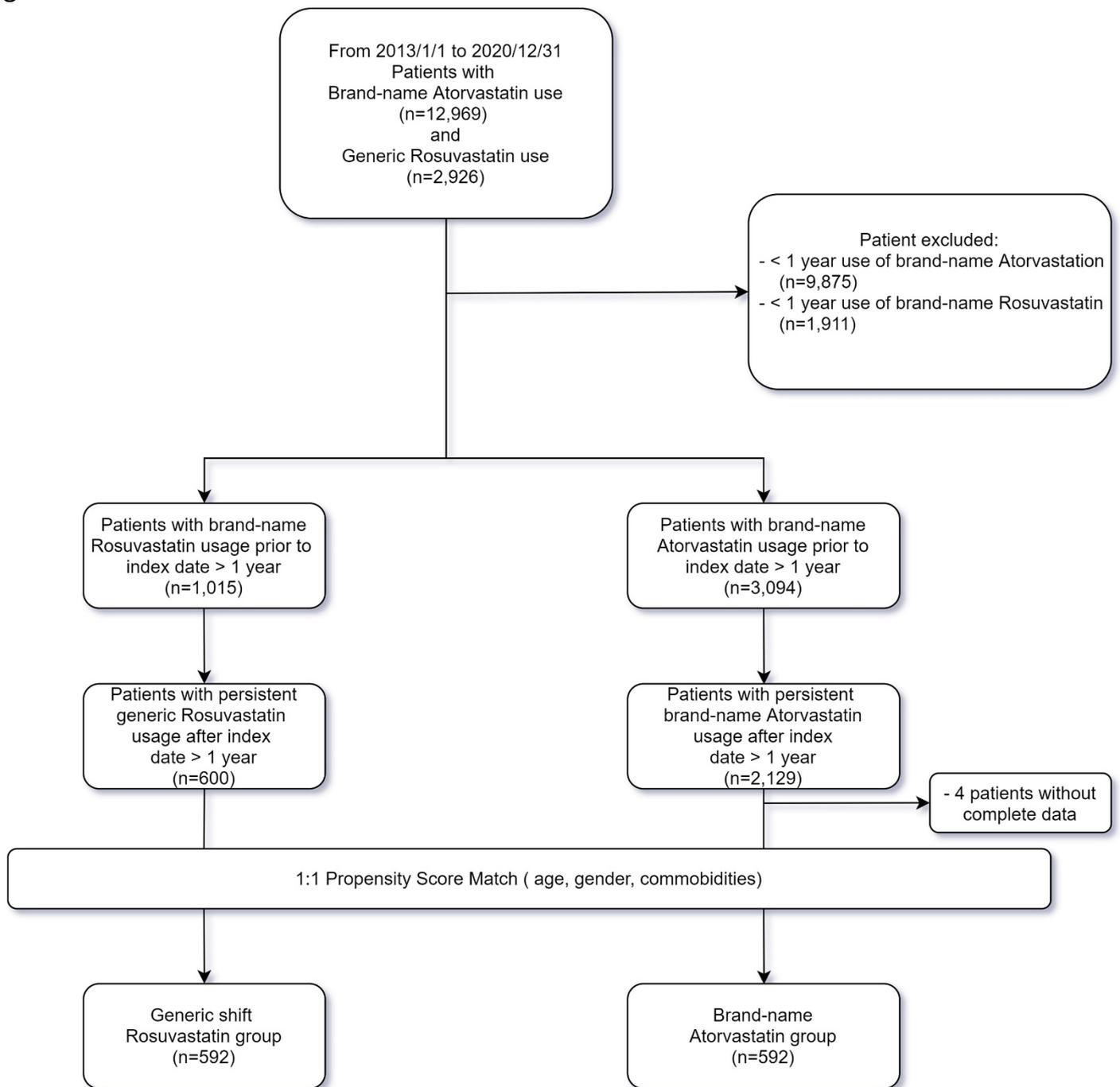
1 Table 3. Clinical outcomes between matching treating groups with switch effect of brand-
 2 name atorvastatin and generic rosuvastatin use

	Rosuvastatin (n=592)		Atorvastatin (n=592)		P*
	Number	Percentage	Number	Percentage	
	From landmark index date				
Median follow up time (day)	820		822.5		
Primary					
Major cardiovascular adverse event	16	2.70%	23	3.89%	0.265
Secondary					
All-cause mortality	8	1.35%	11	1.86%	0.498
Myocardial infarction	8	1.35%	10	1.69%	0.649
Ischemic stroke	0	0.00%	3	0.51%	0.084
	From statin initiation date				
Median follow up time (day)	1803.5		2359		
Primary					
Major cardiovascular adverse event	27	4.56%	39	6.59%	0.664
Secondary	18	3.04%	23	3.89%	0.826
All-cause mortality	8	1.35%	11	1.86%	0.706
Myocardial infarction	18	3.04%	23	3.89%	0.826
Ischemic stroke	2	0.34%	6	1.01%	0.255

*Log-rank *P*

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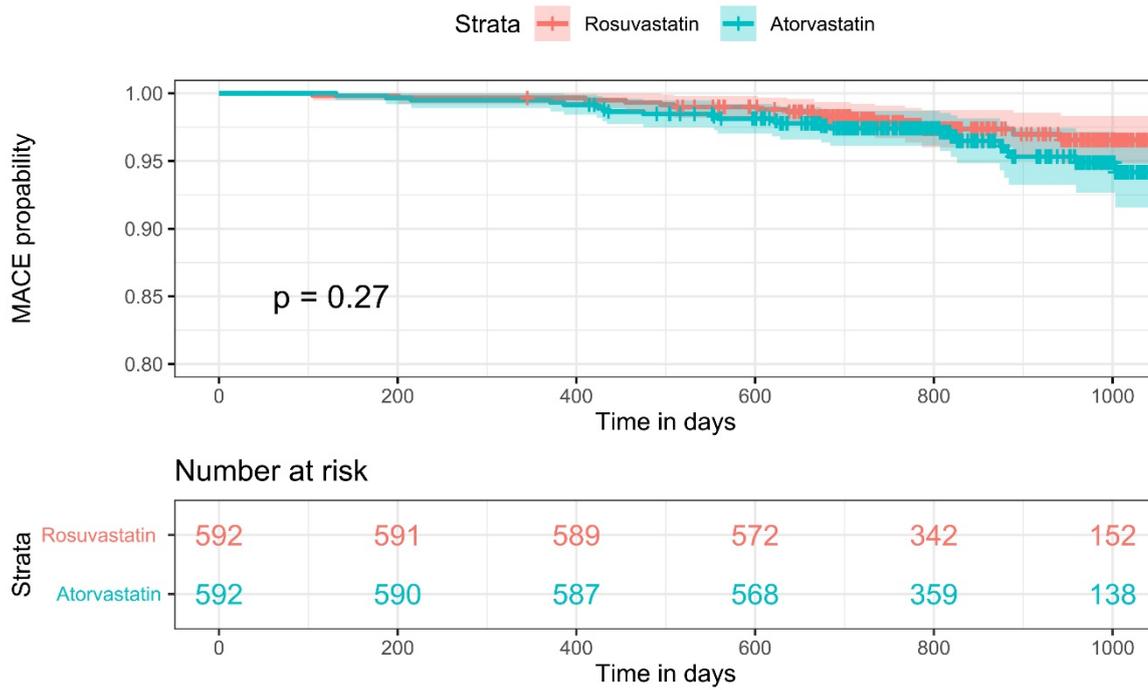
1 Figure 1



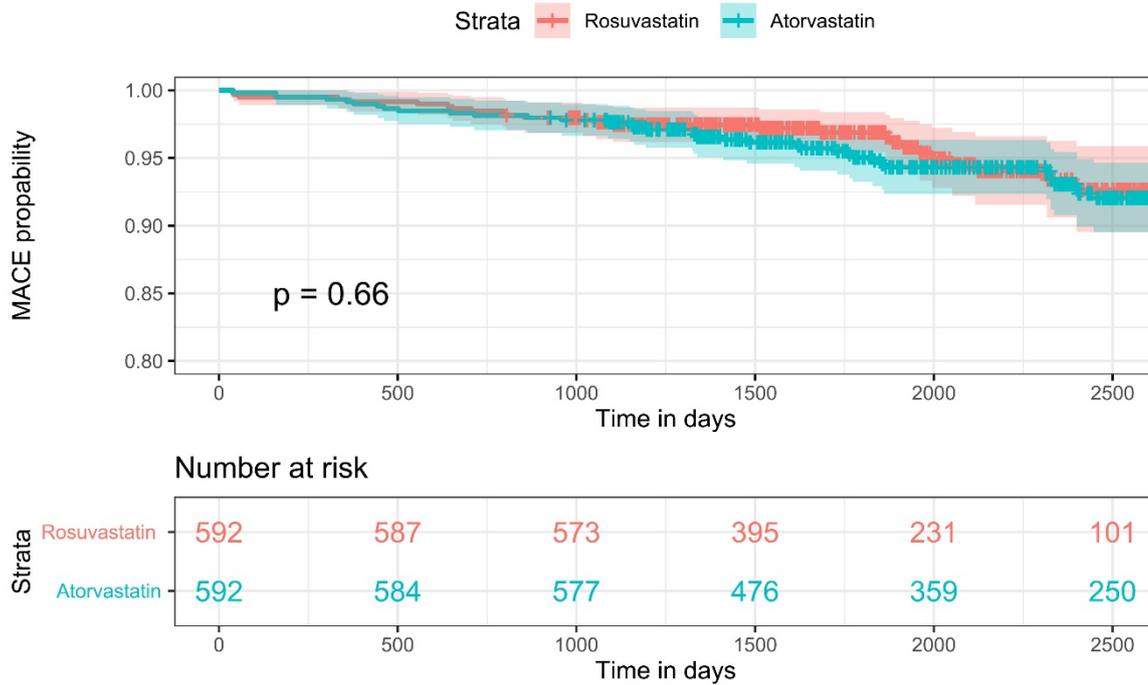
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1 Figure 2

After medication switch index date



After medication initiation date



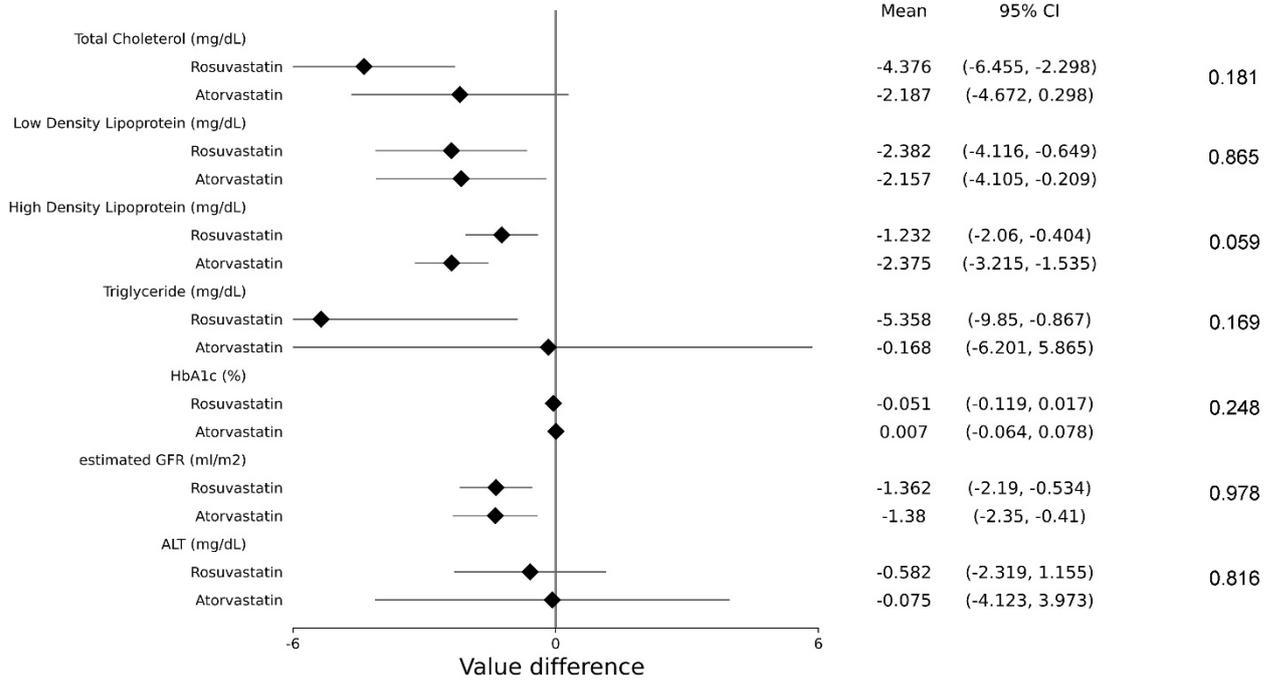
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1 **Figure 3**

Laboratory Data (Both n=592)

Patient-paired difference

P value

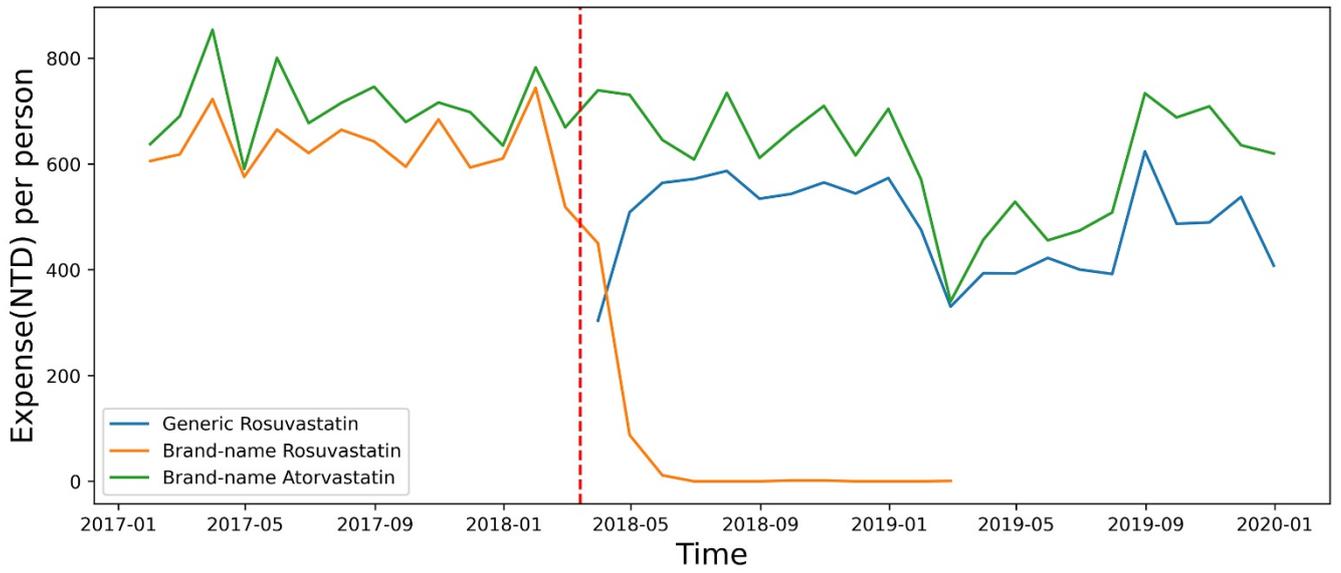
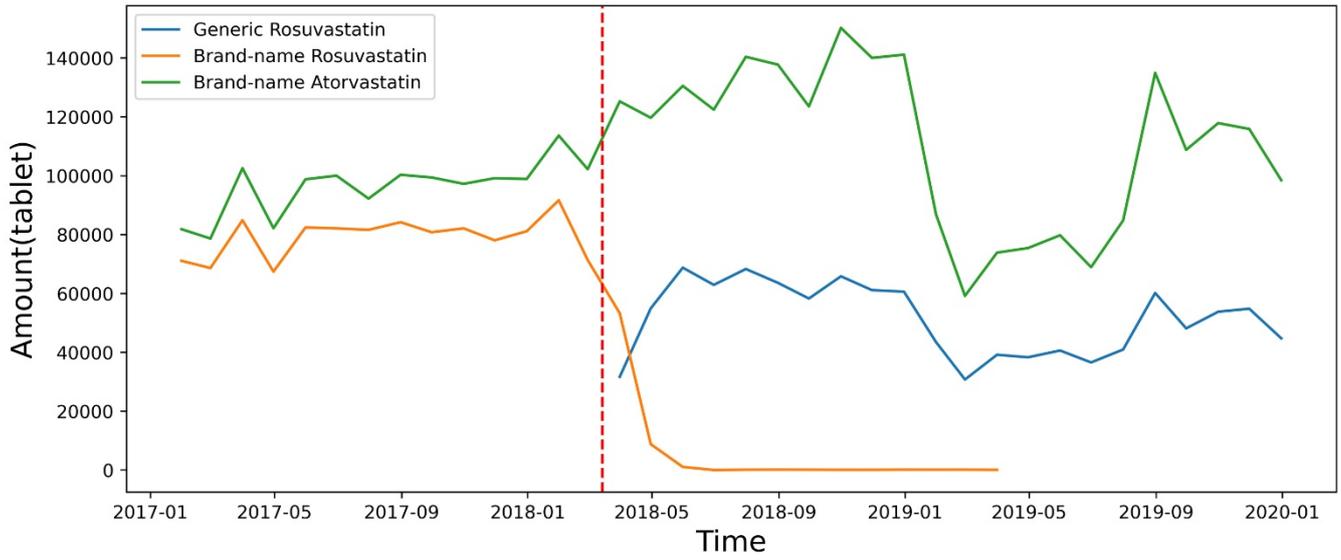


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1 Figure 4

Medication Prescription - Time



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