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Generic atorvastatin and rosuvastatin in the South Korean market: time of introduction in relation to manufacturer characteristics

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- The characteristics of the **pharmaceutical market in South Korea** can be summarized as follows ^{1,2}.
 - First, **originator drugs** account for approximately **60%** of the total pharmaceutical market, which is high compared with other high-income countries.
 - The majority of originator drugs are imported from the United States, the United Kingdom, Switzerland, and Germany ^{1,2}.
 - Second, **excessive competition** exists among manufacturers in the market for **generic drugs**.
 - Currently, **416 manufacturers**, which are composed mainly of **small- and medium-sized local manufacturers**, are functioning at any phase of the manufacturing, processing, or packaging of a particular drug product ^{1,2}.

- Given the substantial market size of statins and the number of available drugs in the market ⁷⁻⁹, statin utilization in the health system has been the subject of interest in many countries from the perspective of public health and health financing ¹⁰⁻¹².
 - European countries have restricted the prescribing of originator drugs when generic drugs become available on the market at a discounted price ^{13,14}.
- Thus, many studies have described the market structure of statins in various countries ^{7,15-18}.
 - Similarly, the market share of statins with various active ingredients, including simvastatin, atorvastatin, and rosuvastatin, has been well reported in previous literature ¹⁵⁻¹⁸.

- While the literature has described the statin market with a focus on the product^{9-11,16-21}, few have systematically examined the market structures based on the manufacturers²².
 - However, the competition for and market dynamics of generic medicines can be understood by analysing the behaviour of manufacturers.
- In this study, we aim to assess the market for atorvastatin and rosuvastatin, well-known blockbuster drugs, in South Korea by focusing on manufacturers.
 - Specifically, we analysed generic atorvastatin and rosuvastatin that were introduced onto the South Korean market from 2002 to 2018 and their corresponding manufacturers.

Subject

- We are interested in the market structure of local manufacturers who were granted regulatory approval for atorvastatin and rosuvastatin by the MFDS in South Korea from 2002 to 2018.
 - It is noteworthy that modified versions of brand-name drugs, including new formulations, are also available on the market.

Data source

- The MFDS provides information on the approved drugs, including the drug's name, active ingredients and strength, date of marketing approval, and manufacturers.
- KISVALUE was used to capture the current manufacturer size.
- Finally, we retrieved documents on the MOHW website to collect information on the designation of manufacturers as innovative manufacturers .

Statistical analysis

- First, we used **descriptive analysis** to capture the characteristics of the market, including the number of generics of atorvastatin and rosuvastatin that enter the market and the types of manufacturers.
- Second, we **calculated the duration** between **the date of marketing approval** for the first generic and that of the remaining generics.
 - We **separated generic drugs** into two groups: **first movers** and **latecomers**.

Statistical analysis

- Finally, we performed **an event history analysis** for a statistical estimation of the duration.
 - We used **a cumulative distribution function** to capture the number of drugs available on the market and **applied a proportional hazard model** to determine the relative impact of the characteristics of local manufacturers on the duration of selected generics.
 - Data management and analysis were conducted using R statistical software (version 3.4.3). Statistical significance is noted by p-values less than 0.05.

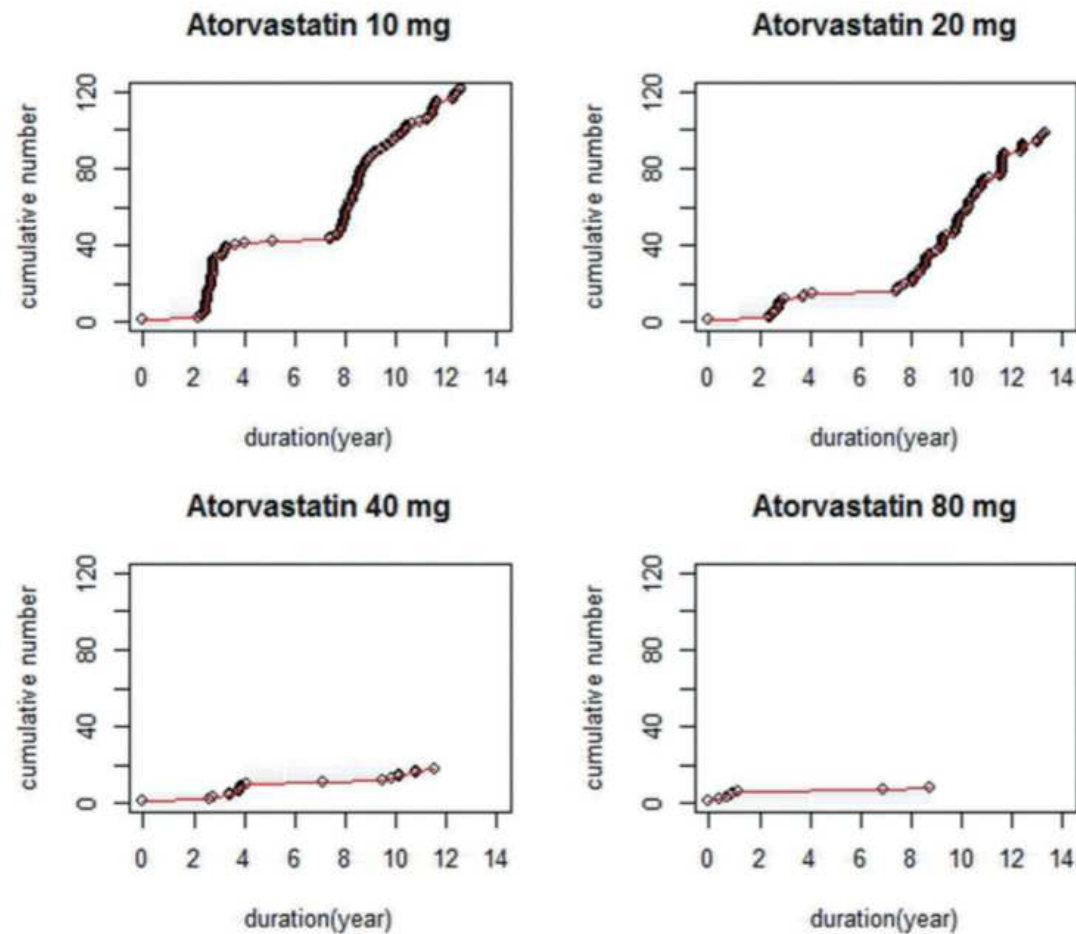
Characteristics of reference products

Table 1. Characteristics of reference products and their new formulation.

Portfolio	Reference product	Product category	Product characteristics	Date of approval	Date of the first generic entry	Number of manufacturers	Number of Local manufacturers
Atorvastatin	Atorvastatin 20 mg	Reference	20 mg	10/25/2004	3/9/2007	97	94
		New co-formulation #1	Combined with ezetimibe	1/23/2015	None	1	0
	Atorvastatin 40 mg	Reference	40 mg	10/25/2004	3/9/2007	18	15
		New co-formulation #1	Combined with ezetimibe	1/23/2015	None	1	0
	Atorvastatin 10 mg	Reference	10 mg	11/25/2004	1/17/2007	119	116
		New co-formulation #1	Combined with ezetimibe	1/23/2015	None	1	0
	Atorvastatin 80 mg	Reference	80 mg	10/18/2007	3/24/2008	8	7
		New co-formulation #1	Combined with ezetimibe	1/23/2015	None	1	0
Rosuvastatin	Rosuvastatin 10 mg	Reference	10 mg	1/15/2002	11/7/2008	116	113
		New co-formulation #1	Combined with ezetimibe	6/8/2015	9/24/2015	29	28
	Rosuvastatin 20 mg	Reference	20 mg	8/31/2004	1/28/2010	97	94
		New co-formulation #1	Combined with ezetimibe	6/8/2015	9/24/2015	29	28
	Rosuvastatin 5 mg	Reference	5 mg	12/29/2005	1/28/2010	78	75
		New co-formulation #1	Combined with ezetimibe	6/8/2015	9/24/2015	29	28
		New co-formulation #2	Combined with omega-3 fatty acid	7/31/2015	None	1	1

Cumulative number of atorvastatin and rosuvastatin generics

Appendix 1. Cumulative number of atorvastatin sorted by reference product



Note) Duration 0 means the introduction of the original drug in the market.

Cumulative number of atorvastatin and rosuvastatin generics

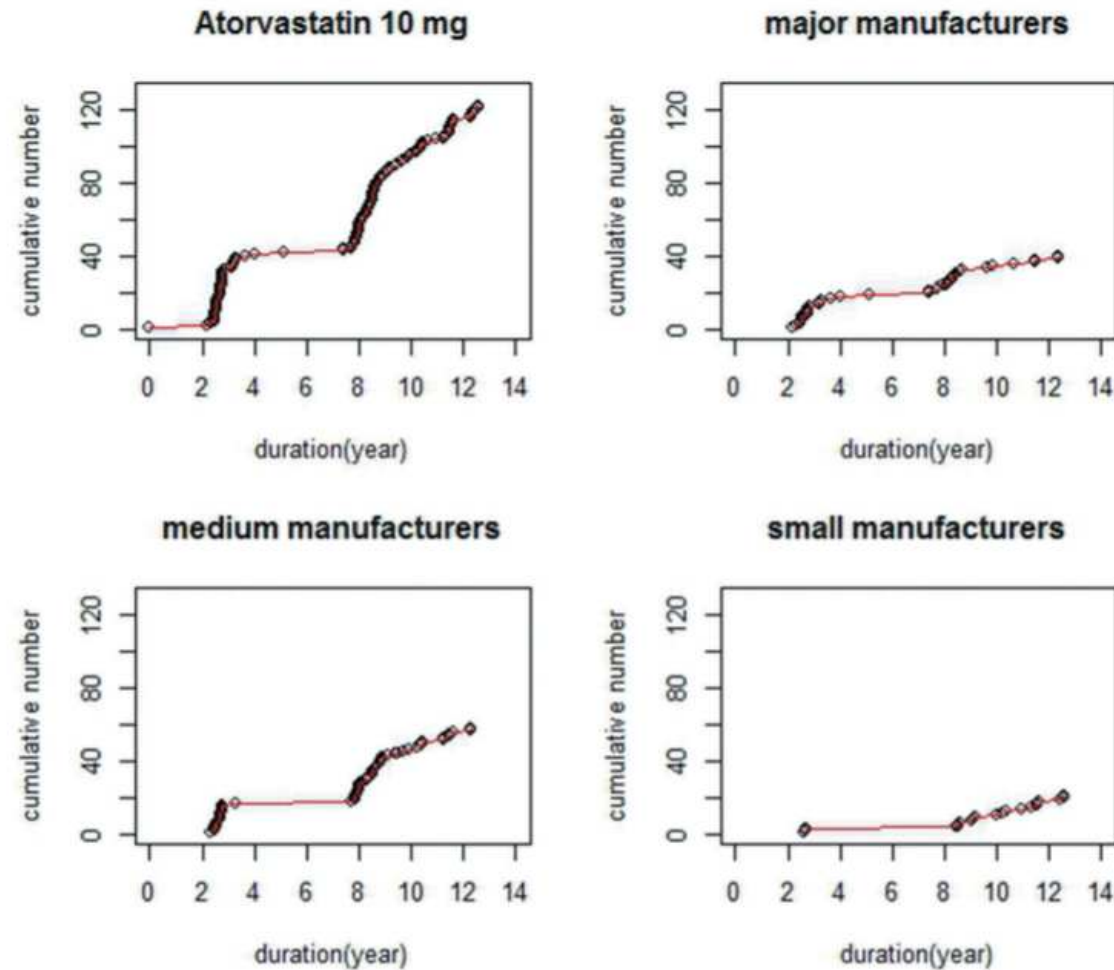
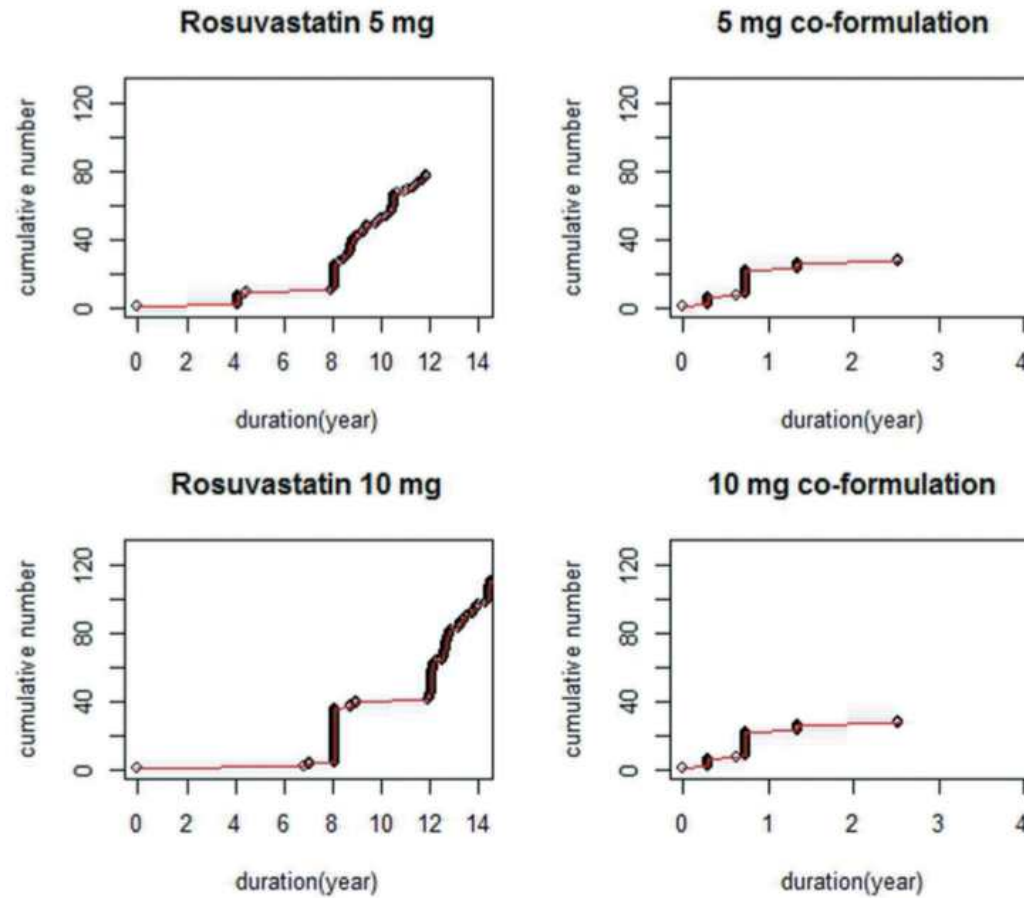


Figure 1. Cumulative number of atorvastatin 10 mg sorted by manufacturer size.

Note) Duration 0 means the introduction of the original drug in the market.

Cumulative number of atorvastatin and rosuvastatin generics

Appendix 2. Cumulative number of rosuvastatin sorted by reference product



Note) Duration 0 means the introduction of the original drug in the market.

Two types of generics: first movers and latecomers

Table 2. Characteristics of first movers and latecomers for selected medicines.

	Atorvastatin 10 mg N = 116			Rosuvastatin 10 mg N = 113		
	First mover N = 35	Latecomers N = 81	P value	First mover N = 38	Latecomers N = 75	P value
Size			0.0258			0.0023
Major manufacturers	17	22		23	22	
Medium-sized	16	41		13	35	
Small-sized	2	18		2	18	
Innovative manufacturers			0.0066			0.2120
Yes	12	9		10	11	
No	23	72		28	64	

Two types of generics: first movers and latecomers

Table 2. Characteristics of first movers and latecomers for selected medicines.

	Rosuvastatin 10 mg co-formulated					
	Scenario 1_current situation N = 28			Scenario 2_assumption ¹⁾ N = 113		
	First mover N = 27	Latecomers N = 1	P value	First mover N = 26	Latecomers N = 87	P value
Size			N/A			<0.0001
Major manufacturers	24	1		23	22	
Medium-sized	3	0		3	45	
Small-sized	0	0		0	20	
Innovative manufacturers			N/A			<0.0001
Yes	15	0		14	7	
No	12	1		12	80	

Cox proportional hazards model

Table 3. Results from the Cox model with duration starts at the date the first generic entered.

	Atorvastatin 10 mg N = 116			Rosuvastatin 10 mg N = 113		
	Coefficient	Standard error	P value	Coefficient	Standard error	P value
Size (reference major manufacturers)						
Medium-sized	−0.1154	0.2709	0.6699	−0.6022	0.2559	0.0186
Small-sized	−0.9588	0.3417	0.0050	−0.6526	0.3080	0.0341
Innovative manufacturers (reference No)						
Yes	0.2008	0.3215	0.5321	0.5440	0.3046	0.0741

Interesting findings

- First, we confirmed that many manufacturers have marketed generic drugs in South Korea, and these manufacturers could be categorized as first movers and latecomers.
 - For instance, 119 local manufacturers of atorvastatin 10 mg introduced generics on the market, and approximately 30% of the manufacturers were grouped as first movers.
- Second, latecomers account for **a large portion of the manufacturers** of generics in the South Korean market
 - Latecomers have entered the market steadily, even after the market matured with a number of manufacturers.
- Third, the characteristics of the manufacturers were closely related to manufacturers' behaviours in the market.
 - We captured that as the size increases, the likelihood of being the first movers of generic drugs increases, while as size decreases, the likelihood of being the latecomers of generics increases.

Number of generic manufacturers in the market

- The generic market of atorvastatin in the United States was different from that of South Korea.
 - Only a single generic drug and one authorized generic were available for the first 180 days after the first generic entrant on the market.
 - However, few manufacturers in the market had not changed, even after 180 days of exclusivity: only an additional four generic drugs received marketing approval by the FDA ²¹.
 - Similarly, fewer than ten generic drugs are reported to be paired with the original drugs in Germany and Canada ^{25,26}.

- The **chronological order of manufacturers** entering the market can affect the **market share of drugs**;
 - The market favoured the first entrant because of the **pre-emption of competition** and **brand loyalty** ^{27,28}.
 - This phenomenon are defined as the order-of-entry effects in pharmaceutical markets ²² and reported in various countries over different therapeutic areas ^{20,22}.

- Note the small number of manufacturers of generic drugs in the United States, Germany, and Canada ^{25,26}.
 - The limited number of generic drugs in these markets is closely related to price competition among generics ^{20,25}.
 - Companies consider profit rather than market share when they decide to enter the market ²².
 - Given these behaviours, some researchers argue that the order-of-entry effects are simply the causal effect of the chronological order of discounted products accumulated over the product life cycle ^{27,28}.

Order-of-entry effect

- Not surprisingly, manufacturers will **not enter the market** if there is **little expectation of profits with price competition**, as observed in other markets.
 - For instance, the price of the originator drug and that of the generic drug were **similar** in the United States when there was **only one generic manufacturer** in the market.
 - Specifically, the price of the generic drug is approximately **87%** the price of the original drug. However, the price of the second and the third generic drugs **dramatically dropped** in the market to **77%** and **60%** of the price of the original drug, respectively ²⁰.
- However, the South Korean pharmaceutical market is different.
 - Price competition is **very rare** in the market, and the price of generic drugs **remains at the regulated maximum price** ²⁹.
 - Therefore, many manufacturers of generic drugs steadily enter the market in South Korea **with expecting substantial profits**, even several years after the date the first generic entered the market.
 - In other words, **the order-of-entry effect** of generic drugs, which is commonly observed in other markets, **is marginal** in South Korea.

Limitations

- First, this study used drug approval data provided by the MFDS that **do not contain information on drug utilization**.
 - Thus, we could not assess the **market share of each manufacturer** in the statin market. However, it is realistic to assume that the market share of statins would be concentrated among few players, including the original drug manufacturers ^{1,2}.
 - Similarly, this study could not access the **price information of drugs**. The price of drugs, especially generic drugs, is closely related to market competition. However, it is noteworthy that incentives to lower the regulated maximum price of generic drugs do not exist in the South Korean market ²⁹.
- Second, this study used KISVALUE to capture the current information on size and assumed that **the size of the company does not change during the study period**.
 - However, few manufacturers might grow or shrink in size.
- Lastly, this study was **conducted on only two statins**.
 - Therefore, the results should be interpreted with caution. However, it is realistic to assume that the same principles demonstrated in this study might be applicable to other drug classes.

- We confirmed that many local manufacturers entered the generic market in South Korea.
- Furthermore, we noted that generics produced by small-sized manufacturers entered the market steadily, even after the market had matured with a number of generics. In other words, the order-of-entry effect, which is commonly observed in other markets, is marginal in the South Korean market.
- This phenomenon is mainly explained by the rare price competition among generic manufacturers. Therefore, latecomers could reasonably expect profit when they market the drug late.
- To enhance market competition, the South Korean government could introduce several options to establish markets with price competition among generic manufacturers.

Thank you