



## Therapeutic Duplication as a Medication Error Risk in Fixed-Dose Combination Drugs for Dyslipidemia: A Nationwide Study

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### ABSTRACT

**Background & Objectives:** Fixed-dose combinations (FDCs) offer advantages in adherence and cost-effectiveness compared to free combinations (FCs), but they can also complicate the prescribing process, potentially leading to therapeutic duplication (TD). This study aimed to identify the prescribing patterns of FDCs for dyslipidemia and investigate their associated risk of TD. **Methods:** This was a retrospective cohort study involving drugs that included statins, using Health Insurance Review & Assessment Service-National Patient Sample (HIRA-NPS) data from 2018. The unit of analysis was a prescription claim. The primary outcome was TD. The risk ratio of TD was calculated and adjusted for patient, prescriber, and the number of cardiovascular drugs prescribed using a multivariable Poisson model. **Results:** Our study included 252,797 FDC prescriptions and 515,666 FC prescriptions. Of the FDC group, 46.52% were male patients and 56.21% were aged 41 to 65. Ezetimibe was included in 71.61% of the FDC group, but only 0.25% of the FC group. TD occurred in 0.18% of the FDC group, and the adjusted risk ratio of TD in FDC prescriptions compared to FC was 6.44 (95% CI 5.30-7.82). **Conclusions:** Prescribing FDCs for dyslipidemia was associated with a higher risk of TD compared to free combinations. Despite the relatively low absolute prevalence of TD, the findings underline the necessity for strategies to mitigate this risk when prescribing FDCs for dyslipidemia. Our study suggests the potential utility of Clinical Decision Support Systems and standardizing nomenclature in reducing medication errors, providing valuable insights for clinical practice and future research.

**KEYWORDS:** Drug prescriptions, dyslipidemias, fixed-dose combination drugs, medication errors, therapeutic duplication

Dyslipidemia, a major risk factor for cardiovascular disease, has rapidly increased in Korea from 1.5 million in 2002 to 11.6 million in 2018.<sup>1-3)</sup> The upward trend is concerning since approximately 75% of dyslipidemia patients are affected by comorbidities such as hypertension or diabetes, which complicate their management and treatment.<sup>3,4)</sup> As a result, the economic burden of chronic diseases in an aging population has risen steeply.<sup>5-7)</sup>

To reduce the health and economic burden of chronic diseases, it is essential to develop efficient treatment plans that

incorporate proper medication utilization.<sup>8)</sup> One such approach involves the use of fixed-dose combinations (FDCs), which have gained popularity for managing dyslipidemia and related comorbidities.<sup>9,10)</sup> FDCs combine multiple ingredients into a single pill, thereby reducing pill burden and enhancing medication adherence.<sup>9,11)</sup> Improved adherence can lead to better health outcomes and potentially lower healthcare costs associated with non-adherence, such as hospitalizations or complications from uncontrolled disease.<sup>12,13)</sup>

However, safety concerns remain with the use of FDCs,

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particularly with regards to potential medication errors such as therapeutic duplication (TD), which occurs when the same or pharmacologically equivalent agents are prescribed concurrently to a patient.<sup>14)</sup> TD can result in limited efficacy, increased adverse events, overuse, and higher healthcare costs.<sup>15,16)</sup> A retrospective study in Ireland revealed an increased risk of TD associated with FDCs for hypertension; however, the risks associated with FDCs for dyslipidemia have not been well-explored in the existing literature.<sup>14)</sup> FDCs for dyslipidemia often include medications for comorbidities such as hypertension and diabetes, which can further complicate the prescription process.<sup>17)</sup>

To ensure patient safety and make informed prescribing decisions, it is essential to have a comprehensive understanding of the association between FDCs and TD. Therefore, we aimed to investigate the utilization patterns of FDCs and free combinations (FCs, individual agents prescribed separately) among statin users and to determine whether using FDCs for dyslipidemia is associated with TD compared to FCs, adjusting for confounders such as age, sex, and the number of cardiovascular drugs.

## Methods

### Data source and study design

This retrospective cohort study used claims data from the Health Insurance Review & Assessment Service-National Patient Sample (HIRA-NPS) for 2018. The dataset represented approximately 98% of the Korean population and included reimbursement claims for national health insurance (NHI), medical aid (MedAid), and veterans' welfare program (VWP). HIRA-NPS data was generated by annual extraction of claims data using stratified sampling methods.<sup>18)</sup>

The study was exempt from review by the Institutional Review Board of Chung-Ang University, with IRB approval number 1041078-202210-HR-244.

### Exposure and potential confounders

FDC prescriptions were defined as those with a statin-based FDC listed on the national beneficiary formulary. (Supplementary Table 1) The same agents as an FDC but prescribed separately were defined as an FC. The FDC group consisted of prescriptions with FDCs, while the remaining prescriptions with FCs were classified into the FC group.

The exposure of interest was the prescription of FDCs for

dyslipidemia. Characteristics such as age, sex, insurance, healthcare facility, specialty, geographic region, and the number of cardiovascular drugs were identified. Variables including age, sex, healthcare facility type, and the number of cardiovascular drugs prescribed were considered potential confounders in the analysis.<sup>14)</sup> The number of cardiovascular drugs included drugs from the following classes, as classified by ATC code: lipid-lowering agents (C10) excluding statins, antihypertensives (C02, C03, C07, C08, C09), antithrombotic drugs (B01), diabetes medications (A10), and other cardiovascular drugs (C01, C04, C05).

### Outcome

The outcome was TD of statins, defined as the presence of two or more different statins in the same prescription. The duplication of the same statin by prescribing multiple doses was not considered TD.

### Statistical methods

The unit of analysis was an individual prescription claim. Descriptive statistics, t-tests for numerical values, and chi-square tests for categorical values were used in analyzing the data. The prevalence of FDC use and TD were expressed as percent (%). Adjusted risk ratios (RR) of TD and 95% confidence intervals (CI) were obtained using a multivariable Poisson model adjusted for age, sex, healthcare facility type, and the number of cardiovascular drugs prescribed. A p-value of less than 0.05 was considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Descriptive statistics

This study analyzed 19,434,191 prescriptions, with 18,976,798 prescriptions for outpatients and 1,223,066 prescriptions containing statins. The final study population consisted of 768,463 prescriptions issued to 129,171 patients; 252,797 prescriptions were allocated to the FDC group and the remaining 515,666 to the FC group (Fig. 1).

There were statistically significant differences between the FDC and FC groups in age, sex, insurance, healthcare facility, specialty, and region. Compared to the FC group, the FDC group had a lower rate of clinic utilization (FDC 64.8% vs. FC 72.4%) and a lower percentage of prescriptions from

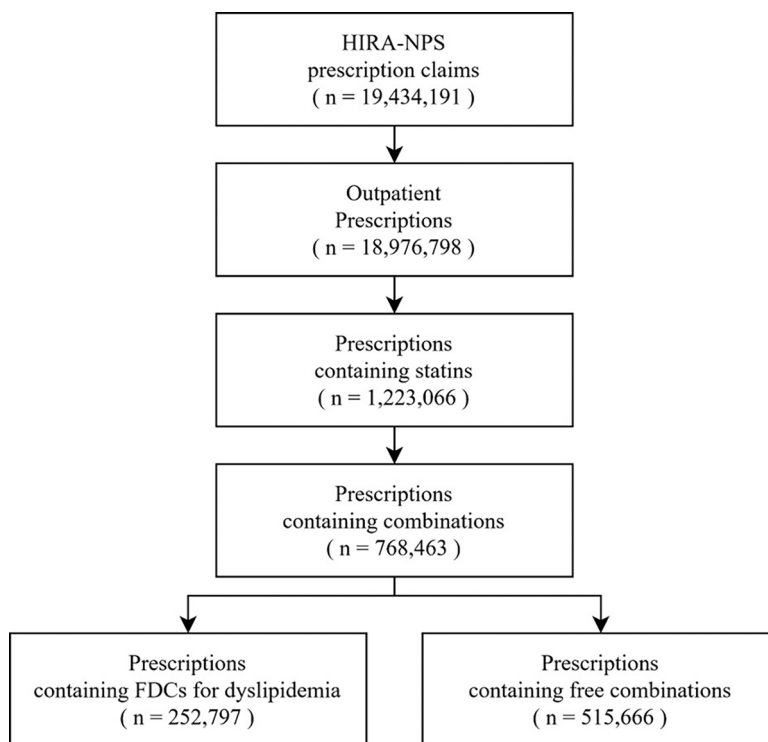


Fig. 1. Data selection flowchart.

HIRA-NPS, health insurance & review assessment service-national patient sample; FDC, fixed-dose combination

general practitioners (FDC 16.2% vs. FC 19.4%) (Table 1).

The utilization rate of three-agent FDCs was low, comprising only 0.86% of the total. In comparison, three-agent FCs accounted for 6.49% of prescriptions. Among FDCs for dyslipidemia, the most prescribed combinations were statin/lipid-lowering agents (185,260 prescriptions), followed by statin/antihypertensives (67,219 prescriptions) and statin/antidiabetics (444 prescriptions). In contrast, FCs more frequently contained statin/antihypertensives or statin/antidiabetics than statin/lipid-lowering agents. (Table 2)

#### Therapeutic duplication associated with fixed-dose combinations

In the FDC group, TD was identified in 466 out of a total of 252,797 prescriptions, yielding an incidence rate of 0.18%. In contrast, the FC group had a prevalence of 0.02%, with TD found in 119 out of 515,666 prescriptions. The crude RR for experiencing TD with FDCs compared to FCs stood at 7.99 (95% CI, 6.53-9.77). After accounting for potential confounding factors, the adjusted RR was determined to be 6.44 (95% CI, 5.30-7.82).

In the “65 or younger” group, TD was found in 0.18% of

FDC prescriptions and 0.02% of FC prescriptions, leading to the adjusted RR of 9.62 (95% CI, 7.02-13.19). In the “66-75 years” age group, TD occurred in 0.18% of FDC prescriptions and 0.03% of FC prescriptions, resulting in an adjusted RR of 5.52 (95% CI, 3.86-7.90). The “76 or older” group had TD in 0.21% of FDC prescriptions and 0.04% of FC prescriptions, with the adjusted RR of 3.96 (95% CI, 2.86-5.60).

Males had TD in 0.21% of FDC prescriptions and 0.03% of FC prescriptions, with an adjusted RR of 5.37 (95% CI, 4.28-6.76). Females showed TD in 0.16% of FDC prescriptions and 0.02% of FC prescriptions, resulting in an adjusted RR of 8.13 (95% CI, 5.76-11.49). In tertiary care facilities, prevalence of TD was 0.76% of FDC prescriptions and 0.07% of FC prescriptions, resulting in an adjusted RR of 9.88 (95% CI, 6.50-15.01). In secondary care facilities, TD occurred in 0.19% of FDC prescriptions and 0.04% of FC prescriptions, with an adjusted RR of 4.77 (95% CI, 3.52-6.47). In primary care facilities, TD was found in 0.11% of FDC prescriptions and 0.02% of FC prescriptions, with an adjusted RR of 6.05 (95% CI, 4.51-8.11).

Among prescriptions with statin/lipid-lowering agents, TD was observed in 0.10% of FDC prescriptions and 0.07% of

**Table 1.** Descriptive characteristics of included prescription prescriptions

Characteristics	FDC		FC		p-value
	Prescriptions	(%)	Prescriptions	(%)	
Total*	252,797	(100.0)	515,666	(100.0)	
Age (years)					<0.001
0-40	8,010	(3.2)	9,979	(1.9)	
41-65	142,107	(56.2)	258,643	(50.2)	
66-75	63,231	(25.0)	142,499	(27.6)	
76-	39,449	(15.6)	104,545	(20.3)	
Sex					0.033
Male	117,605	(46.5)	238,561	(46.3)	
Female	135,192	(53.5)	277,105	(53.7)	
Insurance					<0.001
NHI	232,378	(91.9)	478,026	(92.7)	
MedAid + VWP	20,419	(8.1)	27,640	(7.3)	
Healthcare Facility					<0.001
Tertiary hospital	22,292	(8.8)	28,027	(5.4)	
General hospital	45,329	(17.9)	66,426	(12.9)	
Hospital	16,897	(6.7)	30,850	(6.0)	
Clinic	163,864	(64.8)	373,368	(72.4)	
Public health center	4,415	(1.8)	16,995	(3.3)	
Specialty					<0.001
Internal medicine	178,519	(70.6)	356,230	(69.1)	
General practitioner	40,896	(16.2)	99,804	(19.4)	
Family medicine	10,939	(4.3)	19,998	(3.9)	
Neurology	10,429	(4.1)	16,354	(3.2)	
General surgery	3,523	(1.4)	7,149	(1.4)	
Neurosurgery	3,199	(1.3)	4,777	(0.9)	
Others	5,292	(2.1)	11,354	(2.2)	
Region					<0.001
Metropolitan city <sup>†</sup>	127,562	(50.5)	234,036	(45.4)	
Province <sup>‡</sup>	125,235	(49.5)	281,630	(54.6)	

\*Issued to 129,171 patients

<sup>†</sup>Metropolitan city included Seoul, Busan, Incheon, Daegu, Gwangju, Daejeon, Ulsan, and Sejong

<sup>‡</sup>Province included Gyeonggi-do, Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyung-sangbuk-do, Gyung-sangnam-do, and Jeju-do

FDC, fixed dose combination; FC, free combination; NHI, national health insurance; MedAid, medical aid; VWP, veterans welfare program

FC prescriptions, leading to an adjusted RR of 1.67 (95% CI, 0.81-3.44). Prescriptions with statin/antihypertensives had TD in 0.50% of FDC prescriptions and 0.03% of FC prescriptions, resulting in an RR of 14.93 (95% CI, 12.06-18.49). In a

notable finding, prescriptions with statin/antidiabetics showed TD in 3.15% of FDC prescriptions and 0.01% of FC prescriptions, leading to an adjusted RR of 388.78 (95% CI, 215.39-701.73) (Table 3).

**Table 2.** Drug characteristics of included prescriptions

Drug Characteristics	FDC		FC		p-value
	Prescriptions	(%)	Prescriptions	(%)	
Total	252,797	(100.0)	515,666	(100)	
Number of active ingredients in combination					<0.001
2	250,628	(99.1)	482,201	(93.5)	
3	2,169	(0.9)	33,465	(6.5)	
Type of combination					
Statin/lipid lowering agents*	185,260	(73.3)	10,223	(2)	<0.001
Rosuvastatin, ezetimibe	137,071	(54.2)	566	(0.1)	
Simvastatin, ezetimibe	25,692	(10.2)	37	(0)	
Atorvastatin, ezetimibe	18,074	(7.2)	689	(0.1)	
Rosuvastatin, omega-3-acid ethyl ester	3,071	(1.2)	9,404	(1.8)	
Simvastatin, fenofibrate	1,355	(0.5)	607	(0.1)	
Statin/antihypertensives*	67,219	(26.6)	352,248	(68.3)	<0.001
Atorvastatin, amlodipine	24,133	(9.6)	170,769	(33.1)	
Rosuvastatin, telmisartan	16,241	(6.4)	31,396	(6.1)	
Atorvastatin, irbesartan	8,790	(3.5)	7,653	(1.5)	
Rosuvastatin, olmesartan	5,839	(2.3)	24,641	(4.8)	
Pitavastatin, valsartan	3,518	(1.4)	7,287	(1.4)	
Rosuvastatin, valsartan	2,518	(1)	45,507	(8.8)	
Rosuvastatin, candesartan	2,348	(0.9)	15,545	(3)	
Rosuvastatin, losartan, amlodipine	1,579	(0.6)	12,467	(2.4)	
Rosuvastatin, fimasartan	1,462	(0.6)	9,956	(1.9)	
Rosuvastatin, telmisartan, amlodipine	590	(0.2)	21,015	(4.1)	
Rosuvastatin, amlodipine	229	(0.1)	111,500	(21.6)	
Statin/antidiabetics*	444	(0.2)	253,622	(49.2)	<0.001
Rosuvastatin, gemigliptin	312	(0.1)	13,457	(2.6)	
Rosuvastatin, metformin	78	(0)	107,464	(20.8)	
Atorvastatin, metformin	54	(0)	155,945	(30.2)	

\* The sum of subgroups may exceed the total because of duplicates  
FDC, fixed-dose combination; FC, free combination

## Discussion

This study aimed to investigate the risk of TD when prescribing FDCs for treating dyslipidemia in a Korean healthcare setting. One of the most alarming findings of our study is the significantly increased risk of TD associated with prescribing FDCs for dyslipidemia. Our data indicate a sixfold higher risk when compared to individual drug prescriptions. Although the overall absolute risk of duplication associated

with FDCs was relatively low (0.18%), the increase in relative risk was considerable. Our results align with a previous Irish retrospective study, which also reported a twofold increased risk in TD when prescribing FDCs for hypertension.<sup>14)</sup> In the following sections, we will delve into the limitations of the Drug Utilization Review (DUR) system, complexities in dosing schedules, and other contributing factors.

In Korea, a nationwide Clinical Decision Support System (CDSS) called DUR has been implemented. The system

**Table 3.** Risk ratio for therapeutic duplication according to fixed-dose combination use

Characteristics	FDC			FC			Crude RR	95% CI	Adjusted RR*	95% CI
	Prescriptions	TD	(%)	Prescriptions	TD	(%)				
Overall population	252,797	466	(0.18)	515,666	119	(0.02)	7.99	6.53-9.77	6.44	5.30-7.82
Subgroup analyses										
Age (years)										
0-65	150,117	269	(0.18)	268,622	41	(0.02)	11.74	8.45-16.31	9.62	7.02-13.19
66-75	63,231	114	(0.18)	142,499	37	(0.03)	6.94	4.79-10.06	5.52	3.86-7.90
76-	39,449	83	(0.21)	104,545	41	(0.04)	5.37	3.69-7.80	3.96	2.81-5.60
Sex										
Male	117,605	250	(0.21)	238,561	72	(0.03)	7.04	5.42-9.15	5.37	4.28-6.76
Female	135,192	216	(0.16)	277,105	47	(0.02)	9.42	6.87-12.91	8.13	5.76-11.49
Healthcare settings										
Tertiary care	22,292	170	(0.76)	28,027	21	(0.07)	10.18	6.47-16.00	9.88	6.50-15.01
Secondary care	61,366	114	(0.19)	97,152	35	(0.04)	5.16	3.53-7.53	4.77	3.52-6.47
Primary care	169,139	182	(0.11)	390,487	63	(0.02)	6.67	5.01-8.88	6.05	4.51-8.11
Type of combinations										
Statin/lipid lowering agents										
Yes	185,260	188	(0.10)	10,223	7	(0.07)	1.48	0.70-3.15	1.67	0.81-3.44
No	67,537	278	(0.41)	505,443	112	(0.02)	18.58	14.92-23.13	17.57	14.20-21.74
Statin/antihypertensives										
Yes	67,219	335	(0.50)	352,248	104	(0.03)	16.88	13.55-21.03	14.93	12.06-18.49
No	185,578	131	(0.71)	163,418	15	(0.01)	7.69	4.51-13.12	6.13	3.83-9.81
Statin/antidiabetics										
Yes	444	14	(3.15)	253,622	33	(0.01)	242.34	129.70-452.78	388.78	215.39-701.73
No	252,353	452	(0.18)	262,044	86	(0.03)	5.46	4.33-6.87	3.22	2.59-4.00

\*Adjusted for age, sex, healthcare facility type, and the number of cardiovascular drugs  
FDC, fixed-dose combination; TD, therapeutic duplication; RR, risk ratio; CI, confidence interval

provides real-time alerts to flag potential TD during the prescribing process.<sup>19,20</sup> In 2018, the period covered by our study, FDCs were absent from the DUR system's checklist for TD.<sup>21</sup> As a result, despite the system's capability to alert potential TD, it could not provide alerts for duplications involving FDCs. This may have contributed to the observed high RR of TD in our study. FDCs were added to the checklist in 2020, after our study period.<sup>22</sup>

In our analysis, FDCs containing statins and lipid-lowering agents like ezetimibe were not associated with a higher risk of TD, with a relative risk (RR) of 1.67 (95% CI, 0.81-3.44). In contrast, FDCs that combined statins with either antihypertensive or antidiabetic agents were associated with a significantly

higher risk of TD, with RRs of 14.93 and 388.78, respectively. Based on these results, we can elucidate that the risk of TD may be influenced by complexity due to both similar brand names and multiple dosing options of certain FDCs. For FDCs like statin/ezetimibe, the 10 mg fixed dose of ezetimibe streamlines prescriber choices, reducing complexity.<sup>17</sup> In contrast, FDCs that include antihypertensive or antidiabetic agents have adjustable doses for all components, thereby increasing the complexity and likelihood of prescribing errors.<sup>23,24</sup> In case of amlodipine and rosuvastatin, both of which are available in 5 and 10 mg doses, a prescriber could erroneously substitute an FDC containing telmisartan/amlodipine for one containing telmisartan/rosuvastatin, especially if prescriptions are written

by brand name (for example, *Misartan Twin Tab* vs. *Misartan Star Tab*) instead of by generic name (for example, telmisartan/amlodipine vs. telmisartan/rosuvastatin). This demonstrates how complex dosing options contribute to an elevated risk of TD.

Aside from these systemic factors, individual factors, including prescriber experience, also contribute to the risk. Differences observed among drug type subgroups might correlate with the prescriber's experience with specific FDCs. A lack of experience and training in prescribers can contribute to medication errors, and this includes errors in prescribing FDCs.<sup>25)</sup> Given the complexity of dosing options in some FDCs, less experienced prescribers might be more likely to make errors, including TD, when prescribing these combinations. This study observed variation in the RR of TD across different drug combinations, with distinct prescription counts associated with each. Although a causal relationship between prescription count and RR cannot be directly inferred from this study, the data suggests a possible interaction that warrants further investigation.

In addition, the nomenclature of the medications can also present its own set of challenges. Another contributing factor to the increased risk of TD could be the prevalence of Look-Alike Sound-Alike (LASA) drugs, particularly when drugs are prescribed by their brand names. Prescribing drugs, including FDCs, by brand names can increase the complexity of the FDCs and potentially contribute to an increased risk of prescribing errors due to orthographic and phonological similarities between drug names.<sup>26-29)</sup> This problem may be exacerbated when similar components are part of multiple drug names.

An example of confusion due to similar brand names in Korea is medications that contain the syllable '*Misartan*,' which appears in Telmisartan/Rosuvastatin 80/5mg tablets and Telmisartan/Amlodipine 80/5 mg tablets.<sup>17)</sup> Shared naming elements can create a high risk for prescribing errors. A case in point is a report from the Korean Pharmacists Association's Community Patient Safety Center, which documented an unintentional prescribing error. In this case, '*Misartan Star Tab 80/5 mg*' (Telmisartan/Rosuvastatin 80/5 mg) and Rosuvastatin 5 mg were both prescribed in the same prescription.<sup>30)</sup> This case underscores the potential for confusion given the phonological and orthographic similarities between these drug names and emphasizes the importance of precise prescribing practices to avoid potential TD. One of the underlying issues

contributing to such errors is the lack of a review process for LASA problems in brand names in Korea. Generic drugs can have brand names, and there is no review process to minimize confusion with LASA drugs when a new brand name is registered.<sup>31,32)</sup>

FDCs improve medication compliance, cost-effectiveness, and patient convenience.<sup>33-35)</sup> A national drug utilization study in Korea showed a significant increase in FDC usage, indicating their appeal to prescribers.<sup>36)</sup> In this study, we found that FDCs were the preferred choice for prescribing a combination of statin and ezetimibe. Statin/ezetimibe FDCs, with 180,837 prescriptions, were prescribed significantly more often than the corresponding FCs, which had 1,292 prescriptions. FDCs might be preferred in this context because ezetimibe is typically used with a statin without the need for dose adjustments, making these combinations a standard treatment regimen for dyslipidemia.<sup>1,4,37,38)</sup>

Additionally, our study found differences in FDC prescribing practices across healthcare settings and age groups. In tertiary care facilities, the rates of FDC and FC prescriptions were similar. This contrasts with primary and secondary care settings, where FCs were more commonly prescribed. This could imply a more active adoption of FDCs in tertiary care facilities. Similarly, FDC prescriptions were more common in the age group younger than 65 years. This could suggest that newly diagnosed patients are more likely to be started on FDCs, as switching from existing medications might be less preferred. Given these additional observations, future research could benefit from a deeper exploration into how healthcare settings and patient demographics influence the prescription of FDCs for dyslipidemia.

Our analysis unveils multiple factors that contribute to the risk of TD when prescribing FDCs for dyslipidemia. These factors include brand names, the dosing complexity of certain FDCs to the absence of a comprehensive TD checklist in the DUR system, and diverse experience levels among prescribers. To address these interrelated challenges, regulatory agencies could implement more rigorous review processes for drugs with similar names to prevent medication errors. The United States Food and Drug Administration (US FDA) implemented a brand name review system, and national efforts were reported to reduce medication errors.<sup>39,40)</sup> While not directly reviewing brand names, the Ministry of Food and Drug Safety (MFDS) of Korea mandated new FDCs to include the names of up to three active ingredients in the product name in

2022.<sup>41)</sup> Future research could explore whether these nomenclature revisions have contributed to safer drug use. Another solution could be to display generic names, such as INNs, on labels.<sup>27)</sup> INNs are generic names recognized internationally and assigned by the World Health Organization (WHO).<sup>42)</sup> A study conducted in a simulated setting demonstrated that using generic name labeling resulted in a lower number of errors, although the difference was not statistically significant when compared to using brand name labeling.<sup>43)</sup>

CDSS alerts could improve patient safety by helping professionals prevent medication errors.<sup>44)</sup> A study that examined the impact of incorporating TD alerts into Korea's DUR system found an 89% absolute reduction in TD cases involving single-agent nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>20)</sup> Future studies should assess whether the inclusion of FDCs in the DUR system has led to a reduction in TD. This would not only evaluate the efficacy of the current DUR system but also inform clinical practice in a more comprehensive manner.

To further minimize the risks of TD, it is essential to focus on prescriber education and training. Given the complexity associated with dosing certain FDCs, less experienced prescribers may be potentially more prone to errors. Prescribers should be aware of the inherent risks of TD associated with FDCs and employ strategies to minimize such medication errors. This includes utilizing CDSS for systemic duplication warnings and promoting the use of INNs over brand names. Moreover, improving the evaluation process for LASA drugs can further reduce prescribing complexity and prevent medication errors.

While our study provides insights into the risks tied to FDC prescriptions for managing dyslipidemia, certain limitations should be kept in mind when interpreting our findings. First, the claims data we used does not confirm whether the prescribed medication was administered to the patient. Second, due to the inherent limitations of the claims database, prescriptions intentionally containing two statins to switch treatment could not be differentiated from TD. Because we considered two or more statins in a prescription as TD, the TD may have been overestimated. Third, our analysis focused on the prescriptions itself and did not account for patients' medical histories. Consequently, there is a possibility that the risk of TD may be overestimated due to these unconsidered variables.

Despite these limitations, our study stands as the first to delve into the nature of FDC prescriptions for dyslipidemia and to quantify the relative risk for TD. The robustness of our subgroup analysis outcomes emphasizes the importance of careful FDC prescription practices in the management of dyslipidemia, bearing significant implications for patient safety and clinical decision-making.

While our findings are based on the Korean healthcare system, the mechanisms contributing to TD, such as complex dosing options and prescriber experience, may not be unique to this setting. Therefore, our study's insights could have broader applicability, extending to different healthcare systems. Future research should investigate the safety and efficacy of FDCs in diverse healthcare settings and examine the influence of improved labeling and nomenclature practices in reducing medication errors. By implementing these measures, healthcare professionals can ensure that patients receive optimal care while minimizing the risk of medication errors associated with FDCs.

## Conclusion

Our study reveals a significantly higher risk of TD when prescribing FDCs for dyslipidemia compared to FCs, due to factors like dosing complexity and LASA drug names. Despite recent updates to Korea's DUR system, more comprehensive measures are needed. We recommend that prescribers use systemic duplication warnings and favor INNs over brand names. Stricter drug naming regulations could also reduce LASA errors. Future research should focus on evaluating the efficacy of these interventions.

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## Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.



## References

- Committee of Clinical Practice Guideline. Korean guidelines for the management of dyslipidemia. 5th ed. Seoul, Korea: The Korean Society of Lipid and Atherosclerosis, 2022.
- Arnett DK, Blumenthal RS, Albert MA, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation* 2019;140(11):e596-e646.
- Cho SMJ, Lee H, Lee H-H, *et al.* Dyslipidemia fact sheets in Korea 2020: An analysis of nationwide population-based data. *J Lipid Atheroscler* 2021;10(2):202-9.
- Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk: The task force for the management of dyslipidaemias of the european society of cardiology (ESC) and european atherosclerosis society (EAS). *Eur Heart J* 2019;41(1): 111-88.
- World report on ageing and health. Geneva: World Health Organization, 2015.
- Kim TE, Lee RG, Park SY, Oh IH. Measuring trends in the socioeconomic burden of disease in Korea, 2007-2015. *J Prev Med Public Health* 2022;55(1):19-27.
- Primary medical chronic disease management pilot project guide (translated title). 3rd ed. Sejong, Korea: Ministry of Health and Welfare, 2021.
- Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization, 2003.
- Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *Am J Med* 2007;120(8):713-9.
- Chung S, Ko Y-G, Kim JS, *et al.* Effect of fixed-dose combination of ARB and statin on adherence and risk factor control: The randomized FIXAR study. *Cardiol J* 2022;29(5):815-23.
- Castellano JM, Sanz G, Peñalvo JL, *et al.* A polypill strategy to improve adherence: Results from the focus project. *J Am Coll Cardiol* 2014;64(20):2071-82.
- Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Affairs* 2011;30(1):91-9.
- Poulter NR, Borghi C, Parati G, *et al.* Medication adherence in hypertension. *Journal of Hypertension* 2020;38(4):579-87.
- Moriarty F, Bennett K, Fahey T. Fixed-dose combination antihypertensives and risk of medication errors. *Heart* 2019;105(3): 204-9.
- Yang S-Y, Jang S, Kwon S, *et al.* Effectiveness of the pilot project for polypharmacy management (translated title). *Health and Social Welfare Review* 2020;40(3):563-91.
- Koo H, Lee JW, Choi HE, Je NK, Jeong KH. Class duplication prescriptions in patients taking fixed-dose combination antihypertensives (translated title). *Korean J Clin Pharm* 2022;32(2):125-32.
- National health insurance reimbursement medicine list (translated title). Sejong, Korea: Ministry of Health and Welfare, 2018.
- Kim L, Kim J-A, Kim S. A guide for the utilization of health insurance review and assessment service national patient samples. *Epidemiol Health* 2014;36:e2014008.
- Drug utilization review. Wonju, Korea: Health Insurance Review & Assessment Service; 2013. Available from: [https://www.hira.or.kr/eng/news/01/\\_icsFiles/afieldfile/2013/10/15/brochure\\_6.DUR.pdf](https://www.hira.or.kr/eng/news/01/_icsFiles/afieldfile/2013/10/15/brochure_6.DUR.pdf). Accessed September 11, 2023.
- Jung SY, Jang EJ, Choi S, *et al.* Effect of a nationwide real-time drug utilization review system on duplicated nonsteroidal antiinflammatory drug prescriptions in Korea. *Arthritis Care Res (Hoboken)* 2020;72(10):1374-82.
- Therapeutic duplicate medication product list December 1, 2018 (translated title). Wonju, Korea: Health Insurance and Assessment Service, 2018.
- Notice on DUR review of therapeutic duplication for combination medicines and information on discontinued production, import, and supply of medicines (translated title). Wonju, Korea: Health Insurance Review & Assessment Service, 2020.
- Velo GP, Minuz P. Medication errors: Prescribing faults and prescription errors. *Br J Clin Pharmacol* 2009;67(6):624-8.
- Institute of Medicine (US) Committee on Quality of Health Care in America. To err is human: Building a safer health system. Washington (DC): National Academies Press (US), 2000.
- Tully MP, Ashcroft DM, Dorman T, Lewis PJ, Taylor D, Wass V. The causes of and factors associated with prescribing errors in hospital inpatients. *Drug Saf* 2009;32(10):819-36.
- Lambert BL, Chang K-Y, Lin S-J. Effect of orthographic and phonological similarity on false recognition of drug names. *Soc Sci Med* 2001;52(12):1843-57.
- Lambert BL, Lin S-J, Tan H. Designing safe drug names. *Drug Saf* 2005;28(6):495-512.
- Aronson JK. Medication errors resulting from the confusion of drug names. *Expert Opin Drug Saf* 2004;3(3):167-72.
- Bramley DE. The ability of anaesthetists to identify generic medications from trade names. *Anaesth Intensive Care* 2009;37(4): 624-9.
- Kim S-J. Patient safety incident reporting status and pharmacist intervention cases (translated title). In: Korean Pharmaceutical Association Patient Safety and Medication Administration Web Symposium, Seoul, Korea, September 24, 2022.
- Lee JH, Cho CA, Lee YJ, *et al.* Proposals for nomenclature of generic drugs to prevent medication errors. *J Kor Soc Health-Syst Pharm* 2008;25(2):159-68.
- Kim JE, Lim SC. A study on correlations between medication error and prescription by trade name. *Yakhak Hoeji* 2019;63(4):238-46.
- Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A meta-analysis. *Hypertension* 2010;55(2):399-407.
- Pappa E, Rizos CV, Filippatos TD, Elisaf MS. Emerging fixed-dose combination treatments for hyperlipidemia. *J Cardiovasc Pharmacol Ther* 2019;24(4):315-22.
- Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: A meta-analysis of health care costs and adherence. *J Clin Hypertens (Greenwich)* 2011;13(12):898-909.
- Lee Y, Shin J, Kim Y, Kim D-S. Consumption of single products versus fixed-dose combination medicines for hypertension and hyperlipidemia during 2015-2019 in South Korea. *PLOS ONE* 2021;16(12):e0259467.
- Label: Zetia-ezetimibe tablet. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=174e45e0-45bb-48b7-9e60-8f6cfd22bb>. Accessed September 11, 2023.
- Grundy SM, Stone NJ, Bailey AL, *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/

- PCNA guideline on the management of blood cholesterol: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation* 2019;139(25): e1082-143.
39. Best practices in developing proprietary names for human prescription drug products; guidance for industry. Silver Spring, MD: U.S. Food and Drug Administration, 2020.
  40. Are national efforts to reduce drug name confusion paying off? ISMP Medication Safety Alert. 2018 November 29:1-6.
  41. Lee SJ, Moon HJ, Kim YS, *et al*. Drug product name assignment casebook (translated title). 4th ed. Cheongju, Korea: Ministry of Food and Drug Safety, 2022.
  42. INN and Classification of Medical Products. Guidance on the use of international nonproprietary names (INNs) for pharmaceutical substances. Switzerland: World Health Organization (WHO); 2017. Available from: <https://www.who.int/publications/m/item/guidance-on-the-use-of-inns>. Accessed September 11, 2023.
  43. Garcia BH, Elenjord R, Bjornstad C, Halvorsen KH, Hortemo S, Madsen S. Safety and efficiency of a new generic package labelling: A before and after study in a simulated setting. *BMJ Qual Saf* 2017;26(10):817-23.
  44. Kuperman GJ, Bobb A, Payne TH, *et al*. Medication-related clinical decision support in computerized provider order entry systems: A review. *J Am Med Inform Assoc* 2007;14(1):29-40.