several years after FDA approval, and we excluded continuation-in-part and divisional patents because they may not have identical specifications. We extracted patents listed on these drugs in the FDA's *Approved Products With Therapeutic Equivalence Evaluations* (Orange Book) from January 1, 2000, to December 31, 2021, and categorized each patent as original or continuation using the Google Patents Public Data Sets on Google BigQuery. We calculated the ratio of original and continuation patents per brand-name drug approval during each year. A similar analysis was conducted for litigated patents, based on litigation brought by either the drug manufacturer or generic competitor. Litigated patents were identified using Lex Machina, a commercial database covering 2000-2022.

Analyses were descriptive and completed in Excel version 16.

Results | From 2000 to 2015, the FDA approved 1421 new brand-name drugs. Manufacturers listed with the FDA 3967 distinct patents on these drugs through 2021 (2110 [53%] original; 1857 [47%] continuation). The ratio of the number of FDA-listed patents per drug increased from 1.9 for those approved in 2000 to 3.2 for those approved in 2015 (68% relative increase). While the ratio of the number of original patents per approval increased by 15% from 1.3 for drugs approved in 2000 to 1.5 for drugs approved in 2015, the ratio of continuation patents increased 200% from 0.6 for drugs approved in 2000 to 1.8 for drugs approved in 2015 (**Figure**, A).

There were 1936 litigated patents (985 [51%] original; 951 [49%] continuation). While the ratio of the number of litigated original patents per approval increased by 63% from 0.38 for drugs approved in 2000 to 0.62 for drugs approved in 2015, the ratio of litigated continuation patents increased 213% from 0.22 for drugs approved in 2000 to 0.69 for drugs approved in 2015 (Figure, B).

Discussion | Brand-name drug manufacturers listed with the FDA an increasing number of continuation patents on drugs approved from 2000 to 2015. More continuation patents mean that generic firms seeking to challenge existing protections on brand-name drugs must contest and potentially litigate more patents. Continuation patents are typically invalidated at a higher rate than patents on active ingredients.[2] However, lawsuits brought by brand-name firms on patents listed with the FDA can earn 30-month stays on generic drug approval even if these lawsuits eventually fail. Study limitations include that the frequency of successful challenges on litigated continuation patents was not examined.

These findings suggest that continuation patents are becoming increasingly common in drug patent thickets, likely delaying or deterring generic competition,[2,5] and thus potentially contributing to delays in patient access to generic medications and increases in health care spending.

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COMMENT & RESPONSE

Treating Coronary Artery Disease With Treat-to-Target or High-Intensity Statin

To the Editor A recent article[1] investigated whether a treat-to-target strategy was noninferior to a strategy of high-intensity statin use for 3-year clinical outcomes in patients with coronary artery disease. We have some concerns about this study's research design.

During the 3-year follow-up, the percentage of high-intensity statin treatment increased from 47% to 56% in the treat-to-target strategy group but decreased from 100% to 89% in the high-intensity statin treatment group. This means that almost half of the patients received high-intensity

statin treatment in the treat-to-target group. While the effect of statin treatment on reducing clinical events is not solely caused by suppression of low-density lipoprotein cholesterol (LDL-C) level, and the authors adjusted for confounders, genetic factors such as apolipoprotein E gene polymorphisms may contribute to coronary artery disease and type 2 diabetes.[2,3] Individual variations in the response to statin treatment may be closely associated with genetic factors, and the recommendation of a treat-to-target LDL-C strategy for patients with cardiovascular disease should be made after understanding the magnitude of genetic contribution to the ability of LDL-C reduction and prevention of cardiovascular events.

Additionally, this study included substantially more men (n = 3172) than women (n = 1228), and the authors did not comment on sex difference in this study.[1] The majority of women in this study were likely postmenopausal, and dyslipidemia increases over a woman's life span, with adverse changes occurring around menopause.[4]

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In Reply We appreciate Dr Kawada's comments about our study, which demonstrated that a treat-to-target LDL-C strategy of 50 to 70 mg/dL as the goal was noninferior to a high-intensity statin therapy for the 3-year composite of death, myocardial infarction, stroke, or coronary revascularization.[1]

First, we agree with Kawada that individual variations in the response to statin therapy may be closely related to genetic factors, and there has been accumulating evidence regarding the use of pharmacogenomics in cardiovascular medicine.[2,3] However, currently there is no consensus or clinical guideline about adopting pharmacogenomic biomarkers to guide selection of a drug or dose in statin therapy in daily practice.[3-5]

Second, regarding sex difference in our study, there was no significant interaction between sex and statin therapy strategy (treat-to-target group vs high-intensity statin group) in terms of the primary end point (8.5% vs 9.1%; difference, −0.7% [95% CI, −2.7% to 1.3%] for men and 7.3% vs 7.6%; difference, −0.3% [95% CI, −3.2% to 2.7%] for women) as well as an achievement of LDL-C level below 70 mg/dL at 3 years (58.1% vs 60.6%; difference, −2.5% [95% CI, −6.6% to 1.6%] for men and 58.6% vs 57.2%; difference, 1.3% [95% CI, −5.2% to 7.9%] for women). Although the proportion of women was relatively low in our study,[1] perhaps due to sex difference in epidemiology of coronary artery disease (a higher prevalence among men), it was higher compared with the previous randomized trial regarding intensive statin therapy.[6] However, we agree with Kawada that the effect of sex should be cautiously considered, and further research focusing on sex and statin therapy is warranted.

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Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19

To the Editor A recent study[1] of treatment effects of therapeutic-dose heparin in patients hospitalized for COVID-19 analyzed patients on the ward (treatment-dose heparin was efficacious) separately from critically ill patients (treatment-dose heparin was not efficacious). The authors described this trial design as "fortuitous."[1] However, we are concerned that the no-difference result in critically ill patients may have occurred because subcutaneous depot dosing of low-molecular-weight heparin (LMWH) has poor systemic exposure in critically ill patients, particularly in those receiving vasopressors.