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# Using a single noninferiority margin or preserved fraction for an entire pharmacological class was found to be inappropriate

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## Abstract

**Objective:** To assess the impact on noninferiority decisions when using a single margin or single preserved fraction (PF) for all noninferiority trials within a pharmacological class.

**Study Design and Setting:** A search in PubMed, EMBASE, and CENTRAL resulted in seven active-controlled statin trials (nine noninferiority comparisons) for treating hyperlipidemia. The impact of using a single margin was assessed by calculating whether this margin corresponds to different PFs among comparator statins which will demonstrate that the threshold of demonstrating noninferiority (in terms of the PF) varies among comparator statins. The use of a single PF was assessed by reanalyzing noninferiority in the included trials with new margins (based on the single PF) for each comparator statin.

**Results:** The use of a single margin resulted in PFs that range between 81% and 89% for the different comparators (i.e., different thresholds). The use of a single PF resulted in four of nine (44%) different noninferiority conclusions compared with the original analyses.

**Conclusion:** The threshold of demonstrating noninferiority with a single margin or single PF of the effect per pharmacological class may not be consistent with using a margin/PF for each comparator separately and may impact the conclusions of noninferiority. 

*Keywords:* Methodology; Noninferiority; Drug regulation; Clinical trials; Biostatistics; Randomized controlled trials

## 1. Introduction

Noninferiority trials aim to demonstrate that a new drug is not worse than an active comparator by more than a prespecified noninferiority margin, usually the largest clinically acceptable difference between the new drug and active comparator [1−3]. Demonstrating noninferiority will prove that the new drug preserved a clinically significant fraction, that is, the preserved fraction (PF), of the effect of the active

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**What is new?**

**Key findings**

- Analyzing noninferiority using a single noninferiority margin or single preserved fraction (PF) that was specified for an entire pharmacological class may lead to conclusions that are different from those of the recommended approach (i.e., using a margin and PF based on the effect of the active comparator estimated from the historical placebo-controlled trials).

**What this adds to what was known?**

- A single margin or a margin that is defined based on a single PF for an entire pharmacological class may be too wide or too narrow for the analysis of noninferiority. This depends mainly on the effect size of the comparator that was estimated from the historical placebo-controlled trials.
- Using a single margin or PF for an entire pharmacological class may result in thresholds of noninferiority that vary between comparators from this class (i.e., noninferiority could be demonstrated more easily with some comparators compared with others).

**What is the implication and what should change now?**

- Before deciding whether a single margin or single PF can be used to analyze noninferiority for a particular pharmacological class, a careful and systematic assessment is required of the evidence for each member in this pharmacological class. Otherwise, we may end up with inappropriate margins and hence incorrect conclusions from noninferiority trials.

comparator that was established in historical trials. Regulators recommend that the margin should be defined based on historical placebo-controlled trials of the active comparator [1,4−7]. Theoretically, this means that if more than one active comparator are planned to be used in testing noninferiority in one or more trials, a separate noninferiority margin has to be defined for each comparison.

The approval of pitavastatin, a hydroxymethylglutaryl-CoA reductase inhibitor, by the Food and Drug Administration (FDA) in 2009 for the treatment of primary hyperlipidemia and mixed dyslipidemia was based on the results of noninferiority trials that were analyzed using a noninferiority margin of 6% reduction in the low-density lipoprotein cholesterol (LDL) from the baseline [8]. This 6% margin seems to be an acceptable margin to analyze noninferiority of statins by the FDA because it was used in all pitavastatin noninferiority comparisons regardless of the chosen comparator statin. Doubling the dose of a statin would result in a 6% reduction of the LDL, which is why it was used in published trials as stated by the FDA. Moreover, the FDA assessment summary states that using the historical trials of the comparator statins would result in a lenient margin [8,9]. However, a summary of the effect of each comparator statin from the historical placebo-controlled trials on the percentage reduction of LDL was not provided. Therefore, it was not exactly known how much of the effect of each comparator statin was preserved by pitavastatin.

Another approach that regulators have started to accept is the use of a single PF for a pharmacological or therapeutic class. For example, 50% and 90% PFs are generally accepted by the FDA for drugs that prevent cardiovascular outcomes and for antibiotics, respectively [4]. The idea is to simplify the clinical argument on what percentage of the effect of each comparator from a certain class must be preserved. However, whether this would lead to a different conclusion in comparison with defining a PF for each comparator has not been assessed.

The aim of this case study about statin noninferiority trials was to assess the impact of using a single margin or a single PF for all noninferiority trials within a pharmacological class on the consistency of the noninferiority conclusion.

## 2. Methods

### *2.1. Search strategy and study selection of statin noninferiority trials*

To collect the evidence about noninferiority statin trials, a systematic literature search was performed in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) until May 31, 2016. The search was conducted in PubMed and CENTRAL using a combination of keywords ‘‘hydroxymethylglutaryl-CoA reductase inhibitors[Mesh]’’ OR ‘‘statin’’ AND ‘‘non-inferiority’’ OR ‘‘noninferiority’’ OR ‘‘non-inferior*’’ OR ‘‘noninferior*’’. The search in EMBASE ‘‘hydroxymethylglutaryl Coenzyme A reductase inhibitor’’ AND ‘‘non inferior’’. A trial was included if the comparison was for statin monotherapy (statin versus statin) and the noninferiority analysis was conducted based on the percentage reduction of the LDL from the baseline. Noninferiority trials that compared generic statins to the original ones were excluded unless the generic statin offers a better method of administration (controlled release vs. immediate release).

### *2.2. Analysis of noninferiority trials*

The point-estimate method and the fixed-margin method are the most commonly used methods to analyze noninferiority using margins that are defined based on historical trials of the active comparator [1,4−7,10]. For both methods,

noninferiority is demonstrated if the confidence interval (CI) of the test versus comparator drugs that was estimated in the noninferiority trial lies entirely below (or above such as in our case study) the noninferiority margin. The difference between the two methods is that the margin in the point-estimate method is based on the pooled estimate from historical trials of the active comparator (no direct consideration of the uncertainty in the effect estimates from the past trials). On the other hand, the margin in the fixed-margin method (also known as the 95%−95% CI method) is based on the limit of the CI of the pooled estimate that is closest to the null effect (i.e., the uncertainty in the pooled effect estimate based on the historical trials is taken into account) [1,4,11,12]. For example, if it was decided that the new drug must preserve at least 50% of the pooled effect estimate of the active comparator from the historical trial, the noninferiority margin is the remaining 50% of that pooled effect estimate (the same approach is applied to calculate the margin based on the limit of the CI in the fixed-margin method).

### *2.3. Using a single margin to analyze noninferiority of statins*

We evaluated how the 6% LDL reduction from the baseline noninferiority margin (the margin that is accepted by the FDA) corresponds to the PF for each comparator statin. This will show how much does the 6% LDL reduction margin rely, in terms of the stringency of demonstrating noninferiority, on the effect of each comparator statin from the historical trials. If the 6% margin corresponds to different PFs, it implies that noninferiority could be demonstrated more easily with some comparator statins than with others, which questions the usefulness of a single margin for analyzing noninferiority for an entire pharmacological class. For each comparator statin, the estimated effect compared with placebo was obtained from the meta-analysis by Law et al. [13]. In that meta-analysis, the efficacy of six statins on the percentage reduction of the LDL from the baseline was pooled (for each statin) from 164 placebo-controlled trials.

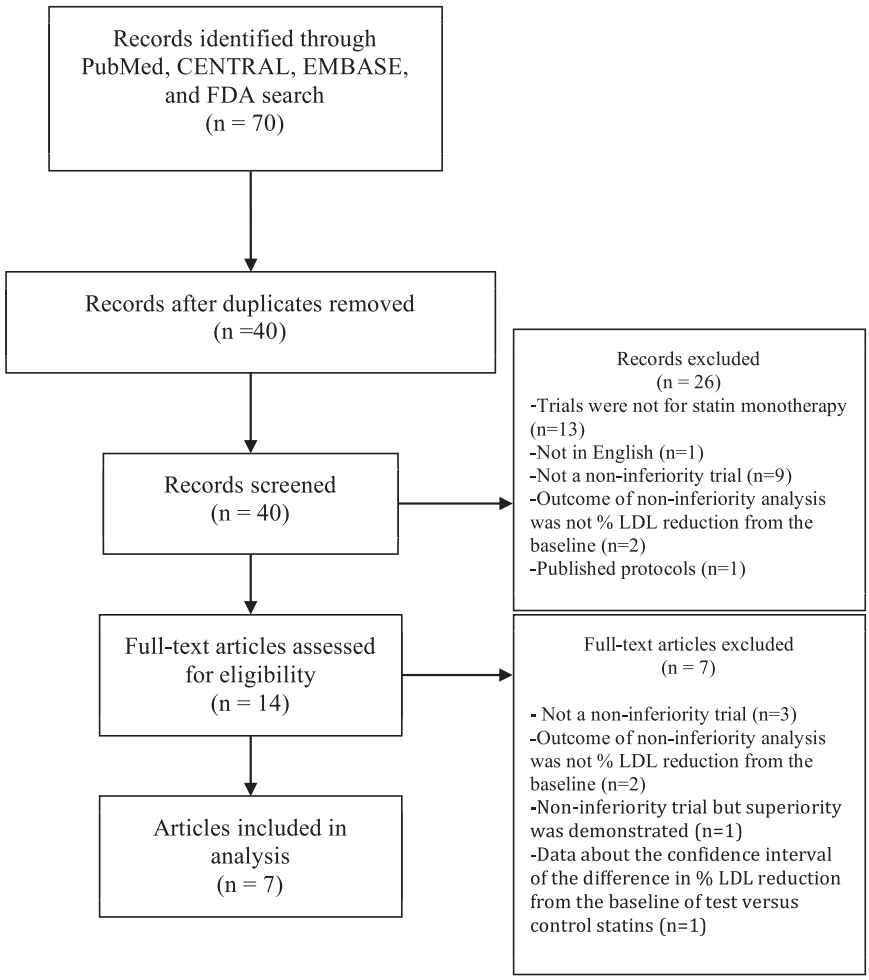


**Fig. 1.** Flow chart of the systematic literature review of noninferiority statin trials.

### 2.4. Using a single PF to analyze noninferiority of statins

Four noninferiority margins were defined for the comparator statin in each included trial based on the pooled estimate and the 95% CI from the Law et al. meta-analysis. Two margins were used that preserve 50% and 85% of the pooled estimate (point-estimate method), and another two margins that preserve 50% and 85% of the lower limit of the CI of the pooled estimate (fixed-margin method). The 50% PF was chosen because it is the most commonly used fraction for both methods [10]. The 85% PF was used in the noninferiority published trials [10]. In each trial, the results of the noninferiority analysis using these four PF-based margins were compared with the original result. If conclusions are different and vary among PFs and among the methods of analysis in comparison with the original results, it suggests that using a single PF may not only lead to a margin that is too wide or too narrow for the chosen comparator statin, but also lead to a scenario that is similar to using a single margin: noninferiority could be demonstrated more easily with some comparator statins compared with others.

## 3. Results

### 3.1. Identification of the included trials

The systematic literature search resulted in seven trials, comprising nine noninferiority comparisons, which were included in the analysis (details in Fig. 1 and

**Table 1.** Studies included in the reanalysis of noninferiority statin trials

| Trial | Test statin | Comparator statin | Indication | Noninferiority margin used |
|---|---|---|---|---|
| Yi et al 2014 [14] | Simvastatin 20 mg/d controlled release (CR) | Simvastatin 20 mg/d immediate release (IR) | Chronic kidney disease (CKD) and dyslipidemia | −6.5% |
| Eriksson et al 2011 [15] | Pitavastatin 4 mg/d | Simvastatin 40 mg/d | Hypercholesterolemia or combined dyslipidemia and at least two risk factors for coronary heart disease | −6.0% |
| Gumprecht et al 2011 [16] | Pitavastatin 4 mg/d | Atorvastatin 20 mg/d | Type 2 diabetes and combined dyslipidemia | −6.0% |
| Lablanche et al 2010[a] [17] | Rosuvastatin 20 mg/d | Atorvastatin 80 mg/d | Acute coronary syndrome | −3.0% |
| Ose et al 2009 [18] | Pitavastatin 4 mg/d | Simvastatin 40 mg/d | Hypercholesterolemia or combined dyslipidemia | −6.0% |
| Study NK-104-301[a,b] [8] | Pitavastatin 2 mg/d<br>Pitavastatin 4 mg/d | Atorvastatin 10 mg/d<br>Atorvastatin 20 mg/d | Hypercholesterolemia or combined dyslipidemia | −6.0% |
| Park et al 2005 [19] | Pitavastatin 2 mg/d | Simvastatin 20 mg/d | Hypercholesterolemia | −7.0% |

[a] Trials with two noninferiority comparisons.
[b] Trial retrieved from the FDA database.
[c] The effect estimate was not provided.

Table 1). The justification for the choice of the margin was stated only in two trials. Four of the included trials were phase III trials of pitavastatin that were submitted to the FDA. Atorvastatin was used as the comparator statin in three trials (five noninferiority comparisons: one with 10 mg/d, two with 20 mg/d, and two with 80 mg/d doses). Simvastatin was used in four trials (four noninferiority comparisons: two with 20 mg/d and two with 40 mg/d doses).

### 3.2. Using a single margin to analyze noninferiority of statins

The 6% LDL reduction margin corresponds to different PFs either based on the pooled estimates or the lower limit of the CIs of the controlled statins (81% to 89% and 82% to 88% PFs, respectively). This means that the stringency of demonstrating noninferiority, in terms of the PF, varies among the comparator statins. This is mainly attributed to the difference in the effect size of the pooled effect estimate of each comparator statin from the historical placebo-controlled trials as shown in Fig. 2. This figure shows how the threshold of demonstrating noninferiority (i.e., how high the PF is) is set by the 6% margin. It shows that with the 6% margin, the PF (of either the pooled effect estimate or its lower limit of the 95% CI) becomes higher for comparator statins with higher historical effect estimates. This means that demonstrating noninferiority is more difficult for test statins that are expected to be equipotent to atorvastatin 80 mg (if the latter is chosen as an active comparator), compared with demonstrating noninferiority to atorvastatin 40 mg with equipotent test statins.

**Table 1** (*continued*)

| Justification for the choice of the margin | Duration of the trial | Number of patients in each arm | The effect estimate (95% CI) conclusion of the study |
|---|---|---|---|
| The margin was chosen because it was used in similar trials. | 8 wk | Test = 59<br>Comparator = 59 | 0.5% (−6.0 to 5.0%)<br>Noninferiority was demonstrated |
| Not reported | 12 wk | Test = 223<br>Comparator = 119 | 0.3% (−2.5 to 3.1%)<br>Noninferiority was demonstrated |
| Not reported | 12 wk | Test = 275<br>Comparator = 137 | 2.3% (−6.2 to 1.5%)<br>Noninferiority was not demonstrated |
| Not reported | 12 wk | Test = 369<br>Comparator = 384 | 0.3% (−2.1 to 2.7%) (at 1 mo)<br>−1.0% (−3.5 to 1.6%) (at 3 mo)<br>Noninferiority was demonstrated at 1 mo, but not at 3 mo |
| The margin was used in previously published statins trials and is accepted by the European Medicines Agency (EMA) as clinically relevant difference which approximates to the LDL reduction obtained by doubling the dose of a statin | 12 wk | Test = 319<br>Comparator = 110 | 1.1% (−2.1 to 4.3%)<br>Noninferiority was demonstrated |
| The margin approximates to the LDL reduction obtained by doubling the dose of a statin. In addition, the use of the past trials of the control statins will result in a lenient margin | 12 wk | Test = 315<br>Test = 298<br>Comparator = 102<br>Comparator = 102 | −0.2% (−3.4 to 3.1%)<br>1.0% (−2.3 to 4.2%)<br>Noninferiority for both comparisons were demonstrated |
| Not reported | 8 wk | Test = 49<br>Comparator = 46 | (−6.1 to 3.8%)[c]<br>Noninferiority was demonstrated |

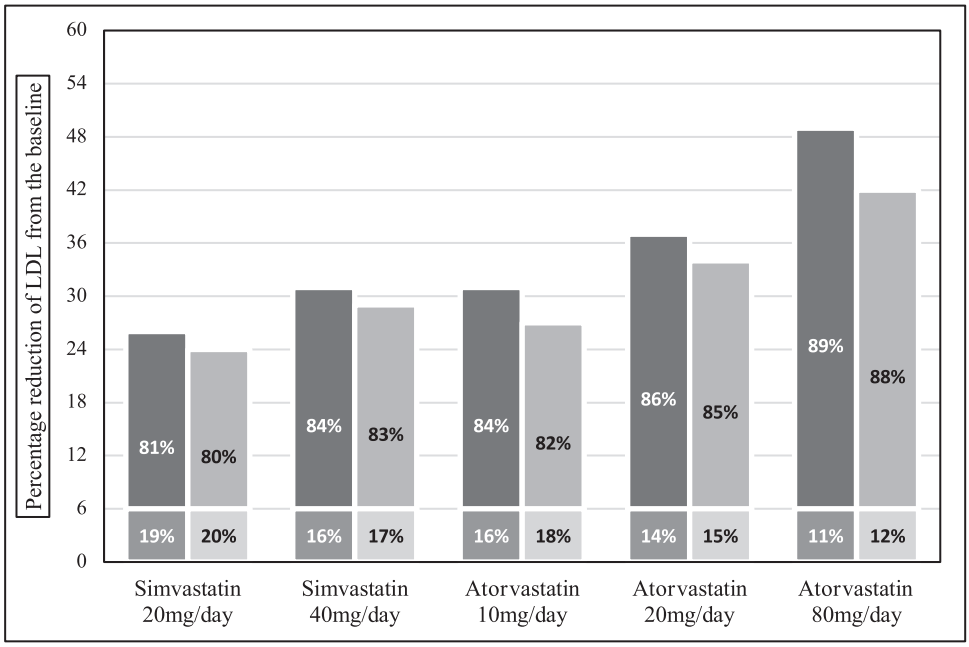


**Fig. 2.** Fractions of pooled effects of comparator statins that are preserved by the noninferiority margin of 6% LDL reduction. The horizontal white line shows the point where the noninferiority margin of 6% LDL reduction from baseline crosses the historical pooled effect estimate of each comparator statin (the dark gray columns) and the lower limit of the 95% CI of the pooled effect estimate (the light gray columns). The part below the line is the fraction that corresponds to the margin (the clinically insignificant fraction); the part above the line corresponds to the PF.

However, this inconsistency in the threshold of demonstrating noninferiority was not observed among comparator statins with similar pooled historical effect estimates as shown in the figure (e.g., simvastatin 40 mg and atorvastatin 10 mg).

### *3.3. Using a single PF to analyze noninferiority of statins*

Discrepancy between the new analyses using 50% and 85% PFs and the original analyses was found in four of nine comparisons (44%) (Table 2). For example,

**Table 2.** The re-analysis of noninferiority statin trials

| Trial | Test statin | Comparator statin | The estimate and 95% CI for the difference between the test and the comparator statins | Margin used in the noninferiority trial |
|---|---|---|---|---|
| Yi et al [14] | Simvastatin 20 mg/d controlled release | Simvastatin 20 mg/d immediate release | −0.5% (−6.0 to 5.0%) | −6.5% |
| Eriksson et al [15] | Pitavastatin 4 mg/d | Simvastatin 40 mg/d | 0.3% (−2.5 to 3.1%) | −6.0% |
| Gumprecht et al [16] | Pitavastatin 4 mg/d | Atorvastatin 20 mg/d | 2.3% (−6.2 to 1.5%) | −6.0% |
| Lablanche et al[c] [17] | Rosuvastatin 20 mg/d | Atorvastatin 80 mg/d | 0.3% (−2.1 to 2.7%) (at 1 mo) | −3.0% |
| | | | −1.0% (−3.5 to 1.6%) (at 3 mo) | |
| Ose et al [18] | Pitavastatin 4 mg/d | Simvastatin 40 mg/d | 1.1% (−2.1 to 4.3%) | −6.0% |
| NK-104-301[c] [8] | Pitavastatin 2 mg/d | Atorvastatin 10 mg/d | −0.15% (−3.4 to 3.1%) | −6.0% |
| | Pitavastatin 4 mg/d | Atorvastatin 20 mg/d | 1.0% (−2.3 to 4.2%) | |
| Park et al [19] | Pitavastatin 2 mg/d | Simvastatin 20 mg/d | (−6.1 to 3.8%)[d] | −7.0% |

[a] Obtained from Law et al. meta-analysis [13].
[b] The conclusion is not consistent with the original analysis.
[c] Two noninferiority comparisons were evaluated in each trial.
[d] The estimate was not provided in the trial.

noninferiority was demonstrated in the original analysis of Yi et al. trial using a 6.5% LDL reduction margin. However, repeating the analysis using the point-estimate and the fixed-margin methods with a PF of 85% led to a different conclusion (Fig. 3 illustrates the reanalysis in this trial using the point-estimate method with both PFs). Similarly, noninferiority was not demonstrated in the trial by Gumprecht et al. using the 6% LDL reduction margin; however, noninferiority was demonstrated in a reanalysis using the point-estimate method with either 50% or 85% PFs as well as in a reanalysis using the fixed-margin method with a 50% PF.

## 4. Discussion

We showed in this case study on statin noninferiority trials that applying a single margin may not lead to preserving a fixed fraction of the effects of the comparator statins. This will result a situation where demonstrating noninferiority could be achieved more easily when choosing certain comparators over others. A similar scenario may also result on using a single PF irrespective of the comparator statin. Both could affect the trial's assay sensitivity (the ability of a trial to distinguish between an effective treatment and a less effective one) [1].

Using a single margin for an entire pharmacological class will spare researchers and regulators from the extensive statistical and clinical efforts that precede the final choice of the margin. This is accepted by regulators for some therapeutic and pharmacologic groups (such as 0.3% or 0.4% reduction of HbA1c from the baseline for antidiabetics, the 6% LDL reduction for statins, and 1.5 geometric mean titers ratio for seasonal influenza vaccines) [8,20–22]. We also found in a systematic review that this approach was adopted in many comparisons in which the margin was chosen because it was used previously in similar trials [10]. However, as we showed in this case study, the use of 6% LDL reduction from the baseline across different comparators from the same pharmacological class lead to a condition where the fraction of the effect that must be preserved by the new drug is different for different comparators, be it that the PF did not differ that much in an absolute sense (81% to 89% depending on the comparator statin). Importantly, however, the conclusions regarding noninferiority changed when applying the different margins in the various noninferiority statin trials. The obvious, yet exceptional, situation in which a single margin (or PF) can be used for an entire pharmacological class is when different comparators from the same pharmacological group have similar effect estimates in historical trials against placebo.

The use of a single PF for an entire pharmacological class could lead to a similar problem (i.e., that the percentage LDL reduction from baseline differs between different comparator statins). Choosing a single PF will obviate the need for lengthy discussions to decide the fraction of the effect of the comparator that is clinically relevant. However, it may lead to a noninferiority margin that is too wide, which affects the assay sensitivity of the trial, or too narrow

**Table 2** (*continued*)

| The pooled estimate and 95% CI of the effect of the comparator statin from the historical placebo-controlled trials[a] | Margins defined for the point-estimate method | | Margins defined for the fixed-margin method | |
|---|---|---|---|---|
| | 50% Preserved fraction | 85% Preserved fraction | 50% Preserved fraction | 85% Preserved fraction |
| −32.0% (−34.0 to −30.0%) | −16.0% | −4.8%[b] | −15.0% | −4.5%[b] |
| −37.0% (−40.0 to −35.0%) | −18.5% | −5.6% | −17.5% | −5.3% |
| −43.0% (−47.0 to −40.0%) | −21.5%[b] | −6.5%[b] | −20.0%[b] | −6.0% |
| −55.0% (−62.0 to −48.0%) | −27.5% | −8.3% | −24.0% | −7.2% |
| | −27.5%[b] | −8.3%[b] | −24.0%[b] | −7.2%[b] |
| −37.0% (−40.0 to −35.0%) | −18.5% | −5.6% | −17.5% | −5.3% |
| −37.0% (−41.0 to −33.0%) | −18.5% | −5.6% | −16.5% | −5.0% |
| −43.0% (−47.0 to −40.0%) | −21.5% | −6.5% | −20.0% | −6.0% |
| −32.0% (−30.0 to −34.0%) | −16.0% | −4.8%[b] | −15.0% | −4.5%[b] |

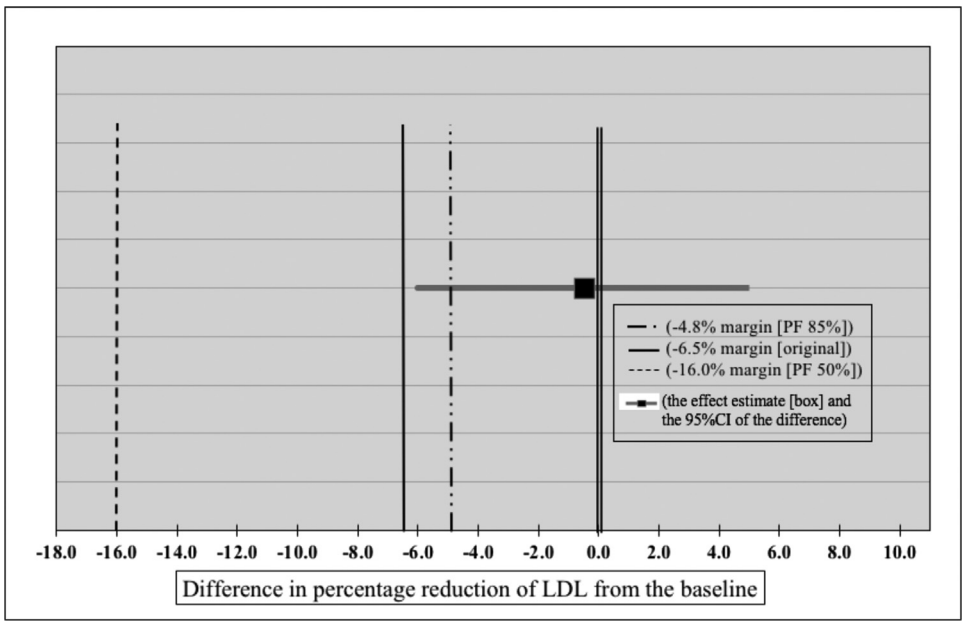


**Fig. 3.** Demonstration of reanalysis of the noninferiority trial by Yi et al. of simvastatin 20 mg/day (controlled release [CR]) vs. simvastatin 20 mg (immediate release [IR]). Analysis based on the point-estimate method using the two margins that were defined based on 50% and 85% PFs of simvastatin 20 mg/d (IR).

which will affect the feasibility of the trial due to the need for a large sample size.

This study was the first to assess the usefulness of applying a single margin or a single PF to analyze noninferiority in an entire pharmacological class. However, we only found seven statins head-to-head noninferiority trials, which limit the range of scenarios we could evaluate. In addition, we illustrated the impact of our objectives in only one pharmacological class. Further assessment should be performed using other pharmacological and therapeutic classes.

## 5. Conclusion

A careful and systematic assessment must be performed to the evidence of each member in a pharmacological class before deciding whether a single margin or single PF can be used to analyze noninferiority for this pharmacological class. Otherwise, we may end up with inappropriate margins and hence incorrect conclusions from noninferiority trials.

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All authors read and approved the final article.

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