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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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Ethics approval: ethics approval was not required.

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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,