ELSEVIER

Journal of Clinical Epidemiology 65 (2012) 954–961

Journal of Clinical Epidemiology

A survey of physicians show a one-third reduction in harmful outcomes to be a clinically important difference for statin therapy

Kathy K. Li[a,d,*], Anne M. Holbrook[b,c,d,e], Lehana Thabane[c,d,f], Koon K. Teo[d,e]

[a]*Centre for Health Economics and Policy Analysis, CRL-210, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4K1*
[b]*Division of Clinical Pharmacology and Therapeutics, McMaster University, Hamilton, Ontario, Canada*
[c]*Centre for Evaluation of Medicines, St Joseph's Hospital, Hamilton, Ontario, Canada*
[d]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*
[e]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada*
[f]*Biostatistics Unit, St Joseph's Healthcare—Hamilton, Hamilton, Ontario, Canada*

Accepted 19 February 2012; Published online 27 June 2012

Abstract

Objective: To establish a minimal clinically important difference (MCID) for outcomes of statin therapy with physicians using a cross-sectional design. The MCID was defined as the smallest benefit of statin therapy that would result in physicians recommending it to their patients after considering potential harm and cost.

Study Design and Setting: A self-administered questionnaire was sent to family practitioners, internal medicine specialists, and cardiologists practicing in Hamilton. They provided an MCID of statin therapy using clinical scenarios based on 5-year risk of vascular outcomes, namely coronary death, nonfatal myocardial infarction, stroke, and coronary revascularization.

Results: Two hundred nine physicians participated, of which 638 were initially approached. Physicians would recommend statin therapy if it would at least reduce the relative risk of vascular events by about one-third. For patient scenarios involving a 30%, 13%, and 5% baseline risk of developing a vascular event in 5 years, physicians would recommend treatment if it would reduce the baseline risk by 31.4% (standard deviation [SD], 19.8), 34.6% (SD, 18.0), and 46.2% (SD, 24.6), respectively.

Conclusion: Physicians were consistent in their choice of MCID for statin therapy across vascular events. They required a larger benefit of statin therapy for patients at a lower baseline risk (5%) of developing a vascular event before they would recommend treatment.

Keywords: Minimal clinically important difference; Clinical importance; Measurement; Questionnaires; Statin therapy; Physicians

1. Introduction

Statin use has increased in the past decade. Global pharmaceutical sales of lipid-lowering drugs totaled $35 billion in 2009, ranking number two among all other leading therapeutic classes [1]. In 2007, Canadians spent about $1.9 billion on statins, which represented a total of 26.1 million market claims (public, private, and cash) of the drug [2]. In British Columbia, the annual prevalence of statin use by adults increased by 1.28–6.59% between 1998 and 2004 [3]. The benefit of statin therapy in reducing death, coronary events, and stroke is well established in the literature. Based on the data from a recent prospective meta-analysis of 14 randomized trials, each millimole per liter reduction in low-density lipoprotein (LDL) cholesterol resulted in a 23% decrease in major coronary events (nonfatal myocardial infarction [MI] and coronary death), 19% decrease in coronary mortality, 17% reduction in stroke (fatal and nonfatal), and 12% reduction in all-cause mortality [4]. Absolute and relative risk reduction (RRR) of any major vascular event overall was 3.7% and 21%, respectively, per millimole per liter of LDL cholesterol reduction [4]. Another meta-analysis on the effectiveness of statin therapy (primary and secondary prevention combined) conducted in the United Kingdom also had similar findings [5]. Statin therapy compared with placebo was associated with a statistically significant reduction in the risk of all-cause mortality, nonfatal MI, and fatal MI [5].

Concerns have been raised regarding the safety of statin therapy. Data from a meta-analysis of statin trials showed that the drug was not associated with increased incidence of cancer [4]. The 5-year excess risk of developing rhabdomyolysis was also small (0.01%) and not significantly

* Corresponding author. Tel.: 905-525-9140x22122; fax: 905-546-5211.
E-mail address: likk2@mcmaster.ca (K.K. Li).

0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2012.02.019

What is new?

- This study contributes to the current knowledge about methods of selecting minimal clinically important difference (MCID). Using a self-administered mail survey, we elicited the opinions of family practitioners, internal medicine specialists, and cardiologists on the MCID of statin therapy.
- Physicians would recommend statin therapy if it would reduce the relative risk of coronary death, nonfatal myocardial infarction, stroke, coronary revascularization, and any major vascular event by at least approximately one-third.
- Physicians required a larger benefit of statin therapy for patients at a lower baseline risk of developing a vascular event before they would recommend treatment. This finding is consistent with a similar study conducted by McAlister et al.
- It is hoped that the study findings will draw attention to the importance of determining the MCID of other therapies.
- Further research is needed to investigate under what circumstances would it be beneficial to include the opinions of other groups (general public, policymakers) to determine the MCID. The size of MCID may vary depending on the perspective obtained.

different than placebo [4]. Another meta-analysis of statin-related adverse events (AEs) suggested that serious events such as creatine phosphokinase more than 10 times the upper limit of normal or rhabdomyolysis were uncommon (numbers needed to harm = 3,400), and rhabdomyolysis was rare (numbers needed to harm = 7,438) [6]. Although the benefit of statins based on high-quality trials is not in question, few of the trials reported an expected minimal clinically important difference (MCID).

The expected clinical relevance or importance of study results is often related to the delta value [7], and, therefore, it is important to explicitly identify the delta value as the clinically important difference. The current and revised Consolidated Standards of Reporting Trials statement specifically recommends that authors discuss the clinical importance of their results [8,9]. Despite clear guidelines, details about the choice of delta are rarely described in reports of clinical trials. A critical review of 36 randomized controlled trials of statin therapy (published up to 2008) found that reporting of the delta (the difference that investigators consider as worth detecting in sample size calculation) is inadequate [10]. More than two-thirds of the studies reviewed did not provide a justification for the size of the delta, did not indicate whether the delta represented the MCID, and did not provide an adequate interpretation regarding the clinical importance of their study results. Hence, there is still a lack of data available about the MCID of clinical outcomes commonly used to evaluate the treatment effect of statin therapy.

We define MCID here as the smallest benefit (e.g., reducing a major coronary event), for which clinicians should or would recommend them to their patients after considering potential harm (e.g., a slight increase in the risk of developing rhabdomyolysis), costs of the medication, and inconvenience (e.g., taking a pill every day and going to the physician and pharmacy for refills).

The concept of MCID has major implications for clinical practice at the individual patient and population levels. For example, it may influence or impact the utilization of health services because the demand for health care and treatments is often driven by patients' and clinicians' perceptions of their efficacy and safety. Despite this importance, there is not a conventional or standard method of determining the size of an MCID.

This study examined the following research questions: (1) What is the smallest benefit of statin therapy (reduction of the 5-year risk of coronary death, nonfatal MI, stroke, coronary revascularization) that would result in clinicians (family practitioners, general internists, and cardiologists) recommending it to their patients after considering potential harms and cost? (2) Are physician characteristics, such as gender, specialty, years in practice, number of cholesterol-lowering therapy prescribed, associated with the MCID selected?

2. Methods

2.1. Approaches of determining the MCID

Currently, there is no known gold standard method for establishing an MCID. In our study, we used an anchor-based approach to determine an MCID for statin therapy. An anchor-based approach examines the relationship of an outcome measure and an independent criterion (anchor) to ascertain a particular degree of change. Anchors may be objective or subjective clinical measures and from expert opinion. Objective anchors may be surrogate outcomes, such as hemoglobin A1C, blood pressure, LDL cholesterol, derived from prognostic and therapy trial data. For example, aggressive treatment of blood pressure has been shown in meta-analysis of randomized trials involving 56,000 patients to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic, thereby decreasing vascular events by 46–63% [11]. The quality of the associations is high, but the concept of *minimum* change associated with important clinical outcome improvement is subjective.

The MCID may also be ascertained by eliciting patient or expert (clinician) opinion. Reed et al. [12] used time trade-off and standard reference gambling techniques to