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Differing predictive relationships between baseline LDL-C, systolic blood pressure, and cardiovascular outcomes

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ABSTRACT

Background: Traditional cardiovascular risk factors, such as hypertension and dyslipidemia, predispose individuals to cardiovascular disease, particularly patients with diabetes. We investigated the predictive value of baseline systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) on the risk of vascular outcomes in a large population of patients at high risk of future cardiovascular events.
Methods: Data were pooled from the TNT (Treating to New Targets), CARDS (Collaborative Atorvastatin Diabetes Study), and IDEAL (Incremental Decrease in End-Points Through Aggressive Lipid Lowering) trials and included a total of 21,727 patients (TNT: 10,001; CARDS: 2838; IDEAL: 8888). The effect of baseline SBP and LDL-C on cardiovascular events, coronary events, and stroke was evaluated using a multivariate Cox proportional-hazards model.
Results: Overall, risk of cardiovascular events was significantly higher for patients with higher baseline SBP or LDL-C. Higher baseline SBP was significantly predictive of stroke but not coronary events. Conversely, higher baseline LDL-C was significantly predictive of coronary events but not stroke. Results from the subgroup with diabetes (5408 patients; TNT: 1501; CARDS: 2838; IDEAL: 1069) were broadly consistent with those of the total cohort: baseline SBP and LDL-C were significantly predictive of cardiovascular events overall, with the association to LDL-C predominantly related to an effect on coronary events. However, baseline SBP was not predictive of either coronary or stroke events in the pooled diabetic population.
Conclusions: In this cohort of high-risk patients, baseline SBP and LDL-C were significantly predictive of cardiovascular outcomes, but this effect may differ between the cerebrovascular and coronary systems.
Trial Registration Number: NCT00327691 (TNT); NCT00327418 (CARDS); NCT00159835 (IDEAL).

1. Introduction

Observational studies have linked blood pressure (BP) and serum cholesterol to vascular mortality in patients with [1,2] and without [3,4] type 2 diabetes. Many large clinical trials have found that control of these risk factors corresponds to a reduction in the rates of cardiovascular outcomes [5,6]. Systolic BP (SBP) is a recognized risk factor for cardiovascular disease (CVD), and is strongly associated with stroke mortality [3]. The relationship between cholesterol and coronary heart disease (CHD) is well established [4,7–9]. However, the association between cholesterol and stroke mortality is controversial [4,10–12].

Abbreviations: BMI, body mass index; BP, blood pressure; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; MCVE, major cardiovascular event; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack; TNT, Treating to New Targets.

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Patients with diabetes are at increased risk of cardiovascular events compared with nondiabetic patients such that those with diabetes but without prior myocardial infarction (MI) have a coronary risk similar to those without diabetes but with a history of previous MI [13]. Baseline SBP has been shown to be predictive of cardiovascular events within this high-risk population [1]. When adjusted for age and sex, low-density lipoprotein cholesterol (LDL-C) is a significant driver of CHD risk among patients with diabetes [2].

In this analysis, we assessed the effect of baseline SBP and baseline LDL-C on cardiovascular events, coronary events, and stroke in patients at high risk for cardiovascular events. By pooling the populations from three large clinical trials, which provide detailed information on patients' medical history and subsequent cardiovascular events, we were able to conduct an in-depth analysis of a large population of high-risk patients.

2. Methods

2.1. Study design, participants and outcomes

A total of 21,727 patients (10,001 from TNT [Treating to New Targets], 2838 from CARDS [Collaborative Atorvastatin Diabetes Study], and 8888 from IDEAL [Incremental Decrease in End Points Through Aggressive Lipid Lowering]) were included in this analysis. Two pooled datasets were analyzed: one contained the entire TNT, CARDS, and IDEAL populations; the other contained the diabetic patients from TNT (n = 1501), IDEAL (n = 1069), and CARDS (n = 2838). TNT, CARDS, and IDEAL were large, prospective, parallel-group studies evaluating atorvastatin in high-risk populations and have been described in detail elsewhere [14–19]. All patients gave informed written consent, and studies were approved by local research ethics committees or institutional review boards at each participating center.

TNT (NCT00327691) was a large, double-blind, parallel-group trial with a median follow-up of 4.9 years. After an 8-week run-in period on atorvastatin 10 mg/day, patients with stable CHD and a mean serum LDL-C concentration < 130 mg/dL (3.4 mmol/L) were randomized to treatment with atorvastatin 80 mg/day (n = 4995) or 10 mg/day (n = 5006). The primary endpoint was time to a major cardiovascular event (MCVE), defined as CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke [14]. Secondary study outcomes included major coronary events, any coronary event, cerebrovascular events, peripheral vascular disease, hospitalization with a primary diagnosis of congestive heart failure, any cardiovascular event, and all-cause mortality.

CARDS (NCT00327418) was a double-blind, placebo-controlled trial with a median follow-up of 3.9 years. Patients with type 2 diabetes and one other CHD risk factor (retinopathy, albuminuria, current smoking, or hypertension), but no history of CVD and a mean LDL-C < 160 mg/dL (4.14 mmol/L) were randomized to placebo (n = 1410) or atorvastatin 10 mg/day (n = 1428). The primary endpoint was time to an MCVE, consisting of acute coronary events, coronary revascularization, or stroke [16].

IDEAL (NCT00159835) was a prospective, randomized, open-label, blinded endpoint trial with a median follow-up of 4.8 years. Patients with a history of acute MI were randomized to treatment with atorvastatin 80 mg/day (n = 4439) or simvastatin 20 mg/day (n = 4449), with the option of titrating to 40 mg/day at week 24. The primary endpoint was time to first occurrence of a major coronary event, defined as coronary death, nonfatal MI, or cardiac arrest with resuscitation [18]. Secondary endpoints included MCVEs, defined as major coronary events and stroke.

2.2. Statistical analyses

SBP has been shown to be an informative single measurement in predicting cardiovascular risk [20,21]. The predictive effect of a 10-mm Hg increase in baseline SBP and a 10-mg/dL (0.26-mmol/L) increase in baseline LDL-C on cardiovascular events, coronary events, and stroke was evaluated using multivariate Cox proportional hazards models. Baseline SBP and baseline LDL-C were included in each model as predictor variables. To enhance the predictive model, additional predictors were entered into the model using stepwise selection, with an entry criterion of p = 0.05, and the following demographics and baseline characteristics were considered: age, diastolic BP, body mass index (BMI), triglycerides (log-transformed), high-density lipoprotein cholesterol, gender, smoking history, and history of diabetes, hypertension, ischemic heart disease (IHD), or stroke or transient ischemic attack (TIA).

The analysis was performed on each study separately and on pooled data from the three studies, both for the total population and for the subset of patients with diabetes. Analyses of the pooled study data were stratified by study. The interactions between the four treatments represented in the studies and baseline SBP, and between treatment and baseline LDL-C, were assessed for the pooled analysis.

Statistical analyses were performed using SAS 9.1 or later (SAS Institute, Cary, NC, USA). Two-sided p-values <0.05 were considered statistically significant.

3. Results

3.1. Study population

Baseline characteristics that were similar between the TNT, CARDS, and IDEAL populations included age and BMI (Table 1). All of the participants in CARDS had type 2 diabetes, compared with 15% in TNT and 12% in IDEAL. Other differences in baseline characteristics included gender, smoking status, hypertension, and history of IHD. In the total pooled population, the mean age was 61.4 years, mean SBP was 135 mm Hg, and mean LDL-C was 110 mg/dL (2.8 mmol/L) at baseline; 24.9% of patients had type 2 diabetes and nearly half of the patients had hypertension (Table 1). The most frequently used concomitant medications among patients included in the pooled analysis were beta-adrenoceptor-blocking drugs (33.8%), lipid-lowering drugs (31.9%), antihypertensive drugs (excluding beta-blockers; 27.5%), vasodilators (19.3%), and anticoagulants (12.1%).

During a median follow-up of 3.9–4.9 years, a total of 4489 (20.7%) patients experienced a CHD event and 657 (3.0%) patients experienced a stroke event in the pooled population overall. The incidence of CHD events and stroke events was lower in CARDS compared with TNT and IDEAL (Table 2). In the pooled diabetic population, a total of 849 (15.7%) patients had a CHD event and 207 (3.8%) patients had a stroke event. The proportion of patients with CHD and stroke events was greater in the diabetic TNT and IDEAL populations compared with the TNT and IDEAL populations overall (Table 2).

3.2. Effect of baseline SBP in the total study populations

Each 10-mm Hg increase in baseline SBP was associated with a significantly increased risk of all cardiovascular events in the TNT, CARDS, IDEAL, and total pooled populations (Fig. 1A). Increased SBP at baseline was associated with a significantly increased risk of all coronary events in the IDEAL population, but not the TNT (p = 0.6607), CARDS (p = 0.2987), or the total pooled (p = 0.1778) populations (Fig. 1B). A 10-mm Hg increase in baseline SBP significantly increased the risk of stroke in the TNT and the total pooled populations, but not in the CARDS (p = 0.1502) or IDEAL (p = 0.1762) populations (Fig. 1C). There were no significant interactions between baseline SBP and the four treatment regimens for cardiovascular events, coronary events, or stroke in the pooled analysis (data not shown).

3.3. Effect of baseline LDL-C in the total study populations

Each 10-mg/dL increase in baseline LDL-C was associated with a significantly increased risk of both cardiovascular and coronary events in the TNT, CARDS, IDEAL, and total pooled populations (Fig. 2A, B). However, a 10-mg/dL increase in baseline LDL-C was not associated with a significant increase in the risk of stroke in the TNT (p = 0.1027), CARDS (p = 0.5835), IDEAL (p = 0.9589), or total pooled (p = 0.4004) populations (Fig. 2C). There were no significant interactions between baseline LDL-C and the four treatment regimens for cardiovascular events or stroke for the pooled analysis (data not shown); however, significant interactions were found between baseline LDL-C and the four treatments for coronary events. The hazard ratios (HRs) and 95% confidence intervals (CIs) for the interactions between baseline LDL-C and atorvastatin 80 mg, baseline LDL-C and atorvastatin 10 mg, baseline LDL-C and simvastatin 20 mg, and baseline LDL-C and placebo were 1.05 (1.04–1.07), 1.08 (1.05–1.11), 1.03 (1.01–1.05), and 1.13 (1.04–1.24), respectively.

3.4. Effect of baseline SBP in the diabetic populations

Each 10-mm Hg increase in baseline SBP significantly increased the risk of cardiovascular events in the CARDS and pooled diabetic populations, but not in the diabetic TNT (p = 0.4641) or IDEAL (p = 0.2341)