

Prevalence, Predictors, and Outcomes in Treatment-resistant Hypertension in Patients with Coronary Disease

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ABSTRACT

BACKGROUND: Increasingly, apparent treatment-resistant hypertension has been recognized. However, much of the prevalence, predictors, and outcomes are largely unknown, especially in patients with coronary artery disease.

METHODS: We evaluated 10,001 patients with coronary artery disease who were enrolled in the Treating to New Targets trial. Apparent treatment-resistant hypertension was defined as blood pressure ≥ 140 mm Hg despite 3 antihypertensive agents or < 140 mm Hg with ≥ 4 antihypertensive agents. The primary outcome was major cardiovascular events (composite of fatal coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, and stroke).

RESULTS: Among the 10,001 patients in the trial, 1112 (11.1%) had apparent treatment-resistant hypertension. In a multivariable model adjusting for baseline differences, the treatment-resistant hypertension group had a 64% increase in primary outcome (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.39-1.94; $P < .001$), driven by a 69% increase in coronary heart disease death (HR, 1.69; 95% CI, 1.22, 2.34; $P = .001$) and 73% increase in nonfatal myocardial infarction (HR, 1.73; 95% CI, 1.39-2.16, $P < .0001$) when compared with the no apparent treatment-resistant hypertension group. In addition, patients with apparent treatment-resistant hypertension had a 71% increase in major coronary event ($P < .0001$), 45% increase in death ($P = .001$), 33% increase in heart failure ($P = .05$), 53% increase in any cardiovascular event ($P < .0001$), 60% increase in any coronary event ($P < .0001$), 68% increase in angina ($P < .0001$), and 51% increase in coronary revascularization ($P < .0001$) when compared with the no apparent treatment-resistant hypertension group. Results were largely similar whether the definition of apparent treatment-resistant hypertension was based on a blood pressure ≥ 140 mm Hg despite 3 agents or a blood pressure < 140 mm Hg with ≥ 4 agents.

CONCLUSIONS: In patients with coronary artery disease, apparent treatment-resistant hypertension is associated with a marked increase in the risk of cardiovascular morbidity and mortality, including an increase in all-cause death.

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Over the past decade, considerable progress has been made to improve awareness, increase recognition and treatment, and enhance control rates of hypertension.¹ Despite this progress, 1 in 2 patients still have uncontrolled blood pressure.¹ Although there are a number of reasons for uncontrolled blood pressure, including physicians' inertia to up-titrate or switch medications, patients' noncompliance, and various secondary causes of hypertension, there is increasing recognition over the last few years that some forms of hypertension may be resistant to treatment.² Despite this, treatment-resistant hypertension has remained an ill-recognized clinical entity. The American Heart Association (AHA) defines treatment-resistant hypertension as blood pressure that stays above goal despite concurrent use of 3 antihypertensive agents of different classes or blood pressure that is controlled with 4 or more medications.³ In many epidemiologic studies, the term "apparent treatment-resistant hypertension" is used rather than treatment-resistant hypertension because comprehensive workups to rule out secondary causes are not done, and thus individuals with pseudo-resistance cannot be identified and excluded.^{4,5} There is wide variability in the reported prevalence of treatment-resistant hypertension with reported rates of 3% to 30%,⁵⁻⁷ and data on the prognosis of these patients are scant.⁶ Therefore, it is not surprising that treatment-resistant hypertension has been identified as a priority area by the AHA.³

The prevalence and prognosis of apparent treatment-resistant hypertension in a high-risk cohort of patients with coronary artery disease are unknown. Our objective was to evaluate the prevalence, predictors, and outcomes of apparent treatment-resistant hypertension in patients with coronary artery disease.

MATERIALS AND METHODS

Patient Population

The Treating to New Targets (TNT) trial was a double-blind, parallel group study in patients aged 35 to 75 years who had clinically evident coronary artery disease defined by 1 or more of the following: previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic coronary artery disease, or a history of coronary revascularization, with a low-density lipoprotein <130 mg/dL who were randomized to atorvastatin 80 mg versus atorvastatin 10 mg. The design and results have been described in detail.^{8,9} The TNT trial is registered on clinicaltrials.gov (NCT00327691).

Treatment-Resistant Hypertension

For the purpose of this analysis, apparent treatment-resistant hypertension was defined using the AHA definition: those with blood pressure ≥ 140 mm Hg despite concurrent use of 3 antihypertensive agents of different classes or those with blood pressure <140 mm Hg but controlled with ≥ 4 medications.⁵ The use of a diuretic was not a requirement for this study given a cohort with coronary artery disease, in whom beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are preferentially used for coronary artery disease and treatment of hypertension.

Follow-up

Patients were followed up at 12 weeks and at 6, 9, and 12 months during the first year and then every 6 months thereafter. At each visit, vital signs (including blood pressure), clinical end points, adverse events, and concurrent medication information were collected. Before the double-blind phase of the TNT trial, blood pressure measurements were performed at screening, 8 weeks, 4 weeks, and 2 weeks before randomization. Blood pressure measurements were performed according to the sites' local practice, reflecting a real-world clinical practice. Antihypertensive medication up-titration was per local practice to a target systolic pressure of <130 to 140 mm Hg based on national and international hypertension guidelines for a coronary artery disease cohort.

Study Outcomes

The primary outcome was the occurrence of a major cardiovascular event, defined as death from coronary heart disease, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Secondary outcomes included a major coronary event (defined as death from coronary heart disease, nonfatal nonprocedure-related myocardial infarction, or resuscitation after cardiac arrest), a cerebrovascular event, hospitalization for congestive heart failure, peripheral-artery disease, death from any cause, any cardiovascular event, and any coronary event (defined as a major coronary event, revascularization procedure, procedure-related myocardial infarction, or documented angina), angina pectoris, transient ischemic attacks, or need for coronary revascularization (coronary angioplasty or coronary bypass graft surgery), similar to that of the main trial.⁹

CLINICAL SIGNIFICANCE

- The prevalence, predictors, and outcomes of apparent treatment-resistant hypertension are unknown, especially in patients with coronary artery disease.
- Among the 10,001 patients in the Treating to New Targets trial, 11.1% patients had apparent treatment-resistant hypertension.
- Patients with apparent treatment-resistant hypertension had a significant increase in the risk of cardiovascular morbidity and mortality, including an increase in death, myocardial infarction, heart failure, angina, and coronary revascularization with numerically increased risk of stroke.

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