Editorial Commentary

Hypertension Treatment
How Important Is Consistency of Effect?

Domenic A. Sica

There has been a steady stream of large outcomes trials in the last 20 years that have attempted to answer important questions in cardiovascular disease with the INternational VErapamil SR-TRandolapril (INVEST) Study being one such trial.1 The original intent of the INVEST Study was to compare mortality and morbidity outcomes in patients with hypertension and coronary artery disease treated with a calcium channel blocker (CCB)–based strategy versus a β-blocker–based strategy. The premise behind this study was a rather simple one, and at the end of the day, this study showed that a verapamil-based regimen (CCB strategy) and an atenolol-based regimen (β-blocker strategy) similarly reduced the primary composite end point of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke.1

Outcome trials are often monumental undertakings with the perception of end-of-study results ranging from the common “so what” to a less frequent “that’s an important finding.” In these trials, the sense of indifference to neutral (or negative) findings typically endures unless secondary or posthoc analyses provide additional helpful information. Even then, many remain nonplussed with the statistical acrobatics needed to show one treatment to somehow be more meaningful than another.

How do these issues then relate to the INVEST trial, where the findings were primarily neutral ones?1 Shortly after its original publication, a series of posthoc analyses was undertaken with the INVEST data set to supplement the original findings. These analyses showed the following: (1) the use of verapamil SR and trandolapril in this coronary artery disease population reduced the risk of new-onset diabetes;2 (2) the risk for the primary outcome, all-cause death, and myocardial infarction, but not stroke, progressively increased with a diastolic blood pressure (BP) <70 to 80 mm Hg (J-shaped curve relationship);3 and (3) an increased risk for adverse outcomes was associated with conditions related to the severity of coronary artery disease and diminished left ventricular function.4 Although each of these findings generated some interest, none could be viewed as being sufficiently newsworthy to “stop the presses.”

Such, however, is not the case with the study by Mancia et al5 in this issue of Hypertension. In a posthoc analysis of the large database compiled from the INVEST Study, they have carefully evaluated a 22 576-patient cohort of patients with hypertension and coronary artery disease as to the relationship between the study’s composite outcome (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death) and the proportion of study visits in which BP was controlled to a value <140/90 mm Hg.

This is the first time that such an analysis has been undertaken, let alone in a study of this magnitude. In this posthoc analysis, patients were separated into 4 groups according to the percentage of visits (<25%, 25% to <50%, 50% to <75%, and ≥75%) in which BP was controlled. A particular strength of this analysis was the number of visits for each patient (6, 12, 18, and 24 weeks and every 6 months thereafter), as well as the length (average patient follow-up of 2.7 years) of the study; thus, interpretation of these data was not confounded by either small numbers or a condensed period of surveillance.

The findings from this analysis were enlightening in that the risk of cardiovascular morbidity and mortality, as well as the risk of myocardial infarction or stroke, was inversely related to the percentage of on-treatment visits in which BP was observed to be controlled. This relationship was found in diabetic and nondiabetic subjects and was maintained after adjustment for differences in all of the pertinent demographic, clinical, and therapeutic characteristics of the patient cohort; moreover, this positive relationship was independent of the baseline BP levels in the individual percentage of visit groups; thus, once again, strong evidence emerges in support of the timewise nature of BP control as a critical determinant of event rate reduction.6,7

There are a number of important considerations relating to this particular posthoc analysis of the INVEST Study. Older, black, diabetic, and overweight patients had the least reduction in BP and had the lowest proportion of visits with BP under control. These patient demographics are typically viewed as predictors of a poor BP response to therapy and now can also be considered as indicators of a lesser consistency of response.

The data in this analysis were pooled; that is, the results from the β-blocker atenolol and the CCB verapamil groups were merged. Of note, at 24 months, in the CCB-based treatment group, 6391 patients (81.5%) were taking verapamil-sustained release; 4934 (62.9%) were taking trandolapril; and 3430 (43.7%) were taking hydrochlorothiazide. In the β-blocker group, 6083 patients (77.5%) were taking atenolol; 4733 (60.3%) were taking hydrochlorothiazide; and 4113 (52.4%) were taking trandolapril.

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The question arises in this study as to whether “pooling” of data could have diluted the positive outcomes resulting from better BP control, as qualified by below-goal BP readings at a greater proportion of visits. The authors state that the results were similar for both treatment strategies; therefore, this, together, with the similarity in BP control, legitimated pooling. Pooling of treatment group data, however, might mask a pleiotropic effect attributable to angiotensin-converting enzyme inhibitor and/or CCB therapy by way of a negative effect from use of the β-blocker atenolol; conversely, a lesser effect with atenolol may possibly have been masked by a potentially “positive” pleiotropic influence from angiotensin-converting enzyme inhibitor and/or CCB therapy.

Careful examination of the large scale drug-versus-drug hypertension trials suggests that the initial drug choice is, for the most part, of token importance and that better BP control is the primary determinant of superior outcomes. The best long-term outcome for hypertensive patients is typically seen when antihypertensive therapy has controlled BP effectively throughout 24-hour cycles of treatment. Outcome trials have, for the most part, relied on office-based BP determinations, a technique that typically uses single point-in-time measures of BP to qualify between-treatment differences.

Office-based BP determinations in outcome trials have been increasingly critiqued in that they may fail to detect important differences in outside-the-office BP, particularly as can occur during sleep. It is now apparent from the study of Mancia et al5 that the functional use of office-based readings can occur during sleep. It is now apparent from the study of important differences in outside-the-office BP, particularly as been increasingly critiqued in that they may fail to detect measures of BP to qualify between-treatment differences.

In conclusion, more pieces have been added to the puzzle regarding the optimum BP for preventing cardiovascular events: persistence and consistency of effect. It would seem that the more often in the course of a clinical trial that the BP is at goal, the better the outcome. It is surprising that the concept brought forward by Mancia et al5 has not previously been brought to bear in the analysis of outcome trials. Future studies should analyze their data according to on-treatment control and not just by the change in BP from beginning to end of the study.

Disclosures
None.

References
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