T
here 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 mor-
tality, 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?2 Shortly after its
original publication, a series of posthoc analyses was under-
taken 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;3 (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);1 and (3) an increased risk for adverse
outcomes was associated with conditions related to the
severity of coronary artery disease and diminished left ven-
tricular 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 relation-
ship 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 characteris-
tics of the patient cohort; moreover, this positive relationship
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 reduc-
tion 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 consis-
tency 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 verap-
amil-sustained release; 4934 (62.9%) were taking trandola-
pril; 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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editors or of the American Heart Association.

From the Section of Clinical Pharmacology and Hypertension, Divi-
sion of Nephrology, Virginia Commonwealth University Health System,
Richmond.

Correspondence to Domenic A. Sica, Box 980160 MCV Station,
Richmond, VA 23298-0160. E-mail DSICA@HSC.VCU.EDU

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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, legitimatized 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 al that the functional use of office-based readings can be further fortified if BP control is viewed in a longitudinal fashion, and the better it is controlled during the period of surveillance, the more likely it is that a favorable outcome will arise. This might be best conceptualized as an area under the curve for overall BP control with the time axis being months to years rather than “day(s),” as is the case when 24-hour ambulatory BP monitoring is used.

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 al 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

Hypertension Treatment: How Important Is Consistency of Effect?
Domenic A. Sica

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