

Controlled-onset extended-release verapamil was not equivalent to standard therapy for preventing cardiovascular disease

Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial. *JAMA*. 2003;289:2073-82.

QUESTION

In patients with hypertension, is initial therapy with controlled-onset extended-release (COER) verapamil equivalent to standard therapy for preventing cardiovascular disease (CVD) events?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, and data analysts),* placebo-controlled trial with median 3-year follow-up (Controlled Onset Verapamil Investigation of Cardiovascular End Points [CONVINCE] trial).

SETTING

661 centers in 15 countries.

PATIENTS

16 602 hypertensive patients ≥ 55 years of age (mean age 66 y, 55% women) with ≥ 1 other established risk factor for CVD. Follow-up was 93%; 16 476 patients (99%) were included in the analysis.

INTERVENTION

Patients were stratified by site and standard care (atenolol or hydrochlorothiazide) in blocks of 2, 4, or 6, and were allocated to initial treatment with COER verapamil, 180 mg ($n = 8241$), or standard therapy (atenolol, 50 mg or hydrochlorothiazide, 12.5 mg) ($n = 8361$). All patients received placebo of the alternate treatment. If blood pressure could

not be controlled, doses were doubled and any antihypertensive agents (except non-dihydropyridine calcium antagonist, thiazide diuretic, or β -blocker) could be added.

MAIN OUTCOME MEASURES

Composite of first occurrence of acute myocardial infarction (MI) (satisfying ≥ 2 of acute MI symptoms lasting > 15 min, electrocardiographic changes [new persistent ST-segment elevation or pathologic Q waves in 2 contiguous leads], and increased cardiac enzymes [> 2 times the upper limit of normal]), stroke (presence of focal neurologic deficit lasting > 24 h), and CVD death. Secondary outcomes included CVD, all-cause mortality, and hospitalization for bleeding (excluding hemorrhagic stroke).

MAIN RESULTS

Analysis was by modified intention to treat (2 sites were excluded because of data integrity concerns). Both COER verapamil

and standard therapy lowered blood pressure. The hazard ratio for the composite endpoint of MI, stroke, or CVD death was 1.02 (95% CI 0.88 to 1.18, $P = 0.77$) (Table). The upper limit of the CI exceeded the prespecified boundary (1.16) for showing equivalence. More patients in the COER verapamil group died or were hospitalized because of bleeding than those in the standard-therapy group (Table). The groups did not differ for any other secondary outcome.

CONCLUSION

In patients with hypertension, controlled-onset extended-release verapamil was not equivalent to standard therapy for preventing cardiovascular disease events.

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*See Glossary.

Controlled-onset extended-release (COER) verapamil vs standard therapy (atenolol or hydrochlorothiazide) for hypertension at median 3 years†

Outcomes	COER verapamil	Standard therapy	Hazard ratio (95% CI)
Composite endpoint‡	4.5%	4.4%	1.02 (0.88 to 1.18)
Death or hospitalization caused by bleeding	1.4%	1.0%	1.54 (1.15 to 2.04)

†CI defined in Glossary.

‡Composite endpoint = first occurrence myocardial infarction, stroke, or cardiovascular-related death.

COMMENTARY

The primary aim of CONVINCE was important: to determine whether extended-release verapamil was equivalent to atenolol and hydrochlorothiazide for preventing CVD events. The investigators had planned to evaluate 16 000 patients over 5 years; however, the study closed after only 3 years of follow-up for "commercial reasons." As a result of the reduced study length as well as an unexpectedly large (nearly 50%) dropout rate, the study suffered from the crucial flaw of having insufficient statistical power to detect significant differences between treatment groups.

Publication of the study and its accompanying editorial (1) facilitated a compelling discussion of an ethical dilemma: that physicians, the public, and study participants will not benefit from the potentially insightful completed data comparing the effects of a calcium channel-centered antihypertensive regimen with that of a β -blocker and diuretic-centered regimen. One of the limitations of the landmark ALLHAT study (2) was the exclusion of β -blockers as one of the principal treatment arms.

As in other recent trials, many patients in CONVINCE were not controlled with monotherapy and required additional treatment.

Attention to a standardized protocol for adding medications would strengthen future trials of antihypertensive treatment.

Definite conclusions regarding the comparative rate of overall CVD-related events and adverse events among treatment groups cannot be drawn from the results of this abbreviated clinical trial. But what can be learned from it? This study is consistent with others in providing no evidence that any antihypertensive agent is superior to diuretic therapy for initial treatment of hypertension. In addition, the finding of slightly increased bleeding risk and greater cost supports the argument that calcium channel blockers are not ideal as first-line choices for hypertension treatment.

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References

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2. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-97.