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Questions and Answers Related to the INternational VErapamil SR/trandolapril STudy (INVEST)

What is INVEST?

The INternational VErapamil SR/trandolapril STudy (INVEST) is an ongoing international, multicenter, prospective, randomized, controlled clinical trial comparing a calcium-antagonist treatment strategy (verapamil SR) with a noncalcium-antagonist treatment strategy (atenolol) for the control of hypertension in a primary care patient population with coronary artery disease (CAD). In this study, 22,599 patients were enrolled between September 1997 and December 2000 by 862 investigators from around the world. The study is in the follow-up phase and should be completed in December of 2002. Further information regarding INVEST can be accessed via the Internet (http://invest.biostat.ufl.edu).

What are the treatment strategies used in INVEST?

The calcium-antagonist-based strategy uses verapamil SR at an initial dose of 240 mg/day. After 6 weeks, an angiotensin-converting enzyme (ACE) inhibitor (trandolapril) may be added at a dose of 1–8 mg/day. If blood pressure remains uncontrolled, a diuretic (hydrochlorothiazide) may also be added at a low dose (12.5–25 mg/day). Physicians may increase the dosage of the verapamil SR/trandolapril combination and the diuretic, as necessary, to control blood pressure. The calcium-antagonist strategy may use trandolapril at any time if required for a special population (diabetes, left ventricular dysfunction, renal insufficiency).

The noncalcium antagonist-based strategy does not contain a calcium antagonist. Hypertension management is initiated with a beta blocker (atenolol) at a dose of 50 mg/day. If blood pressure targets are not achieved, a diuretic (hydrochlorothiazide) may be added at a low dose (12.5–25 mg/day), then the ACE inhibitor (trandolapril) (1–8 mg/day) may be added. In both strategies, physicians are prompted to increase doses of the calcium antagonist, the beta blocker, the diuretic, and/or the ACE inhibitor as necessary to achieve target blood pressure values. Target blood pressures are < 140/< 90 mmHg in general, and < 130/< 85 mmHg for those special populations identified in the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).

What are the objectives of the study?

The primary objective of this trial is to examine the hypothesis that hypertension treatment with a calcium antagonist-based treatment strategy is equivalent or superior to a noncalcium antagonist-based treatment strategy in terms of the risk for adverse outcomes in hypertensive patients with documented CAD. The primary adverse outcome is a composite of death, nonfatal myocardial infarction, or nonfatal stoke.

The secondary objectives are to determine that these hypertension care strategies are at least equivalent in the control of blood pressure and symptoms of myocardial ischemia, and in the number of major adverse experiences.

What is unique about INVEST's approach to data management?

INVEST uses a specially designed electronic communication and data management system on the Internet; therefore, the study does not require the use of paper. Web-based clinical trials offer many advantages for investigators, monitors, patients, and sponsors. The risks of error are minimized by providing on-screen protocol data entry and randomization information. Monitors, sponsors, and investigators have access to all data in real time, 24 h a day. The system is capable of controlling drug dispensing and modification of prescribed drug and dose. The start-up time of INVEST was minimized because of reduced training times, and no complex hardware or software installations were necessary.

Why is INVEST likely to affect future hypertension management guidelines?

INVEST is the first clinical trial to use the JNC VI guidelines as goals for therapy. The JNC VI guidelines set a blood pressure goal of < 140/90 mmHg for patients who do not have diabetes or renal failure. For patients with preexisting diabetes or renal failure, the target blood pressure is < 130/85 mmHg. With 22,599 patients enrolled in the trial, INVEST will reveal much new information regarding the attainability and benefits of the JNC VI guidelines. Furthermore, with this sample size, there are adequate numbers of diabetics, Hispanics, obese patients, and other special populations to draw meaningful conclusions.

Are there any preliminary data available on cardiovascular outcomes that have taken place in the enrolled population?

For the overall trial (both treatment groups), the blood pressure control rates appear excellent when compared with other completed clinical trials and clinical practice. Overall, the cardiac event rate in the study is approximately 2.5% per year among randomized patients. These data are preliminary, but the cardiac event rate is as expected when the study was designed.

Will the Web-based clinical design of INVEST eliminate the need for monitor visits in clinical trials?

Monitoring visits will continue to occur in clinical trials, but the process will likely change. Monitors will still be required to confirm that data in a patient's medical record agree with data entered in a database. In addition, monitors will be required to check informed consent forms and other documents. However, monitoring visits will be fewer in number and more efficient as a result of electronic data entry. Because monitors will have access to site data prior to the visit, they will be more efficient at the site in reviewing source documentation and complete the monitoring visit in an expedited manner.