Editorials

Managing hypertension in European patients with coronary artery disease: design, results, and clinical implications of INVEST

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Introduction

Coronary heart disease (CHD) remains the principal cause of death among Europeans, as well as other parts of the industrialized world. In Europe, for example, CHD accounts for almost 2 million deaths each year[1]. In recent decades, sharp rises in CHD mortality have been observed in most Central and Eastern European countries, while such rates have declined in most Northern and Western European nations and in some Southern European countries. In Italy, for example, CHD mortality rates decreased 35% in men and 52% in women from 1968 to 1993[1]. Nonetheless, the prevalence of CHD in Europe is considerable and will remain so as populations age and more patients survive CHD-related events. Moreover, recent epidemiologic studies have found that many comorbid conditions are common in this high-risk population, including diabetes, obesity, hypercholesterolemia, and hypertension[1-4]. Managing CHD, or coronary artery disease (CAD), has become, more often than not, the management of several disorders.

Rationale for controlling hypertension

Controlling hypertension in CAD patients is critical because of its association with increased risk of stroke, as well as acute coronary events and death[5], in a population that is already at high risk for such events. Alarmingly, there is a high prevalence of hypertension in CAD patients that is not adequately controlled. The EUROpean Action on Secondary and primary Prevention through Intervention to Reduce Events (EUROASPIRE) surveys I (1995-1996)[3] and II (1999-2000)[4] have provided valuable information on the clinical characteristics and treatment of CAD patients in 15 European countries. Despite increases in the use of antihypertensive agents from EUROASPIRE I to II (85 to 91%, respectively) and combination antihypertensive therapy (53 to 61%, respectively), the prevalence of hypertension (blood pressure [BP] ≥ 140/90 mmHg), remained virtually unchanged (55 to 54%, respectively), as did the proportion of patients who were using antihypertensive agents and had controlled BP (44 to 45%, respectively)[6]. BP control remains an elusive goal in the CAD population.

Hypertension in coronary artery disease patients. Clearly, these findings, which are also consistent with those from North America[2,7], highlight a major opportunity to reduce coronary morbidity and mortality in Europe and elsewhere through better, more aggressive management of hypertension in patients with CAD. Additionally, the evidence base on BP management among patients with CAD is very limited. These issues provided the rationale for the INternational VErapamil-trandolapril STudy (INVEST)[8,9]. INVEST was a large, prosp-ective, randomized, open-label, blinded endpoint design[10] trial that investigated the management of hypertension in older patients (≥ 50 years) with established CAD. More than 22 500 patients with CAD and hypertension were randomized at 862 sites in 14 countries between September 1997 and February 2003.

INVEST compared the clinical efficacy of a calcium antagonist-based (verapamil sustained release [SR]) multidrug strategy to that of a beta-blocker-based (atenolol) multidrug strategy. The latter has been considered the "standard of care" for hypertension in CAD patients[11,12]. These strategies were found to be equivalent for the primary outcome of first occurrence of death (all-cause), nonfatal myocardial infarction (MI), or nonfatal stroke[8]. Furthermore, use of these strategies resulted in excellent and well-maintained BP control, particularly when compared with other randomized trials. An unexpected and clinically relevant finding was that new diabetes was less frequent in the verapamil SR multidrug strategy compared with the atenolol multidrug strategy.

The results of INVEST have many important clinical implications for managing hypertension in CAD patients. INVEST is one of the few large trials that incorporated treatment guidelines – the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI)[12] – into its design. This prespecified angiotensin-converting enzyme (ACE)-inhibitor for patients with heart failure, diabetes, or renal insufficiency. The multiple geographic regions represented in the INVEST ensured a diverse population so that primary results would be relevant for different ethnic groups and regions, such as Europe. INVEST included 1461 patients from Europe (Italy, Germany, Hungary, and Turkey), Steering Committee members from Spain, Germany, Hungary, France, and Turkey, as well as Data Safety Monitoring Committee members from England and Sweden. So this study was truly an international effort with a prominent European representation. Although analyses of European patients are ongoing, preliminary analyses of these and other patient subgroups[13-15], have yielded additional and clinically relevant results.

Few trials have examined the management of hypertension in CAD patients. Thus, management has been necessarily based on extrapolation of data from subgroups of large hypertension and post-MI studies. As a result, beta-blockers have remained the standard of care for several years. Both the fifth report of JNC (JNC-V)[11] and JNC-VI[12] recommended initial treatment with a beta-blocker for CAD patients. Beta-blockers effectively reduce BP and have been shown to reduce the risk of mortality and cardiovascular morbidity in prior MI patients[16]. If beta-blockers were ineffective or contraindicated, then long-acting calcium antagonists were recommended. Calcium antagonists reduce BP and anginal symptoms, and "modest" reductions in cardiovascular events and mortality in prior MI patients have been observed with these agents[12]. Heart rate reducing nondihydropyridine calcium antagonists have also been shown to reduce the risk of death and reinfarction in acute CAD trials done in Italy and Scandinavia[17]. European guidelines, at this time, were similar but less specific than JNC-VI, recommending either beta-blockers or calcium antagonists but noting that there were more extensive data on managing hypertension with beta-blockers[18]. Not surprisingly, the use of beta-blockers was high in EUROASPIRE I (54%) and actually increased in EUROASPIRE II (66%)[19].

Hypertension guidelines. Several guidelines, including JNC-VI[12] and the European guidelines[18], have recognized the effectiveness of combination therapy over monotherapy and the necessity of multiple agents to adequately control BP in many patients. By using agents with different mechanisms of action, combination therapy has been shown to improve BP control and reduce drug-related adverse events. However, data supporting use of combination therapy in CAD patients were lacking. Because beta-blockers alone are often ineffective in controlling BP in elderly patients[20], thiazide diuretics are frequently added. But even in the recent and largely European Losartan Intervention For Endpoint (LIFE) trial[21], a beta-blocker-hydrochlorothiazide (HCTZ) combination resulted in < 50% of patients reaching the BP goal of < 140/90 mmHg. More recently, however, the combination of calcium antagonists with ACE-inhibitors has been shown to improve BP control and provide organ protection[22-25].

Although regimens using beta-blockers are clinically effective antihypertensive treatments, the comparative similarities or benefits of these agents over regimens using calcium antagonists have not been convincingly demonstrated in elderly populations likely to have CAD[20,21]. Recent trials in high-risk hypertensive patients have demonstrated that regimens using agents targeting the renin-angiotensin system (i.e., ACE-inhibitors and angiotensin receptor blockers) are more effective than beta-blocker and/or diuretic regimens[21,26]. Furthermore, beta-blockers and diuretics are associated with adverse metabolic effects and increased risk of diabetes[21,27,28]. Clearly, more evidence-based treatment data are needed to help direct the management of hypertension in CAD.

INVEST: design, results, and implications

For INVEST, we hypothesized that a calcium antagonist-based strategy would be equivalent to a beta-blocker-based strategy for the primary outcome of first occurrence of all-cause death, nonfatal MI, or nonfatal stroke (primary outcome). We utilized the JNC-VI guidelines[12] to formulate a complex treatment algorithm to achieve JNC-VI BP targets of < 140/90 or < 130/85 mmHg for patients with diabetes or renal impairment[12]. Because most complex patients require more than one agent to achieve such control and because of the recognized benefits of combination therapy, INVEST was designed to compare multidrug strategies rather than simply the single agents. The calcium antagonist strategy used verapamil SR as the base therapy, and sequentially added the ACE-inhibitor trandolapril and

then the diuretic HCTZ to achieve BP control. The beta-blocker strategy, on the other hand, used atenolol as the base therapy, and sequentially added HCTZ and then trandolapril to achieve BP control. The rationale for this differential sequence was to contrast strategies – a calcium antagonist strategy based mainly on verapamil SR plus trandolapril and a beta-blocker strategy based mainly on atenolol plus HCTZ. In patients with diabetes, heart failure, or renal impairment[12], trandolapril was also recommended at treatment initiation.

Overall population. INVEST randomized 22 576 patients with CAD and hypertension to either the verapamil SR or atenolol strategy[8]. Hispanic, Black, and female patients were well represented. Comorbid conditions, such as hypercholesterolemia and diabetes, were not uncommon. The majority of patients reported the use of one antihypertensive drug at baseline, so it was not surprising that only 18.9% of patients had controlled BP at baseline[8].

European versus non-European population. The majority of European patients (n = 1461) were Caucasian (96.6%) and JNC-VI BP control at baseline was remarkably low (5.0%). Use of combination antihypertensive therapy at baseline was lower in European patients than in non-European patients (34 vs 43%, p < 0.001). Another notable difference between European and non-European patients at baseline was use of aspirin or other antiplatelet drugs; over three quarters of European patients (75.7%) used these drugs and only 6.4% used nonsteroidal anti-inflammatory drugs (NSAIDs), a finding which concurs with EUROASPIRE II[19]. The comparative values for non-European patients were 55.3 and 18.6%, respectively.

US population. Because the majority of the non-European patients were US participants, this finding was not entirely surprising. Aspirin use in the CAD population remains comparatively low (38% in 2001) in the United States despite substantial increases since 1990 when only 5% of CAD patients were using aspirin[29]. In addition, many patients were using other NSAIDs, which are labeled not for use concurrently with aspirin. Concurrent use of NSAIDs and aspirin increases the risk of gastrointestinal complications[30].

Aggressive hypertension management. Results from INVEST clearly demonstrated the benefit of aggressively managing hypertension in patients with CAD. As planned, use of strategy drugs differed between treatment groups. Patients in the calcium antagonist strategy were mainly using verapamil SR and trandolapril in combination, while patients in the beta-blocker strategy were mainly using the combination of atenolol and HCTZ. Both strategies effectively maintained similar and excellent BP reduction over 48 months of follow-up. At 2 years, BP control of < 140/90 mmHg was achieved by > 70% of patients in both treatment strategies[8]; and > 40% of patients with diabetes in both strategies achieved JNC-VI BP control (< 130/85 mmHg)[13], an unprecedented achievement in a large randomized trial. Overall, patients achieving a systolic BP < 140 mmHg had an event rate of 8.1% compared to those with systolic BP ≥ 140 mmHg where the event rate was 14.5% (adjusted hazard ratio 0.65, 95% confidence interval 0.60-0.71)[14]. BP control at 24 months was exceptional in European patients (n = 1016) with nearly 80% of patients achieving levels < 140/90 mmHg and > 70% of patients achieving JNC-VI BP control.

Data on the use of strategy and nonstudy antihypertensive drugs at 2 years indicated that most INVEST patients required multiple drugs to achieve BP control[8]. Almost 70% of patients were receiving ≥ 2 strategy drugs, and more than 80% were receiving ≥ 2 strategy plus nonstudy antihypertensive drugs, with no differences between strategies. The use of 3 strategy drugs also was not uncommon with more than one third of patients in each strategy using such a regimen[8].

Clinical outcomes. INVEST patients were followed for a mean of 2.7 (5.4 maximum) years, accumulating a total of 61 835 patient-years[8]. There were a total of 2380 confirmed adverse outcomes, and 2269 patients had a confirmed event in the primary outcome cluster of all-cause death, nonfatal MI, or nonfatal stroke. Time to first occurrence of death (all cause), nonfatal MI, or nonfatal stroke was similar between the verapamil SR and atenolol strategies, and strategies were statistically equivalent for the primary outcome (relative risk 0.98, 95% confidence interval 0.90-1.06) (Fig. 1). In addition, no differences were observed between strategies for the individual outcomes of all-cause death, cardiovascular death, nonfatal MI, fatal and nonfatal MI, nonfatal stroke, fatal and nonfatal stroke, and cardiovascular hospitalization.

Predictors of risk. Baseline comorbidities associated with an increased risk for the primary outcome included prior heart failure, diabetes, renal impairment, cerebrovascular disease, prior MI, peripheral vascular disease, and prior coronary revascularization[14]. These risk increases were not unexpected, particularly in diabetics who had an almost 2-fold higher event rate compared with nondiabetics (14.3 vs 8.4%, respectively)[8]. Differences in the primary outcome were also observed among Hispanic, Caucasian, and Black patients and appeared to correspond, in part, to differences in BP reduction[15]. Analyses of high-risk patient subgroups demonstrated no differences between strategies for risk of the primary outcome, except those patients with prior heart failure in the atenolol strategy who appeared to do better than those in the verapamil SR strategy (incidence 21.8 vs 26.3%, respectively; p = 0.03 for interaction)[8]. This benefit concurs with recent randomized beta-blocker trials in heart failure patients[31-33].

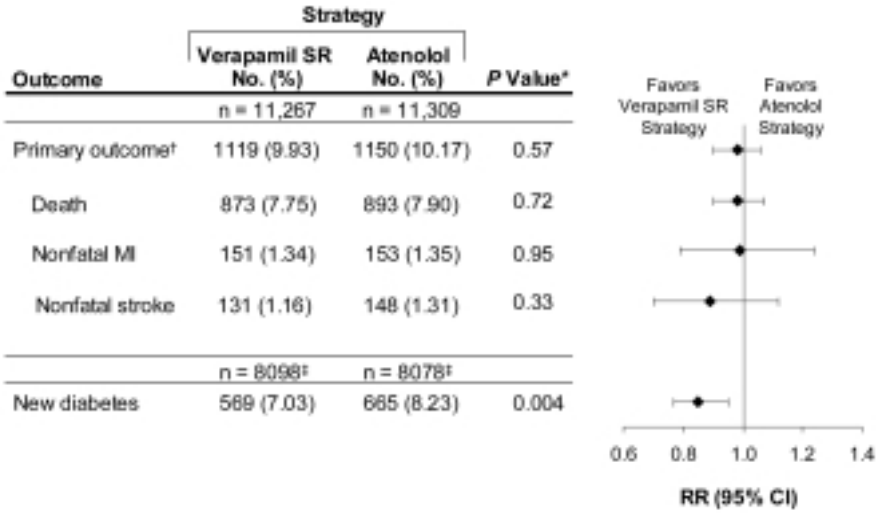

Figure 1. *Incidence and risk of adverse clinical outcomes during the INVEST. * from Kaplan-Meier analysis; † first occurrence of all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke; ‡ patients without diabetes at baseline. CI = confidence interval; RR = relative risk; SR = sustained release. From Pepine et al.[8], modified.*

Effects on indices of transient cardiac ischemia. Other efficacy differences were observed between the 2 strategies[8]. Patients in the verapamil SR strategy had a significantly lower mean frequency of angina episodes than patients in the atenolol strategy (0.77 vs 0.88 episodes/week, respectively; p = 0.02), although this difference may not be clinically significant. It should be noted that patients in the atenolol strategy had a greater reduction in heart rate from baseline to 2 years than the verapamil SR strategy, and thus, the atenolol strategy group had a greater reduction in double product (heart rate × systolic BP). These differences suggest that the antianginal effects of the verapamil SR-trandolapril combination might have been, at least in part, the result of mechanisms other than reduction in cardiac oxygen demands for the verapamil SR strategy. Also, although about three quarters of the patients had angina at entry, only about one fourth reported angina at closeout; and the need for coronary revascularization was very low at only about 2% in each strategy over the course of follow-up. This attests to the effectiveness of good BP control for angina control.

Effects on new diabetes. A clinically significant difference between strategies was the lower risk of new diabetes observed in the verapamil SR strategy compared with the atenolol strategy (Fig. 1; incidence 7.03 vs 8.23%, respectively; relative risk 0.85, 95% confidence interval 0.77-0.95)[8]. Multivariate analysis with drug-dose modeling suggested that increased trandolapril use in the verapamil SR strategy was associated with protection against new diabetes, while HCTZ use in the atenolol strategy was associated with a nonsignificant increase in risk for diabetes[8]. These findings of INVEST are consistent with data from 8 other randomized trials that included over 100 000 patients[34]. In all of these studies, new diabetes occurred less frequently in patients using agents modifying the renin-angiotensin system (i.e. ACE-inhibitors or angiotensin receptor blockers) and/or calcium antagonists than those with regimens containing a high frequency of diuretic and/or beta-blocker use. It has been confirmed that patients who develop diabetes during treatment have less favorable long-term outcomes[35,36].

Safety and tolerability. Both treatment strategies in INVEST were generally well tolerated. A few differences were noted for drug-related adverse experiences[8]. Constipation and cough were significantly more common in the verapamil SR strategy, whereas dyspnea, lightheadedness, symptomatic bradycardia and wheezing were more common in the atenolol strategy. Historically, it has been suggested that calcium antagonists, especially short-acting dihydropyridines, are associated with increased risk of cancer, gastrointestinal bleeding, and all-cause mortality in patients with CAD[37-39]. INVEST[8] and other trials[27,40] have found no evidence to support such a suggestion.

Limitations of INVEST. The INVEST study had some limitations that should be noted. Firstly, it employed JNC-VI BP targets[12], whereas recent epidemiological data and JNC-VII guidelines[41] indicate that systolic BP > 115 mmHg is associated with increased CHD risk. Thus, even lower BP targets than those used in INVEST may have been appropriate. Secondly, despite excellent BP control during follow-up and the permitted use of additional nonstudy antihypertensive drugs, more patients may have achieved BP control had a fourth study drug (with a different mechanism of action) been provided. Finally, the potential clinical importance of other study findings, particularly the apparent protective efficacy of trandolapril against developing diabetes, requires further investigation and confirmation.

There are also important distinctions of INVEST that should be noted. INVEST was the first, large scale trial to use JNC-VI BP targets, which are lower than those used in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[27] and the LIFE study[21]. Also, BP levels were very similar in the two INVEST study groups during follow-up, whereas in ALLHAT and LIFE, BP levels differed among the study groups, which may have influenced outcomes. Another unique aspect of INVEST was the comparison of multidrug strategies that specified and documented in detail the use of 3 antihypertensive agents with differing mechanisms of action in each treatment arm. In addition, the ACE-inhibitor trandolapril was specified for all patients with diabetes, heart failure, or renal impairment to provide organ protection. Further analyses of the INVEST data with drug-dose modeling should provide valuable information on the risks and benefits associated with the 4 strategy drugs when used in combination therapy.

INVEST and guidelines. The principal results of INVEST are an important addition to our evidence base on hypertension management in CAD patients, particularly in light of the 2003 hypertension guidelines issued jointly by the European Society of Hypertension and the European Society of Cardiology (ESH-ESC)[5] and the recent JNC-VII guidelines[41]. The 2003 ESH-ESC guidelines recommend treatment in patients with CAD if BP is > 130/85 mmHg. However, there is no direct guidance about which agents to use. Diuretics, beta-blockers, calcium antagonists, and ACE-inhibitors are all presented as drug classes with evidence of benefit in patients with CAD. In contrast, JNC-VII guidelines recommend beta-blockers followed by long-acting calcium antagonists as the agents of choice for hypertensive patients with ischemic heart disease[41]. Both guidelines recognize the effectiveness of combination therapy in a large proportion of patients with the decision based on the degree of BP lowering required and the presence of comorbidities.

INVEST supports and complements these guidelines. Results demonstrate that BP control is achievable in CAD patients with aggressive multidrug treatment and that verapamil SR- and atenolol-based strategies should be considered equally effective. While nondihydropyridine calcium antagonists and beta-blockers have unique benefits in this patient group and are appropriate cornerstones of therapy, it is also important to recognize that multidrug therapy may be appropriate early on to achieve BP control and to provide benefits beyond BP control (i.e., organ protection) for those patients with comorbid conditions. Hypertension management in CAD patients should concentrate on the overall risk profile of individual patients, and on an entire treatment strategy rather than one agent alone. Patients with preexisting heart failure may be best served by a beta-blocker strategy, whereas patients at high risk for diabetes may derive greater clinical benefit from a calcium antagonist strategy, particularly one including an ACE-inhibitor. ACE-inhibitors are useful components of antihypertensive strategies, particularly for patients with diabetes, heart failure, or renal impairment, because these agents act synergistically to reduce BP and have organ-protective benefits. Ultimately, the decision about how to best manage hypertension in patients with CAD should be based on multiple factors, including physician prudence and a detailed knowledge of the potential for adverse events, and not simply a history of heart failure or high risk for diabetes.

Managing hypertension in Europe. The EUROASPIRE surveys underscore the clinical challenge facing the European medical community in managing hypertension in the CAD population. Preliminary analyses demonstrate that BP control is achievable in European patients with CAD. Several INVEST substudies are underway that will further analyze patient characteristics associated with risk, new diabetes, and outcomes in patients with diabetes. Another substudy is analyzing DNA obtained from 6000 INVEST patients and should help to answer questions about whether genetic profiling is helpful to better direct BP management in CAD patients. Analyses of European patients are also underway. A European ambulatory BP monitoring substudy should provide important new data on the effects of these treatment strategies throughout the day and night. As these supplementary analyses are completed, we believe that the information provided will help to further improve and advance the global management of hypertension in CAD patients.

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