Drug Trends in Cardiology

Treating hypertensive patients with coronary artery disease: renewed interest in INVEST

The INVEST study, a very large study of 22,576 hypertensive patients with coronary artery disease (CAD) has recently been reviewed in the context of more recent studies, such as ASCOT and ACCOMPLISH, all of which focused on the use of a calcium channel blocker-led (CBB) strategy in combination with an ACE inhibitor to reduce cardiovascular events.

The Cardiovascular Journal of South Africa, precursor to the present Cardiovascular Journal of Africa, published expert comment on the results of the INVEST trial in 2003 and reported on the follow-up series of meetings held in South Africa after the 2003 American College of Cardiology (ACC) meeting at which the INVEST trial results were presented. Particularly important for our diverse society is that this trial included 13% black patients, and 52% of the patients were female.

Essential to the understanding of the INVEST study is the context in which it was initiated in the mid-nineties; mainly to answer unanswered management issues in patients with CAD. At that time, diuretics and β-blockers were the standard blood pressure-lowering therapy, although they had not been shown to reduce morbidity and mortality to the levels predicted from epidemiological studies. The newer agents such as CCBs and ACE inhibitors were increasingly being used, although outcome data were lacking at the time.

The INVEST study focused on hypertensive patients with CAD who were older than 50 years. It anticipated that very few patients would achieve target blood pressure on monotherapy and opted to test the combined use of verapamil SR 240 mg/day and trandolapril 4 mg/day against atenolol (twice daily) and hydrochlorothiazide (HCTZ) (Fig. 1). Patients were monitored every six weeks for the first six months, and then every six months until the study end (mean follow-up period 2.9 years).

The overall objective of INVEST was to compare the risk for the primary outcome (PO), defined as all-cause death, non-fatal myocardial infarction (MI) or non-fatal stroke, following treatment with the two strategies. Secondary outcomes included not only all-cause death, non-fatal MI and non-fatal stroke individually, but also new-onset diabetes and trends for cancer, Parkinson’s, Alzheimer’s and autoimmune disease and gastrointestinal bleeding, since these had all been anecdotaly attributed to long-term use of calcium antagonists.

Depression is common in CAD patients and is an important risk factor for subsequent coronary heart disease (CHD) events. Because the use of β-blockers may be associated with generalised fatigue and depression, the substudy Antihypertensive Drugs and Depression Symptoms (SADD-Sx) was carried out to examine the tolerability of the two strategies and to assess for depression at baseline and after one year of treatment.

Another ongoing substudy included ambulatory blood pressure monitoring (ABPM), in which a portion of the INVEST population underwent ABPM at baseline and after one year of follow up.

### TABLE 1. KEY FINDINGS OF INVEST

- A verapamil SR-plus-trandolapril strategy was equivalent to an atenolol (twice daily)-plus-hydrochlorothiazide strategy with regard to reduction in cardiovascular outcomes, with similar blood pressure reduction and control
- The verapamil SR plus trandolapril strategy was associated with a reduced risk for new-onset diabetes
- Elderly patients with hypertension and CAD require multi-drug therapy for blood pressure control. Lean, elderly patients should be treated carefully and blood pressure should not be lowered too far in this population
- Blood pressure reduction and reduction in angina episodes were associated with an improved feeling of well being
- Atenolol, when dosed twice daily, was not associated with increased risk of stroke or other adverse cardiovascular outcomes

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**Fig. 1. INVEST treatment strategies.** The drugs, order of addition and recommended doses for each step of each strategy are summarised. Non-study antihypertensive drugs could be added to control blood pressure except for β-blockers in those assigned to the atenolol arm.
Analysis from this substudy is underway and publications will be forthcoming.

Overall, the primary outcome of INVEST was not statistically significantly different between the two treatment arms; although new-onset diabetes was lower in the verapamil SR/trandolapril arm than in the atenolol/HCTZ arm. In fact, patients in the verapamil plus trandolapril-based group were 15% less likely to develop new-onset diabetes during follow up. Blood pressure lowering was almost identical in both treatment strategies, with more than 70% of patients reaching target blood pressure of less than 140/90 mmHg.

Angina episodes were reduced by some 50%, with fewer angina episodes being experienced with the verapamil SR/trandolapril strategy. Interestingly, patients with diabetes were taking on average three antihypertensive medications. Depression improved significantly in the verapamil-treated group, as did quality of life. Both treatment strategies were well tolerated.

The major contrast between INVEST and the two later studies, ASCOT and LIFE, is that atenolol was dosed twice daily, resulting in the more equivalent outcomes in INVEST.

This expert review of INVEST concludes that the selection of antihypertensive agents should be based on patients co-morbidities and other risks, importantly the risk of developing diabetes. Key findings are summarised in Table 1.

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2. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlopidine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo Scandinavian Cardiac Outcomes Trial – BP lowering arm (ASCOT-BPLA) a multicentre randomised controlled trial. Lancet 2005; 366(9489): 895–906.
3. Jamerson K. ACCOMPLISH ambulatory blood pressure monitoring substudy data presented as late breaking clinical trial at the American Society of Hypertension, 2009 scientific sessions. San Francisco, California, 2009.
4. Drug Trends in Cardiology. INVEST endorses verapamil in hypertensives with CAD highlights diabetes prevention. Cardiovase J South Afr 2003; 14(4): 208, 210–211.
5. Lichtman JH, Bigger JT (jun) Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008; 118(17): 1768–1775.
6. Reid LD, Tueth MJ, Handberg E, Kupfer S, Pepine CJ. A study of antihypertensive drugs and depressive symptoms (SADD-Sx) in patients treated with a calcium antagonist versus an atenolol hypertension treatment strategy in the international verapamil SR-trandolapril study (INVEST). Pharmacogenet Genomics 2007; 17(9): 719–729.

Watch these dates

| Date       | Event                                                                 | Place                  | Contact                                      |
|------------|----------------------------------------------------------------------|------------------------|----------------------------------------------|
| 14–16 March | 59th American College of Cardiology Congress. scientific sessions    | Atlanta, Georgia, USA  | www.acc.org                                   |
| 17–19 March | 7th scientific congress of the Cameroon Cardiac Society (CCS)         | Yaounde, Cameroon      | www.camcarsoc.org                             |
| 26–29 March | Cardiology at the Limits                                             | Cape Town              | www.atthelimits.org                           |
| 23–26 May  | 22nd biennial symposium of Department of Surgery                     | Sandton Convention Centre, Gauteng | www.witsbiennial.co.za                     |
| 16–19 June | World Congress of Cardiology                                         | Beijing, China         |                                               |
| 24–27 July | International Academy of Cardiology, 15th world congress on heart disease | Vancouver, Canada   | www.cardiologyonline.com                      |
| 8–11 August| SA Heart Association congress                                        | Sun City, North West   | www.saheart.org                               |
| 28 Aug – 1 September | European Society of Cardiology Congress (ESC)                      | Stockholm, Sweden      | www.escardio.org                              |
| 14–17 October | Vascular Society of Southern Africa congress (VASSA)               | KwaMaritane, North West Province | www.vascularsociety.co.za                 |
| 13–17 November | American Heart Association                                           | Chicago, Illinois, USA | www.americanheart.org                         |