FROM INSIGHT TO ACTION- REDUCING CV RISK WITH ONCE DAILY NIFEDIPINE

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The INSIGHT trial was the first major randomised outcome trial in hypertension to demonstrate that a long acting dihydropyridine calcium antagonist (nifedipine GITS - a formulation of nifedipine providing a constant concentration of drug over 24 hours or longer) was equally effective as a diuretic based regimen in reducing cardiovascular morbidity and mortality. The calcium channel blocker regimen was particularly effective in reducing blood pressure to normotensive levels but in addition offered important benefits beyond blood pressure control.

ACTION was the largest ever randomised outcome trial of an anti-anginal drug in patients with symptomatic chronic stable angina. Nifedipine GITS or placebo were added to optimal anti-anginal therapy in a double-blind manner in 7665 patients who where then followed-up for a mean period of 4.9 years. The primary endpoint for efficacy (all-cause death, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation) and primary endpoint for safety (all-cause death, acute myocardial infarction and debilitating stroke) did not differ between the two treatment groups. With nifedipine GITS the rate of death and any cardiovascular event or procedure was significantly less than with placebo and there was a significant 29% reduction in new heart failure.

A sub-group analysis of the 52% of ACTION patients who were hypertensive at baseline demonstrated a significant benefit with nifedipine GITS for the primary endpoint for efficacy, all cardiovascular events, death and any cardiovascular event or procedure and vascular events or revascularisation.

Comparison of the different CAD trials is fraught with difficulty in that the entry criteria between the trials, the definitions of endpoints and the constituents of composite endpoints all differ rather substantially. The definition of end-points is a special problem in relation to stroke and myocardial infarction. For example in ACTION the definition of myocardial infarction and heart failure would identify major events whereas in EUROPA the definition of myocardial infarction was that of the European Society of Cardiology which includes troponin positive chest pain. Debilitating stroke was an end-point in ACTION whereas the other trials included TIA and minor cerebral events.

The most clinically pertinent comparison is that between the ACE inhibitor and the calcium antagonist trials. In this context it is important to note that of the trials discussed, ACTION was the only one in which there was no change in protocol during the course of the study.

Comparison of the characteristics of the ACE inhibitor and the calcium antagonist trials reveal some important differences between the trials. These are most evident when HOPE is compared with the other studies. Diabetes and peripheral vascular disease at baseline were more common in HOPE whilst the use of beta blockers and lipid lowering drugs was markedly lower. Such discrepancies are also apparent in the annual mortality in the placebo group of the trials.

As the overall benefit across the ACE inhibitors trials are relatively modest, it seems reasonable to suggest that their therapeutic use should be based upon the anticipated absolute benefit in an individual patient particularly as these agents that provide no symptomatic benefit.

In contrast the ACTION trial conclusively demonstrates that nifedipine GITS can be used safely for the long-term treatment of CAD patients because, in addition to providing symptomatic benefit, it prolongs cardiovascular event and procedure-free survival.