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Closing Remarks: Current Position of Calcium Channel Antagonists in Hypertension – the Role of Manidipine

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These proceedings have clearly established the role of calcium channel antagonists in general, and manidipine in particular, within the context of antihypertensive treatment. The role and safety of calcium channel antagonists in the treatment of hypertension has been subject to rigorous debate since several retrospective, observational, case–control studies suggested in 1995 that short-acting calcium channel antagonists were associated with an increased incidence of coronary morbidity and mortality.[1–3] This debate has been resolved by the results of the Syst-Eur (Systolic Hypertension in Europe),[4] Syst-China,[5] STONE (Shanghai Trial of Nifedipine in the Elderly),[6] and the HOT (Hypertension Optimal Treatment)[7] studies, which showed a reduction in cardiovascular events with dihydropyridine (DHP) calcium channel antagonist-initiated therapy. Subsequent trials, including the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[8] and the VALUE (Valsartan Antihypertensive Long-term Use Evaluation)[9] trial, have compared the effects of calcium channel antagonists with those of other antihypertensive agents including diuretics, β-blockers, and angiotensin-converting enzyme inhibitors. The results of these trials have further supported the conclusion that calcium channel antagonists are as effective as other antihypertensive agents in preventing cardiovascular morbidity and mortality. Furthermore, a recent meta-analysis by the Blood Pressure Lowering Trialists' Collaboration of randomised controlled trials comparing the effects of different blood pressure-lowering regimens on major cardiovascular events substantiated the effectiveness of calcium channel antagonists in reducing the risk of major cardiovascular events in patients with hypertension.[10]

The Guidelines Committee of the European Society of Hypertension – European Society of Cardiology (ESH/ESC) examined the best available evidence from large randomised controlled trials, meta-analyses, and other sources to prepare key recommendations for the management of arterial hypertension. Their 2003 guidelines recommend that calcium channel antagonists be considered among first-choice antihypertensive agents, particularly in elderly hypertensive patients and those with angina pectoris, for whom the benefits have been well proved.[11] In establishing a therapeutic strategy, the choice of drugs should be tailored to the individual patient, taking the patient's preference into account (table I).[11] Patients should always be asked about, and particular attention should be given to, adverse events because even subjective disturbances may be an important cause of non-compliance. The guidelines also stress the point that slow-onset long-acting calcium channel antagonists should be used to avoid cardiac reflex activation in response to peripheral vasodilatation. Calcium channel antagonists, even within the DHP subclass, differ widely in the time course of their action and reported incidence of adverse events. Structural characteristics lead to slow binding of some DHPs, such as manidipine, to active cell membranes

Table I. European Society of Hypertension – European Society of Cardiology position statement on choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are caused by the lowering of blood pressure *per se*
- There is also evidence that specific drug classes may differ in some effect, or in special groups of patients
- Drugs are not equal in terms of adverse disturbances, particularly in individual patients
- The major classes of antihypertensive agents (diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) are suitable for the initiation and maintenance of therapy
- Emphasis on identifying the first class of drugs to be used is probably outdated by the need to use two or more drugs in combination in order to achieve goal blood pressure
- Within the array of available evidence, the choice of drugs will be influenced by many factors, including:
  - Previous experience of the patient with antihypertensive agents
  - Cost of drugs
  - Risk profile, presence or absence of target organ damage, clinical cardiovascular or renal disease or diabetes
  - Patients' preference

Adapted with permission from the Guidelines Committee.[11]

and subsequent prolonged release to the neighbouring calcium channels. The lipophilic, highly vasculature-selective properties of a DHP such as manidipine add important qualities to the antihypertensive properties characteristic of DHPs in general. First, they ensure a slow onset and prolonged duration of action, thus avoiding the abrupt fall in blood pressure and the accompanying sympathetic activation and reflex tachycardia that markedly reduced the tolerability, and perhaps safety, of first-generation DHPs. Second, they probably contribute to further improved tolerability by reducing the occurrence of the most frequent and troublesome adverse events that occur even with recent long-acting DHPs such as amlodipine. For example, it has been clearly demonstrated that antihypertensive treatment with manidipine is associated with much less ankle oedema than amlodipine.[12] This improved tolerability is an obvious advantage in obtaining patients' compliance with antihypertensive therapy, essential for successful blood pressure control and good clinical outcomes. Finally, manidipine has been shown to have potential beneficial effects on renal function unrelated to its antihypertensive activity, and may offer advantages in renal protection, another important goal of antihypertensive therapy.[13–18]

Current evidence-based guidelines recommend that blood pressure be lowered intensively at least to less than 140/90mm Hg, and even lower whenever possible, in all hypertensive patients.[11,19] The availability of an agent that combines powerful blood pressure-lowering properties with an excellent tolerability profile and organ protection potentialities promises to make manidipine an effective new agent for achieving the goal of cardiovascular protection in hypertension.

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