In the past, based on inconsistent data, many authors reinforced the conclusion that available evidence was inconsistent and limited; therefore the case remains open whether CCB have adverse or beneficial effects on the risks of coronary heart disease, cancer, and bleeding.

In the meantime data in favour of a positive effect of CCB were published in the Systolic Hypertension in Europe (SYST-EUR) trial [3]. In this study a long-acting member of the dihydropyridine subclass of CCB was shown to reduce the rate of cardiovascular complications among elderly patients with isolated systolic hypertension. According to these data, the sixth report of the Joint National Committee [4] considered that isolated systolic hypertension was a compelling indication for the therapy with long-acting dihydropyridines.

In 1998 the controversy reappeared with the publication of the results of the ABCD trial in the New England Journal of Medicine [5]. The appropriate blood pressure control in diabetes (ABCD) trial was a prospective, randomized, blinded trial comparing the effects of moderate control of blood pressure (target

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diastolic pressure 80–89 mmHg) with those of intensive control of blood pressure (target diastolic pressure, 75 mmHg) on the incidence and progression of complications of diabetes. The study also compared nisoldipine with enalapril as first-line antihypertensive agents. Analysis of the 470 patients in the trial who had hypertension showed a similar control of blood pressure, blood glucose and lipid concentrations with both antihypertensive drugs. Whereas, a significantly higher incidence of fatal and non-fatal myocardial infarction was found among those assigned to therapy with the CCB nisoldipine compared to those assigned to enalapril. The authors concluded that since the findings were based on a secondary endpoint, they required confirmation. This study prompted an editorial in The Lancet [6]; its authors concluded that until large randomized trials are completed, ACE inhibitors and low dose diuretics remain the preferred first-line agents for hypertensive patients with diabetes.

A few weeks ago the final results of the hypertension optimal treatment (HOT) trial have been published [7]. This trial included a total of 18,790 patients, aged 50–80 years, with hypertension and diastolic blood pressure between 100 and 115 mmHg who were randomly assigned to three different target diastolic blood pressure ≤90 mmHg, ≤85 mmHg and ≤80 mmHg. Felodipine, a long-acting dihydropyridine was given as baseline therapy in every patient with the addition of other agents, according to a five-step regimen. In addition 9399 patients were randomly assigned to 75 mg/day acetylsalicylic acid and 9391 patients were assigned to placebo.

The results of the HOT study demonstrate the benefits of lowering blood pressure in patients with hypertension to 140 mmHg systolic and 85 mmHg diastolic, or lower. Efforts to lower blood pressure further appear to give little further benefits but do not cause additional risk. Active lowering of blood pressure was particularly beneficial in the subgroup of 1500 patients with diabetes mellitus, confirming the importance of intensive treatment of this highly vulnerable population. On the whole, the rate of cardiovascular events seen during follow-up was much lower than that observed in previous prospective trials with diuretic or β-blocker therapy, probably as a consequence of the level of blood pressure control. At least these data provide assurance that claims of cardiac damage from CCB are not valid [8]. On the other hand, the HOT trial also showed that the association of a small dose of acetylsalicylic acid with active antihypertensive treatment reduced the risk of acute myocardial infarction without exaggerating the risk of cerebral bleeding. Clearer conclusions about the choice of blood-pressure-lowering drugs and there balances of risk and benefits for patients with diabetes as well as other groups of patients, will have to await the results of the current generation of randomized trials [9].

On the other hand, the capacity of CCBs to retard the progression of chronic renal failure remains to be elucidated [10]. The controversy on cardiovascular safety of CCBs has contributed to deny these drugs as first-step therapy in patients with chronic renal failure, in particular in those with diabetic nephropathy [11,12]. It is understandable, as stated by Pietro Zucchelli [11] and Robert Schrier [12], that because of their documented effects ACE inhibitors should be preferred as first line agents in patients with renal failure and hypertension. However, the contribution of CCBs to obtain the adequate control of blood pressure and proteinuria, used alone or in association with other antihypertensive agents remains to be elucidated [13]. An ongoing study, the Collaborative Study [14], will greatly contribute to answer this question. In this study a group of almost 1600 type 2 diabetic patients are being followed and treated in a double-blind fashion with irbesartan, amlopidine, or placebo. The goal of blood pressure control in this study is <130/85 mmHg, and the placebo arm will allow us to know the effectiveness of an adequate control of blood pressure per se.

References