

## Recommendations for the Treatment of Hypertension in Patients with DM: Critical Evaluation Based on Clinical Trials

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**Abstract:** Hypertension (blood pressure (BP) >140/90 mmHg) is a common comorbidity of type 2 DM (DM) and a major risk factor for macro- and microvascular complications.

To review the effectiveness of different antihypertensive drugs in reducing BP, and diabetic complications in patients with DM, we analysed clinical trials, reviews and reports, published in Cochrane Library and PubMed from 1991 to 2004.

Evidences suggest that optimal control of hypertension complications is obtained in diabetic patients when BP values are <130/80 mmHg.

Different drug classes result useful to obtain this target BP, but their effects on different metabolic and non-metabolic aspects have to be taken in account and a flexible approach according to individual response to different regimens is essential.

**Keywords:** Hypertension, DM, ACE-inhibitor, Diuretic, Calcium-channel blocker, Angiotensin-receptor blocker.

### INTRODUCTION

As stated by the last guidelines of the American Diabetes Association for Diabetes management, diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is in fact complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes [1].

Among patients with type 2 diabetes, cardiovascular disease (CVD) accounts for 70–80% of mortality, with around 15% of patients dying from stroke. Coronary heart disease (CHD) rates are 2–6 fold higher than in the non-diabetic population and there is a loss of pre-menopausal protection among diabetic women. The strength of the relation between CV risk factors and CHD is similar to non-diabetics but is at a higher level [2].

Hypertension (blood pressure (BP) >140/90 mmHg) is a common comorbidity of diabetes, affecting the majority of people with diabetes, depending on type of diabetes, age, obesity, and ethnicity. [3] Hypertension is also a major risk factor for CVD and microvascular complications such as retinopathy and nephropathy. In type 1 diabetes, hypertension is often the result of underlying nephropathy [4].

In type 2 diabetes, hypertension may be present as part of the metabolic syndrome (i.e., obesity, hyperglycemia, dyslipidemia) that is accompanied by high rates of CVD.

Randomised clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering BP to <140 mmHg systolic and <80 mmHg diastolic in persons with diabetes [5-7].

Epidemiologic analyses show that BP values >115/75 mmHg are associated with increased CV events rates and mortality in persons with diabetes [8,9].

Therefore, a target BP goal of <130/80 mmHg is reasonable if it can be safely achieved.

### NON PHARMACOLOGICAL TREATMENT OF HYPERTENSION

Although there are no well-controlled long-term studies of diet and exercise in the treatment of hypertension in persons with diabetes, reducing sodium intake and body weight (when indicated), increasing consumption of vegetables, and low-fat dairy products, avoiding excessive alcohol consumption, and increasing activity levels have been shown to be effective in reducing BP in non-diabetic individuals. In particular, even when pharmacologic agents are used, there is often a better response when there is concomitant salt restriction due to the volume component of the hypertension that is almost always present [10].

These non pharmacological strategies may also positively affect glycemia and lipid control. However, their effects on CV events have not been well measured yet.

Weight reduction can reduce BP independently of sodium intake and also can improve blood glucose and lipid levels. The loss of one kilogram of body weight has resulted in a decrease in mean 1 mmHg of BP [11]. Moderately intense physical activity, such as 30–45 min of brisk walking most days of the week, has been shown to lower BP, in

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diabetic patients as well [12]. Smoke quitting and moderation of alcohol intake are also recommended by JNC VII and are clearly appropriate for all patients with diabetes.

### THE PHARMACOLOGICAL CLASSES OF ANTI-HYPERTENSIVE AGENTS

In recent years, adequate data from well designed randomized clinical trials, have demonstrated the effectiveness of aggressive treatment of hypertension with one or more drugs in reducing both microvascular and macrovascular diabetes complications. Moreover, an adequate treatment of hypertension is linked to a reduced risk of renal failure in diabetic patients [13].

However, there is a lack of data derived from direct comparison of different antihypertensive drugs on main outcomes. Thus, the choice of drugs to be used is often taken from the metabolic effect of the antihypertensive drug, from its safety profile and from the patient comorbidities [14].

In Table 1 are resumed the antihypertensive drug classes that have shown to be somewhat useful in the treatment of diabetic hypertension: it is easy to note that the table includes the major part of available antihypertensive drugs. In the past, the drug choice was primarily derived from the metabolic neutrality of drugs and from the absolute antihypertensive effect. Today, our choice has been made more evidence-based by the results of many large long-term clinical trials on microvascular and macrovascular complication rate of diabetic patients (hard outcomes).

**Table 1. Antihypertensive Drug Classes that have Shown to Effectively Reduce Blood Pressure in Diabetic Patients; the Major Molecules Available in Italian Market**

-	Angiotensin-converting enzyme (ACE) inhibitors: Ramipril, captopril, enalapril, lisinopril, quinapril
-	Angiotensin receptor blockers (ARBs): losartan, valsartan, irbesartan, telmisartan, olmesartan, candesartan
-	Beta-blockers: Atenolol, carvedilol, bisoprolol, metoprolol
-	Dihydropyridine calcium channel blockers (CCBs): Nifedipine, amlodipine, nicardipine, isradipine, lercanidipine, felodipine, nisoldipine.
-	Diuretics: Chlorthalidone, hydrochlorothiazide, furosemide, spironolactone, amiloride

### LARGE LONG-TERM CLINICAL TRIALS CARRIED OUT ON HYPERTENSIVE DIABETICS

#### SHEP (Systolic Hypertension in the Elderly Program)

In patients  $\geq 60$  years old with isolated systolic hypertension (ISH) stepped care therapy based on chlorthalidone showed a reduction the incidence of major CV events and stroke [15].

In the 583 type 2 diabetic patients enrolled in SHEP, antihypertensive regimen resulted effective in lowering BP with few adverse effects. Based on the 5-year cumulative events rates for all major CV events, SHEP treatment prevented 101 diabetic participants per 1000 from having CVD event, compared to 51 per 1000 non-diabetic patients. Moreover, SHEP treatment demonstrated a similar favourable influence on relative risk (RR) and absolute risk for diabetic as well as non-diabetic patients.

These results suggest that low-dose diuretic therapy should be strongly considered as a first choice treatment of systolic hypertension in the presence of non-insulin treated diabetes and glucose intolerance [16].

A retrospective analysis evaluated the development of DM in all 4736 participants in the SHEP. New cases of diabetes were reported by 8.6% of the participants in the active treatment group and 7.5% of the participants in the placebo group ( $p=0.25$ ). Small effects of active treatment compared to placebo were observed with fasting levels of glucose, total cholesterol, HDL cholesterol and creatinine. Larger effects were seen with fasting levels of triglycerides, uric acid, and potassium. In conclusion, antihypertensive therapy with low-dose chlorthalidone for ISH showed to be effective in lowering BP and CV complications and has relatively mild effects on other CVD risk factors [17].

#### SYST-EUR (SYSTolic Hypertension in EUROpe)

Active treatment with nitrendipine lowered the global incidence of stroke by 42%, of non fatal stroke by 44%, of total CV events (sudden death included) of 26%, of CV death by 27%, of HF by 29%, of myocardial infarction (MI) by 30%, of total mortality by 14%. In conclusion, nitrendipine showed to be effective in reducing the rate of CV complications and cerebrovascular events in patients  $\geq 60$  years old with ISH [18].

In the 492 diabetic patients (10.5%) of the randomized patients in SYST-EUR treatment with nitrendipine (if necessary replaced or combined with enalapril) decreased mortality by 55%, CVD by 76%, strokes by 73% and cardiac events by 63%. Treatment reduction in overall mortality, mortality from CVD, and all CV events was greater among diabetic patients compared to non-diabetic patients ( $p=0.04$ ,  $p=0.02$ , and  $p=0.01$ , respectively).

Antihypertensive therapy based on the long acting dihydropyridine calcium channel blocker (CCB) nitrendipine was beneficial in older patients with hypertension and diabetes and failed to support the notion that long acting CCBs are harmful in diabetics [19].

#### HOT (Hypertension Optimal Treatment Randomized Trial)

This multicenter, international, prospective, randomized, open blinded end-point study aimed at evaluating the optimal target DBP in treated hypertensive patients.

The rate of major CV events was 9.9 events per 1000 patient-years in the  $\leq 90$  mmHg group, 10.0 events per 1000 patient-years in the  $\leq 85$  mmHg and 9.3 events per 1000 patient-years in the  $\leq 80$  mmHg.

The lowest risk of major CV events was achieved at a mean DBP of 82.6 mmHg and SBP of 138.8 mmHg and the lowest risk of CV mortality was at a mean DBP 86.5 mmHg and SBP 138.8 mmHg.

In patients with DM (1501) major CV events occurred at a rate of 24.4, 18.6 and 11.9 events per 1000 patient-years in the three groups ( $\leq 90$  mmHg,  $\leq 85$  mmHg,  $\leq 80$  mmHg) ( $p=0.005$ ), respectively. In diabetic patients total mortality was 15.9, 15.5, and 9.0 per 1000 patient-years, ( $p=0.068$ ), respectively; CV mortality was 11.1, 11.2, and 3.7 per 1000 person-years, ( $p=0.016$ ), respectively. These results demonstrate the benefit of lowering BP (DBP down to 82.6 mmHg) in patients with hypertension to 140 mmHg systolic and 85 diastolic or lower with particular benefit for the subgroups of patients with DM. The rate of CV events observed with treatment initiated with felodipine was much lower than that observed in previous trials with diuretic or beta-blockers initiated treatment. This is probably due to a more effective lowering of BP in HOT. Moreover, association with small dose of acetylsalicylic acid with antihypertensive treatment can be recommended: it shows to be effective in reducing the risk of MI without exaggerating the risk of central bleeding [6].

#### **ABCD TRIAL (Appropriate Blood Pressure Control in Diabetes)**

The purpose of this randomized, double-blind, placebo controlled (normotensive cohort) study were to determine the effectiveness of intensive vs moderate BP control on the outcome of type 2 diabetic end-organ complications in normotensive and hypertensive population and to compare enalapril and nisoldipine as first line antihypertensive drugs in terms of prevention and progression of diabetes complications.

A similar control in BP and no differences in glucose levels, glycosylated haemoglobin (HbA<sub>1c</sub>) and cholesterol were observed both in nisoldipine and enalapril treated groups. There was a lower incidence of fatal and non fatal MI in patients on enalapril (5 events) compared to nisoldipine (25 events) (risk ratio 9.5; 95% CI, 2.3-21.4). These results were similar also in patients with hypertension and type 2 DM, while infarction occurrence was lower in patients treated with enalapril [20].

A subsequent study investigated the effects of intensive vs moderate BP control on type 2 diabetic complications (nephropathy, retinopathy and neuropathy) in hypertensive type 2 diabetic patients enrolled in ABCD.

The mean BP achieved was 132/78 mmHg in the intensive group and 138/86 mmHg in the moderate control group. During the follow up period, no difference in the change of creatinine clearance was observed between intensive vs moderate BP control and between enalapril vs nisoldipine treatment. After 1 year of antihypertensive treatment creatinine clearance was stabilized in both the intensive and moderate BP control group in patients with baseline normo- or microalbuminuria.

In contrast, patients starting with overt albuminuria ( $>300$  mg/day) showed a steady decline in creatinine

clearance, throughout the follow up period, of 5-6 ml/min/1.73m<sup>2</sup>/year, whether they were in moderate or intensive BP control group.

No difference was found between the intervention with regard to individuals progressing from normoalbuminuria to microalbuminuria (25% with intensive therapy vs 18% with moderate therapy,  $p=0.20$ ) or microalbuminuria to overt albuminuria (16% with intensive therapy vs 23% moderate therapy,  $p=0.28$ ). The intensive therapy was associated with lower overall incidence of deaths (5.5% vs 10.7%,  $p=0.037$ ). Over a follow up of 5 years, there was no difference between the intensive and moderate groups in the progression of diabetic retinopathy and neuropathy. Moreover, the effects of nisoldipine and enalapril on diabetic retinopathy and neuropathy were similar.

The ABCD trial suggests that creatinine clearance in hypertensive type 2 diabetic patients can be stabilized over 5 years, for BP values 132/78-138/86 mmHg, if therapy is started before the onset of albuminuria. These effects result independent on the use of nisoldipine or enalapril as the initial antihypertensive medication. There was no difference in the progression of diabetic retinopathy and neuropathy over 5 years between moderate vs intensive BP control and enalapril vs nisoldipine. In conclusion, the more intensive BP control resulted effective in decreasing all cause mortality [21].

#### **FACET (Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial)**

This was an open-label, randomized prospective clinical trial comparing fosinopril to amlodipine in hypertensive people with type 2 DM. The primary aim was to compare the effect of fosinopril and amlodipine on serum lipids and diabetes control in type 2 diabetic patients with hypertension. Prospectively defined CV events were assessed as secondary outcomes.

Both fosinopril and amlodipine resulted effective in lowering BP: at the last visit, SBP was 4 mmHg lower in the amlodipine group compared to fosinopril ( $p<0.01$ ). Patients treated with fosinopril had significantly lower risk of the combined outcome of the acute MI, stroke, or hospitalized angina than those receiving amlodipine (14/189 vs 27/191; HR 0.49, 95% CI, 0.26-0.95,  $p=0.030$ ).

Fosinopril and amlodipine demonstrated similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major CV events compared to the patients randomized to amlodipine [22].

#### **UKPDS (United Kingdom Prospective Diabetes Study)**

It was the largest and the longest clinical trial conducted in the context of DM. It started in 1977 and interested 5000 patients enrolled in 503 centers of the United Kingdom. It was divided into two arms: UKPDS 38 and UKPDS 39.

UKPDS 38 was designed to determine whether tight BP control could reduce micro- and macrovascular complications in patients with type 2 DM.

**Table 2. Main Features of the All Clinical Trials Included in the Text**

NAME (References)	DRUGS	SAMPLES	INCLUSION CRITERIA AND BASELINE PARAMETERS	BP Changes	FOLLOW- UP	EFFECTS ON PRIMARY OUTCOME
SHEP[15-16] (SHEP Cooperative Research group, JAMA 1991)	Chlorthalidone Atenolol Reserpine	4736	≥60 years old ISH SBP 160-219 mmHg DBP < 90 mmHg	Baseline(average) SBP 170 mmHg DBP 77 mmHg  Final SBP 144 mmHg DBP 68 mmHg	4.5 years (average)	Treatment effective vs placebo in lowering BP and CV complications
(J.D. Curb <i>et al.</i> JAMA 1996)	As above	583 (diabetic patients)	As above		5 years	Treatment effective vs placebo in preventing CV events both in diabetic and non-diabetic patients and more favourable for diabetic patients (CHD end-points).
SYST-EUR[18-19] (Staessen JA <i>et al.</i> Lancet 1997)	Nitrendipine Placebo	4695	≥ 60 years old ISH	Reduction in SBP/DBP: -23/-7 mmHg (active treatment) -13/-2 mmHg (placebo)	2 years (average)	Treatment effective in reducing the rate of CV complications and cerebrovascular events. Reduction in total mortality statistically significant.
(Tuomilhto J <i>et al.</i> N Engl J Med)	The same	492 (diabetic patients)	The same	Reduction in SBP/DBP: -8.6/-3.9mmHg (active treatment) -13/-2mmHg (placebo) -10.3/-4.6 mmHg (non diabetics)	2 years (average)	Treatment reduction in overall mortality, mortality from CVD, and all CV events was greater among diabetic patients compared to non-diabetic patients.
HOT[6] (Hansson L <i>et al.</i> Lancet 1998)	Felodipine Aspirin	18790 1501 type 2 diabetics patients	50-80 years old DBP100-115 mmHg	Reduction in the 3 target groups -26.2/-20.3mmHg (≤90mmHg) -28.0/-22.3mmHg (≤85 mmHg) -29.9/-24.3mmHg (≤80 mmHg)	3.8 years	For major CV events the lowest point of risk was at a mean achieved DBP 82.6 mmHg and a mean achieved SBP 138.5 mmHg. Among diabetic patients, in the group randomized to DBP ≤80mmHg an approximate halving of the risk was observed for the major CV endpoints in comparison with the group randomized to DBP ≤90mmHg.

(Table 2. Contd....)

NAME (References)	DRUGS	SAMPLES	INCLUSION CRITERIA AND BASELINE PARAMETERS	BP Changes	FOLLOW-UP	EFFECTS ON PRIMARY OUTCOME
ABCD [20-21]	Nisoldipine Enalapril	470	40-74 years old hypertension (DBP≥90 mmHg) type 2 DM (WHO diagnostic criteria)	Predefined targets of DBP: DBP≤90mmHg DBP<75 mmHg  Final BP:  132/78mmHg(tight BP control)  138/86mmHg(less tight BP control)	5.3 years	Lisinopril lowered incidence of MI. Creatinine clearance stabilized over 5 years with the obtained values of BP (when therapy is started before the onset of overt albuminuria).The more intensive BP control reduced all cause mortality.
FACET [22] (Tatti <i>et al.</i> Diabetes Care 1998)	Fosinopril Amlodipine	380	Hypertension SBP>150mmHg DBP>90mmHg Type 2 DM	Baseline BP: 170±1/95±1mmHg (fosinopril) 171±1/94±1mmHg (amlodipine) Final BP: 157±1/88±1mmHg 153±1/86±1mmHg Difference: 13mmHg (fosinopril) 19mmHg(amlodipine)	2.5-3.5 years	Both treatments resulted effective in lowering BP and led to a similar effect on metabolic parameters in diabetic hypertensive patients.
UKPDS [23] (The UKPDS study group. BMJ 1998) 5	Tight BP vs less tight BP control with captopril and atenolol	1148	25-65 years old BP≥160/90mmHg BP≥150/85mmHg on antihypertensive therapy	Baseline mean BP: 160/90 mmHg  Final BP: 144±14/82±7 mmHg (tight BP control) 154±16/87±7mmHg (less tight BP control)	8.4 years	BP<150/85 mmHg resulted associated with reduction of the risk of death and complications in type 2 DM.  Captopril and aenolol were equally effective in reducing the risk of fatal and non fatal macrovascular and microvascular complications of type 2 DM:
(The UKPDS study group. BMJ 1998)	As UKPDS 38	1148	56.4 years old (average)	Baseline mean BP 160/94mmHg Final BP 144/83mmHg(captopril) 143/81mmHg(atenolol)		
CAPPP [24-25-26] (Hansson <i>et al.</i> Lancet 1999)27 (Niklason A <i>et al.</i> J Hypertens 2004)	Captopril Beta-blockers Diuretics	10985	25-65 years old Treated or untreated primary hypertension: DBP≥100mmHg, no upper limits	Baseline BP in previously untreated patients 166/103mmHg 163/101mmHg For previously treated: NA	6.1 years	An antihypertensive regimen based on ACE-inhibitors is effective as a conventional treatment with diuretics and beta-blockers in prevention of CV morbidity and mortality., and most probably more effective in prevention of diabetes. Primary CV end-point was lower in captopril group than in conventional treatment group. Patients with impaired metabolic control seemed to benefit the most from ACE-inhibitors treatment.
(Niskanen L <i>et al.</i> Diabetes Care 2001)	As above	Diabetics 309 captopril 263 convention al treatment	As above	Baseline BP in diabetics. 163/97	5 years	

(Table 2. Contd....)

NAME (References)	DRUGS	SAMPLES	INCLUSION CRITERIA AND BASELINE PARAMETERS	BP Changes	FOLLOW-UP	EFFECTS ON PRIMARY OUTCOME
CALM [27] (Mogensen CE <i>et al.</i> BMJ 2000)	Candesartan cilixetil Lisinopril	199	30-74 years old DBP 90-110 mmHg type 2 diabetes urinary albumine/creatinine ratio 2.5-25 mg/mmol	Baseline DBP: 90-110 mmHg  Final reduction 16.3mmHg(combined treatment) 10.4mmHg(candesartan) 10.7mmHg(lisinopril)	24 weeks	At the used dosage, candesartan is as effective as lisinopril in reducing BP and microalbuminuria in hypertensive type 2 diabetic patients, combination treatment resulting more effective in reducing BP.
IRMA [28] (Parving HH <i>et al.</i> N Engl J Med 2001)	Irbesartan	590	30-70 years old Type 2 diabetics Persistent microalbuminuria Serum creatinine ≤ 1.5mg/dl (men) ≤1.1mg/dl (women)	Baseline BP: 153±15mmHg 90±9 mmHg  BP throughout the study: 144/83mmHg 143/83mmHg 141/83mmHg	2 years	Irbesartan resulted renoprotective independently of its BP- lowering effects in patients with type 2 DM and microalbuminuria.
IDNT [29-30] (Lewis EJ <i>et al.</i> N Engl J Med 2001)	Irbesartan Amlodipine	1715	30-70 years old Type 2 DM Hypertension SBP≥135mmHg DBP≥85mmHg or antihypertensive treatment protein excretion at least 900 mg/dl serum creatinine: 1.0- 3.0 mg/dl	Baseline BP SBP 159±20 mmHg DBP 87±11 mmHg  BP at subsequent visits: 140/77 mmHg 141/77 mmHg 144/80 mmHg	2.6 years	Irbesartan effective in protecting against the prgression of nephropathy due to type 2 DM.
RENAAL [31] (Brenner BM <i>et al.</i> N Engl J Med 2001)	Losartan	1513	31-70 years old Type 2 DM Nephropathy	Baseline BP SBP162±19 mmHg DBP82±10 mmHg  140/74 mmHg (irbesartan) 142/74 mmHg (placebo)	3-4 years	Losartan conferred significant renal benefit in patients with type 2 DM and nephropathy
ALLHAT [32-33] (Davis BR <i>et al.</i> JAMA 2002) (Berecek KH <i>et al.</i> Curr Hypertens Rep 2004)	Lisinopril Amlodipine Chlorthalidone Doxazosin	15297 diabetics	66 years (average)	Baseline BP: NA  Final BP: NA	4-8 years	Chlorthalidone resulted more effective in reducing CV end-points, but seemed to worsen insulin resistance and incidence of new on-set DM.
LIFE [34-35-36] (Dahlof B <i>et al.</i> Lancet 2002) (Lindholm LH <i>et al.</i> 2002) (Lindholm LH <i>et al.</i> J Hypertens 2002)	Losartan Atenolol	9193 1195 diabetics 7998 non diabetics at baseline	55-80 years old previously treated or untreated hypertension ECG signs of LVH	Baseline BP: 174.4/97.8 mmHg (average)  Final BP: 144.1/81.3mmHg (losartan) 145.4/80.9 mmHg (atenolol)	4.8 years	Losartan prevents more CV morbidity and mortality than atenolol for a similar reduction in BP. New-onset DM seemed to be less frequent among patients treated losartan.

(Table 2. Contd....)

NAME (References)	DRUGS	SAMPLES	INCLUSION CRITERIA AND BASELINE PARAMETERS	BP Changes	FOLLOW-UP	EFFECTS ON PRIMARY OUTCOME
MARVAL [37] (Vibert G <i>et al.</i> Circulation 2002)	Valsartan Amlodipine	332	35-75 years old Normo or hypertensive Persistent microalbuminuria	Baseline BP: NA  Final BP reductions: -11.2/6.(valsartan) -11.6/6.5 (amlodipine)	24 weeks	A statistically significant decrease in AER with valsartan compared with amlodipine.
GEMINI [38] (Bakris GL <i>et al.</i> JAMA 2004)	Carvedilol Metoprolol tartrate	1253	36-85 years old Hypertension (>n 130/80 mmHg) Type 2 DM (HbA <sub>1c</sub> 6.5-8.5%)	Baseline BP: NA  Final BP	35 weeks	Carvedilol in addition to a RAS blocker did not affect glycemic control and seemed to improve some components of metabolic control.
VALUE [39] (Julius S <i>et al.</i> Lancet 2004)	Valsartan Amlodipine	15245	≥50 years old Hypertension (treated or untreated) High risk for CV events (DM included)	Baseline BP: 154.6/87.5 mmHg  Final BP: 139.3/79.2 mmHg (valsartan) 137.5/77.7 mmHg (amlodipine)	4.2 years	The main outcome of cardiac disease did not differ between the treatment groups:  These findings underline the importance of a prompt BP control in hypertensive patients at high CV risk.
DETAIL [40] (Barnett AH <i>et al.</i> N Engl J Med 2004)	Enalapril Telmisartan	250	Type 2 DM Early nephropathy	NA	5 years	Telmisartan resulted not inferior to enalapril in providing long-term renoprotection in type 2 diabetic patients. This support the clinical equivalence of ARBs and ACE-inhibitors in high risk persons.

The absolute risk for any diabetes related end-point was 50.9 and 67.4 events per 1000 patient-years in the tight and less tight control groups (RR 0.76; 95% CI, 0.62-0.92, p=0.0046). Diabetes related death occurred at a rate of 13.7 and 20.3 per 1000 patient-years, respectively (RR 0.68, 95% CI, 0.49-0.94, p=0.019). Total mortality occurred at a rate of 22.4 and 27.2 in the tight and less tight BP control group (RR 0.82, 95% CI, 0.63-1.08, p=0.17). Risk of stroke (RR 0.56, 95% CI, 0.35-0.89, p=0.013), HF (RR 0.44, 95% CI, 0.20-0.94, p=0.0043) and risk of microvascular complications resulted reduced by the tight BP regimen (RR 0.63, 95% CI, 0.44-0.89, p=0.0092). The reduction in microvascular end-points was predo-minantly due to a reduction in the risk of deterioration of retinopathy (p=0.004) and retinal photocoagulation.

UKPDS 38 results demonstrated that tight BP control was associated to reduction in the risk of diabetes related mortality and morbidity in hypertensive patients with type 2 DM [5].

UKPDS 39 was a protocol derived from a subanalysis of UKPDS 38. It was conducted to compare the effect of intensive lowering of BP with captopril vs atenolol on prevention of micro- and macrovascular complications in patients with type 2 DM.

The incidence of any end-point related to diabetes resulted similar in both treatment groups (53.3 vs 48.4 events per 1000 patient-years in the captopril and atenolol groups, respectively; RR for captopril 1.10; 95% CI, 0.86-1.41, p=0.43). UKPDS 39 demonstrated that captopril and atenolol were equally effective in reducing BP and the complications of DM in hypertensive patients. So the study suggests that BP reduction might be more important than the specific therapy used for prevention of diabetes complications [23].

**CAPP (CAptopril Prevention Project Preventing Trial)**

It was a randomized, open-label, parallel group, blinded end-point trial conducted in order to establish whether antihypertensive treatment with captopril reduces CV

mortality and morbidity more than a therapeutic regimen that does not include an ACE-inhibitor. Secondary end-points were to compare total mortality, development or deterioration of a heart disease, LV failure (LVF), atrial fibrillation, DM and possible differences in renal function in the 2 groups.

The incidence of fatal and non fatal MI, stroke and other CV deaths was similar in the captopril and conventional groups (11.1 per 1000 patient-years vs 10.2 per 1000 patient-years; RR 1.05,  $p=0.52$ ). Cardiovascular mortality resulted lower with captopril than with conventional treatment (76 vs 95 events; RR 0.77, 95% CI, 0.90-1.22,  $p=0.092$ ), the incidence of fatal and non fatal MI was similar (162 vs 161), while the incidence of stroke resulted higher in the captopril group (189 vs 148 events, RR 1.25, 95% CI, 1.01-1.55,  $p=0.044$ ) [24].

A recent subanalysis of the CAPPP, focusing on the onset of DM in cohorts of patients enrolled in the study. A lower incidence of DM during captopril treatment was observed in the whole CAPPP cohort that was non-diabetic at baseline ( $n = 10413$ ) as well as in such CAPPP patients that were previously untreated ( $n = 5033$ ).

A captopril-based antihypertensive treatment regimen is associated with a lower risk of DM development, compared to conventional therapy based on diuretics and/or beta-blockers [25].

In a successive study, CV mortality and morbidity in the diabetic subpopulation of CAPPP was further analysed. In patients with DM, captopril was associated to less primary end-point event rate (RR 0.59, 95% CI, 0.38-0.91,  $p=0.019$ ). Specifically, CV mortality tended to be lower in the captopril group (RR 0.48, 95% CI, 0.21-1.10,  $p=0.084$ ), and no difference was observed between the study groups for fatal and non fatal stroke (RR 1.02, 95% CI, 0.55-1.87,  $p=0.96$ ). Fatal and non fatal MIs were less frequent in the captopril group than in the conventional therapy group (RR 0.34 95% CI, 0.17-0.67,  $p=0.002$ ). Total mortality was lower in the captopril compared to the conventional therapy group (RR 0.54, 95% CI, 0.31-0.95,  $p=0.034$ ) and all cardiac events were lower in the captopril than in the conventional therapy group (RR 0.67, 95% CI, 0.46-0.96,  $p=0.029$ ). Patients with impaired metabolic control (with fasting blood glucose  $\geq 8.1$  mmol/L) seemed to benefit the most from ACE-inhibitor-based therapy ( $p=0.033$ ).

These results suggest that captopril is an obvious first-choice drug for preventing CV events in hypertensive patients with DM, especially in those with metabolic decompensation (poor glycemic control, lipid abnormalities) [26].

#### **CALM (Candesartan And Lisinopril Microalbuminuria Study)**

This randomized, parallel-group controlled trial was designed to assess and compare the effectiveness of candesartan cilexetil, lisinopril and their combination on DBP and albuminuria in hypertensive patients with type 2 DM and microalbuminuria. Both SBP and DBP resulted significantly reduced with candesartan cilexetil and lisinopril with no significant differences between the two treatments. The combination of candesartan cilexetil and lisinopril was

more effective than either monotherapy, with a total reduction of SBP by 25.3 mmHg and 16.3 mmHg from baseline. Albumin/creatinine ratio was reduced by 24% in the candesartan cilexetil group, by 39% in the lisinopril group and by 50% with the combination.

Creatinine clearance resulted slightly decreased over 24 weeks in the groups treated with lisinopril (adjusted mean decrease 0.0835 ml/sec,  $p=0.04$ ) and the combination treatment (0.0735 ml/sec,  $p=0.05$ ) but it was not affected in the group treated with candesartan.

Dual blockade of the renin\_angiotensin system (RAS), both at the level of ACE and at the level of the AII receptor, was associated with more effective reduction in BP than observed with a single agent.

The present study could not determine if these further effects on urinary albumin excretion relate to RAS provided additional evidence for a role of agents which interrupt the in conferring renoprotective effects in patients with incipient diabetic nephropathy [27].

#### **IRMA (IRbesartan Micro Albuminuria Type 2 DM in Hypertensive Patients)**

In this randomized, double-blind, placebo-controlled trial, conducted in 96 centers worldwide, the renoprotective effect of irbesartan was evaluated in patients with type 2 DM and persistent albuminuria. The primary outcome was the time to the onset of diabetic nephropathy.

Ten of the 194 patients in the 300 mg group (5.2%) and 19 of the 195 patients in the irbesartan 150 mg group (9.7%; RR 0.30, 95% CI, 0.14-0.61,  $p<0.001$ ) reached the primary end-point, as compared to 30 of the 201 patients in the placebo group (14.9%, 95% CI, 0.34-1.08,  $p=0.08$ ). Irbesartan reduced the level of AER throughout the study (24% reduction in irbesartan 300 mg and 38% reduction in the 300 mg group) vs 2% in the placebo group ( $p<0.001$ ). High dose irbesartan restored normoalbuminuria. Serious adverse events were less frequent among the patients treated with irbesartan ( $p=0.02$ ). Non fatal CV events occurred in 4.5% of the irbesartan 300 mg group vs 8.7% in the placebo group ( $p=0.11$ ).

Irbesartan resulted renoprotective independently of its BP lowering effect in patients with type 2 DM and microalbuminuria [28].

#### **IDNT (Irbesartan Diabetic Nephropathy Trial)**

This prospective, randomized, double-blind clinical trial was conducted in 210 clinical centers. The purpose was to determine whether either irbesartan (ARB) or amlodipine (CCB) slows the progression of nephropathy independently of the antihypertensive effect.

The primary end-point was the composite of a doubled baseline serum creatinine concentration, the onset of end-stage renal disease (indicated by initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg/dl) or death from any cause.

The secondary CV end-point was the composite of death for CV causes, non fatal MI, HF resulted in hospitalization, a

permanent neurologic deficit caused by cerebrovascular events, or lower limb amputation above the ankle.

The risk of the primary composite end-point was lowered by 20% in the irbesartan group compared to placebo ( $p=0.02$ ) group and by 23% in the irbesartan group compared to amlodipine group ( $p=0.006$ ). The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ( $p=0.003$ ) and 37% lower in the irbesartan group than in the amlodipine group ( $p<0.001$ ). Treatment with irbesartan was associated to a RR of end-stage renal disease that was 23% lower than that in both other groups ( $p=0.07$  for both comparisons). Differences achieved in the BP could not explain these results. The serum creatinine concentration increased in the irbesartan group 24% slower than in the placebo group ( $p=0.008$ ) and 21% slower than in the amlodipine group ( $p=0.02$ ). There were no significant differences in the rates of death from any cause or in the CV composite end-point.

The trial demonstrated that irbesartan is effective in protecting against the progression of nephropathy in type 2 DM independently of its antihypertensive effect [29].

The effectiveness of the irbesartan in hypertensive in delaying or preventing diabetic nephropathy in patients with type 2 DM, hypertension and persistent microalbuminuria was also evaluated.

Onset of diabetic nephropathy (defined by persistent albuminuria in overnight specimens, with a AER that was greater than 200  $\mu\text{g}/\text{min}$  and at least 30% higher than the baseline level) was reached by 10 of the 194 patients in the 300 mg group (5.2%) and 19 of the 195 patients in the 150 mg group (9.7%) compared to 30 of the 201 patients in the placebo group (14.9%). HR for diabetic nephropathy was 0.30 (95% CI, 0.14-0.61,  $p<0.001$ ) and 0.61 (95% CI, 0.34-1.08,  $p=0.08$ ) for the two irbesartan groups, respectively in comparison with placebo. The level of AER decreased by 24% and 38% in the 150 and 300 mg irbesartan vs 2% in the placebo group ( $p<0.001$  for the comparison between the placebo and the combined irbesartan groups). Serious adverse events resulted less frequent in patients treated with irbesartan (15.4% vs 22.8% in the placebo group,  $p=0.02$ ) [30].

#### **RENAAL (Reduction of End-Points in NIDDM (Non-Insulin Dependent DM) with Angiotensin II Antagonist Losartan)**

It was an investigator initiated, multinational, double-blind, placebo-controlled trial designed to evaluate the renoprotective effects of losartan in patients with type 2 diabetes and nephropathy. Nephropathy was defined by the presence of two occasions of a ratio of urinary albumin (measured in mg/L) to urinary creatinine (measured in g/L) from a first morning specimen of at least 300 (or a rate of urinary excretion of at least 0.5 g/day) and serum creatinine values between 1.3 and 3.0 mg/dl with a lower limit of 1.5 mg/dl for male patients weighing more than 60 Kg.

The primary outcome was a composite of a doubling of a baseline serum creatinine concentration, end-stage renal disease, or death. Secondary end-points included a composite

of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease.

The primary end-point was reached by 327 patients in the group of losartan (43.5%) and by 359 patients (47.1%) in the placebo group: treatment with losartan resulted in a 16% reduction in the risk ( $p=0.02$ ) of the primary composite end-point. The decrease in risk did not change after adjustment for BP. There were no significant differences in the rates of most CV end-points. The level of proteinuria declined by 35% with losartan ( $p<0.001$  for the comparison with placebo).

Losartan was well tolerated and conferred renal benefits in patients with type 2 DM and nephropathy [31].

#### **ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)**

This randomized, double blind, active-control, multicenter trial had the purpose to assess the incidence of fatal coronary heart disease and non fatal MI in patients treated with 4 types of antihypertensive drugs: chlorthalidone, doxazosin, amlodipine, or lisinopril. The primary outcome measure was fatal CHD or nonfatal MI, analyzed by intent to treat; secondary outcome measures included all-cause mortality, stroke, and combined CVD (CHD death, nonfatal MI, stroke, angina, coronary revascularization, CHF, and peripheral arterial disease); compared to the chlorthalidone group vs the doxazosin group.

Some key messages on the results of ALLHAT are available: the lowering of BP and not the drug used to achieve this, remains the key variable in preventing future CV events. The rates of CHF were higher among patients receiving either amlodipine or lisinopril compared to those treated with chlorthalidone. A small increase in fasting blood glucose levels of 0.2 mmol/L and therefore modestly higher rates of new onset diabetes in the chlorthalidone group compared to the ACE-inhibitor and CCBs groups were observed [32].

The ALLHAT was not designed to prospectively assess the treatment effect in diabetic patients. However the diabetic cohort was predesigned for subgroup analysis. Post hoc power analysis revealed a lower degree of confidence for the detection of a difference between the chlorthalidone and the other treatment arms for the primary outcome of the study (fatal and non fatal CHD). However this analysis showed a higher power of detection of a difference in the secondary outcome of the study (combined CVD) among the diabetic subgroup.

A significant higher six-years rate of HF was observed with amlodipine compared to chlorthalidone (10.2 vs 7.7 respectively, RR 1.38). The lisinopril group had a higher 6-years rate of combined CVD (stroke and CHF), compared to chlorthalidone (33.3% vs 30.9%, respectively).

Optimal control of BP in people with diabetes resulted difficult to achieve and required multiple medications. In a large diabetic cohort with a mean age of 64.5 years (comparable with ALLHAT 66.6 mean age of the diabetic subgroup), a BP goal was achieved in only 25% of patients.

Furthermore an average of 3.1 medications was required to achieve such a BP goal.

Insulin resistance and incidence of new-onset DM resulted worsened in the group treated with diuretics. On the other hand, diuretics demonstrated the reduction of CV mortality, even in higher risk patients (particularly patients with diabetes and/or chronic kidney disease). These contrasting results might be due to an inadequate period of follow up, not long enough to evaluate the effect of diuretics on the development of new diabetes and the long term CVD morbidity and mortality.

Moreover, ALLHAT did not offer relevant information for the diabetic population such as the use of antidiabetic agents, glucose control or microalbuminuria.

Compared to doxazosin, chlorthalidone yields essentially equal risk of CHD death/nonfatal MI but significantly reduces the risk of combined CVD events, particularly CHF, in high-risk hypertensive patients [33].

#### **LIFE (Losartan Intervention For End-Point Reduction)**

This double-blind, randomized, parallel-group trial compared the long term effects of atenolol and losartan on CV mortality and morbidity in hypertensive patients with LV hypertrophy.

Losartan showed to be more effective than atenolol in preventing the combined end-point of CV death, stroke and MI. Losartan significantly reduced the rates of stroke compared to atenolol and tended to reduce CV mortality and total mortality [34].

A substudy of LIFE compared the long term effect of atenolol and losartan on CV mortality and morbidity in hypertensive patients with DM enrolled in LIFE.

Cardiovascular mortality resulted in 6% in the losartan group and 10% in the atenolol group (adjusted HR 0.63; 95% CI, 0.42-0.95,  $p=0.028$ ). Stroke occurred in 9% and 11% of patients, respectively (HR 0.79; 95% CI, 0.55-1.14,  $p=0.204$ ) and MI in 7% and 8%, respectively (HR 0.83; 95% CI, 0.55-1.25,  $p=0.373$ ). The composite end-point of CV death, stroke or MI occurred in 18% of patients in the losartan group vs 23% in the atenolol group (adjusted HR 0.76, 95% CI, 0.58-0.98,  $p=0.031$ ). Total mortality was 11% vs 17%, respectively (0.61, 95% CI, 0.45-0.84,  $p=0.002$ ). Albuminuria was noted in 7% vs 13% ( $p=0.002$ ), respectively. Chest pain was reported by 12% vs 8% of patients, ( $p=0.036$ ), respectively.

Losartan demonstrated to be more effective than atenolol in reducing total and CV mortality as well the composite end-point of CV morbidity and mortality, hospitalization for HF and the risk of developing albuminuria in hypertensive patients with diabetes and ECG signs of LVH [35].

A subanalysis was conducted to study the risk of new-onset diabetes in hypertensive individuals who were at risk of developing DM in the LIFE study. New-onset DM occurred in 242 patients receiving losartan (13.0 per 1000 person-years) and 320 receiving atenolol (17.5 per 1000 person-years) (RR 0.75, 95% CI, 0.63 -0.88,  $p<0.001$ ).

Independently of the calculated risk score, fewer hypertensive patients with LVH developed DM if they were treated with losartan than if they were treated with atenolol [36].

#### **MARVAL (Micro Albuminuria Reduction with VALsartan)**

This multicenter, randomized, double-blind active control, parallel group study was conducted to investigate whether the effect of valsartan on AER was independent of its BP-lowering properties. The primary end-point was the percentage change in AER from baseline to week 24. The secondary end-point was the proportion of patients returning to normoalbuminuria status.

Valsartan compared to amlodipine determined a statistically significant decrease in AER (95% CI, 0.539-0.729,  $p<0.001$ ). Valsartan, in contrast to amlodipine, lowered AER progressively over time to a nadir at 24 weeks. The AER at 24 weeks with valsartan was 56% (95% CI, 49.6-63.0) of baseline, equivalent to a 44% reduction. The AER for amlodipine at week 24 was 92% (95% CI, 81.7 - 103.7) of baseline, with a reduction of only 8%. The treatment effect was highly significant (95% CI, 0.520-0.710,  $p<0.001$ ). These results did not change after the adjustment for baseline hypertensive status.

Subgroup analysis for patients who were hypertensive or normotensive at entry produced a similar pattern of results for change in AER (hypertensive subgroup: 95% CI, 0.482-0.737,  $p<0.001$ ; normotensive subgroup: 95% CI, 0.486-0.772,  $p<0.001$ ). The mean reductions in trough BP from baseline to week 24 were similar in both treatment groups. In normotensive patients there were small decreases in BP with both treatments (valsartan: SBP/DBP, -2.8/-2.7 mm Hg; amlodipine, -1.9/-2.1 mm Hg) and no significant differences between the 2 treatments (DBP,  $p=0.246$ ; SBP,  $p=0.329$ ). True equivalence of BP reduction was thus obtained between the two antihypertensive regimens, and this applied irrespective of normotensive or hypertensive status. The results of the analysis to assess whether changes in BP might explain the differences in AER between treatments showed that both change in DBP and SBP were statistically significant covariates ( $p=0.03$  and  $p<0.001$ , respectively). However, the treatment effect remained significant ( $p<0.001$ ) in both models, indicating that the observed changes in AER were independent of differences in BP reduction. The proportion of patients achieving target BP was similar in the two groups (valsartan, 53%; amlodipine, 45%) and not significantly different (difference 8.3%, 95% CI, (-7%)-20.1%,  $p=0.196$ ).

The secondary end-point analysis showed a significantly greater percentage of patients returning to normoalbuminuria status by week 24 with valsartan (29.9%;  $n=49$ ) than with amlodipine (14.5%;  $n=23$ ) (between-treatment difference 15.4%, 95% CI, 5.6-25.8,  $p<0.001$ ). There was no significant difference in mean change in absolute values of HbA<sub>1c</sub> from baseline to week 24 between valsartan (0.04%) and amlodipine (0.16%) (95% CI, (-0.34)-0.15,  $p=0.427$ ). HbA<sub>1c</sub> remained stable and did not differ throughout the study with either treatment. Eighty five percent of patients received oral

hypoglycemic agents in both treatment groups. Total cholesterol, serum potassium, and serum creatinine were similar at baseline between the two groups and did not change significantly during follow-up [37].

#### **GEMINI (Glycemic Effects in DM: Carvedilol-Metoprolol Comparison in Hypertensives)**

In large clinical trials, beta-blockers have been shown to decrease CV risk in patients with hypertension and type 2 DM, but some components of metabolic syndrome were observed to be worsened by some beta-blockers.

In GEMINI the carvedilol and metoprolol treatment produced different mean change in HbA<sub>1c</sub> from baseline (0.13%; 95% CI, (-0.22%)-0.04%,  $p=0.004$ ) for the modified intention to treat analysis. The mean HbA<sub>1c</sub> (0.02% vs 0.04%,  $p=0.65$ ) increased with metoprolol and not with carvedilol (0.15% vs 0.04%,  $p<0.001$ ). Carvedilol improved insulin-sensitivity (-9.1%,  $p=0.004$ ), but not metoprolol (-2.0%,  $p=0.48$ ), the between-group difference being -7.2% (95% CI, (-13.8%)-(-0.2%),  $p=0.004$ ). Achievements in BP values were similar in the two groups. Progression to microalbuminuria resulted less frequent in the carvedilol group than in metoprolol group (6.4% vs 10.3%, OR 0.60; 95% CI, 0.36-0.97,  $p=0.04$ ).

Both beta-blockers resulted to be well tolerated; use of carvedilol in addition to a RAS blocker did not affect glycemic control and showed to be more effective than metoprolol in improving some components of the metabolic syndrome in participants with DM and hypertension [38].

#### **VALUE (Valsartan Antihypertensive Long Term-Use Evaluation)**

This randomized, double-blind, parallel-group trial was designed to test the hypothesis that, for the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high CV risk.

Both valsartan and amlodipine resulted effective in reducing blood pressure, but the effects of the amlodipine-based regimen were more relevant, especially in the early period. The primary composite end-point occurred in 810 patients in the valsartan group (10.6%, 25.5 per 1000 patient-years) and 789 in the amlodipine group (10.4%, 24.7 per 1000 patient years; HR 1.04, 95% CI, 0.94-1.15,  $p=0.49$ ).

The main outcome of cardiac disease did not differ between the treatment groups. Unequal reductions in BP might be responsible for differences between the groups in cause-specific outcomes.

New onset DM rate was lowered by 23% in the valsartan group ( $p<0.0001$ ). This significant reduction of incidence of new onset diabetes, according to the results obtained in the ALLHAT in lisinopril group, suggests that a positive effect on long term glucose metabolism might be related to blockade of biological effects of angiotensin II [39].

#### **DETAIL (Diabetics Exposed to Telmisartan and Enalapril Study)**

This prospective, multicenter, double-blind, 5-years study was assessed to directly compare the renoprotective

effect of ARBs and ACE-inhibitors. The primary end-point was the change in the glomerular filtration rate (determined by measuring the plasma clearance of iothexol) between the baseline value and the last available value during the 5 years treatment period. The change in the glomerular filtration rate was -17.9 ml per minute per 1.73 m<sup>2</sup> of body-surface area (where the minus sign denotes a decrement) with telmisartan (in 103 subjects), as compared to enalapril -14.9 ml per minute per 1.73 m<sup>2</sup> with enalapril (in 113 subjects), for a treatment difference of -3.0 ml per minute per 1.73 m<sup>2</sup> (95% CI, -7.6 to 1.6 ml per minute per 1.73 m<sup>2</sup>). The lower boundary of the CI, in favour of enalapril, was greater than the predefined margin of -10.0 ml per minute per 1.73 m<sup>2</sup>, indicating that telmisartan was not inferior to enalapril. Telmisartan resulted not inferior to enalapril in providing long-term renoprotection in persons with type 2 DM.

These findings do not necessarily apply to persons with more advanced nephropathy, but they support the clinical equivalence of ARBs and ACE-inhibitors in persons with conditions that place them at high risk for CV events [40].

#### **COMMENTS AND DISCUSSION**

As explained above the major part of the studies regarding hypertension treatment in diabetic patients have absolutely demonstrate that the reduction of BP values significantly diminish CV events and act as a protective agent for targeted organs. On the other hand, many issues regarding the optimal target BP are still partially unsolved as well as the comparison between the efficiency between the different drug classes.

In the UKPDS a tight control in BP clearly resulted in a better control macro and microvascular complications while the SHEP and the SYST-EUR have provided strong evidence of the utility of reducing pure systolic hypertension.

In the diabetics patients randomized in HOT the best results in terms of CV reduction have been obtained with DBP<80 mmHg.

On the other hand, in the UKPDS treatment with ACE-inhibitor ramipril resulted effective in reducing by 25% the different primary combined end-points, despite of a minimal effect on BP. Among the main studies evaluating ACE-inhibitors, the UKPDS and the CAPPP, only CAPPP has demonstrated a significantly major reduction of CV events and mortality with captopril.

Finally, the LIFE has recently showed a more favourable effect of losartan vs atenolol on CV events and mortality.

Moreover, prevention and slowing progression to diabetic nephropathy is a fundamental target in the treatment of type 2 DM: IDNT, IRMA, RENAAL, MARVAL have suggested that reduction in BP values in diabetic patients has a beneficial effect on proteinuria and diabetic nephropathy progression independently of the drug used.

Another issue emerging from literature is the charming possibility that some antihypertensive drugs might be useful in preventing type 2 DM. The major part of evidence supporting this interesting concept come from experiences with drugs active on RAAS system as ACE-inhibitors and ARBs.

In the UKPDS and in the CAPPP patients treated with ACE-inhibitors had lower levels of HbA<sub>1c</sub> or less development of DM compared to those taking beta-blockers or diuretics. Anyway, it is not clear if the difference in development of diabetes observed in these studies is due to a protective effect of ACE-inhibitors or to an adverse effect of beta-blockers or diuretics. Different mechanism could explain and support a possible beneficial effect of ACE-inhibition in preventing DM. First of all hypokaliemia impairs the insulin secretory response to glucose, which may be favourably affected by ACE- inhibitors. Ace-inhibitors also lower aldosterone secretion and renal potassium waisting, thus probably preserving beta-cell functions. Moreover, ACE-inhibitors may reduce insulin resistance in skeletal muscles, by determining an increase in insulin-mediated glucose uptake in this tissue. The increased insulin-mediated glucose uptake is due to increased bradykinin-mediated nitric oxide production and not to reductions in angyotensin 2 production or action. These concepts are suggested by several observations. Finally ACE-inhibitors may also reduce insulin resistance at the liver and fat cells [41].

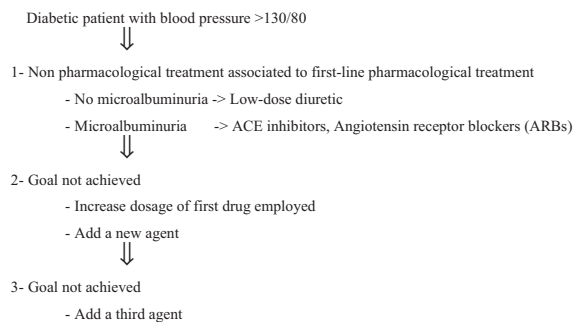
The CALM has demonstrate that the more benefit in diabetic patients has been obtained with dual blockade of RAA system, while the LIFE and the VALUE have suggested that losartan and valsartan could be associated with less incidence of new-onset DM, but systematic investigations are required to well establish a statistically significant relation between ARBs and prevention of DM.

In conclusion, more studies are needed, and particularly prospective trials with prevention of DM in hypertensive patients as primary end-point.

### PRACTICAL SUGGESTIONS

As above reported, an adequate BP reduction is associated with significant improvement in diabetic patients prognosis.

The available evidences would suggest that each diabetic patient has to reach BP values less than 130/80 mmHg. If they have no microalbuminuria, a low-dosed diuretic could be the first approach, if necessary associated with other antihypertensive drugs in order to join the prefixed target. ACE-inhibitors and ARBs are of course the first choice in case of microalbuminuria, while only ARBs in case of macroalbuminuria. Beta-blockers are not to be avoided nor suspended in patients with angina or a previous MI, because their positive effect on CV prognosis is much more relevant than the risk to mask probable hypoglycemic crisis or to slightly impaired glucose metabolism. Dihydropyridine-CCBs are useful as associated therapy, when monotherapy is not sufficient to adequately control BP (Fig. 1). The molecules that could be added have to be selected considering their pharmacokinetics, their safety profile and the co-morbidities of the patient. For instance, beyond CHD, beta-blockers could be indicated in patients with anxiety, essential tremor and recurrent headache, while alpha blockers in patients with symptomatic prostate hypertrophy.



**Fig. (1).** Practical flow-chart for the approach to the hypertensive diabetic patient.

As it regards the molecule choice in a drug class, it is more difficult to give strong suggestions, especially because of lack of data of long-term direct comparison of their efficacy in monotherapy. Of course, a priority should be given to molecules that have clearly showed their efficacy in diabetic patients. Large trials teach us that almost all ACE inhibitors and ARBs appear to be equally effective, when used at adequate dosage.

Some preliminary data from preclinical studies and small clinical studies suggest some interesting properties of single molecules that could have a positive impact on the metabolic control of diabetic patients and consequently on their CV risk. Among them, we would like to remember perindopril and telmisartan [42,43] that appear to have a some regulating activities on the Peroxisome Proliferator Activator Receptor (PPARs). We have yet to wait for specific data about molecules more recently entered in the market, such as olmesartan.

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