Benefits of Tight Blood Pressure Control in Diabetic Patients With Hypertension

Importance of early and sustained implementation of effective treatment strategies

GIANFRANCO PARATI, MD[1,2]
GRZEGORZ BILO, MD[2]
JUAN E. OCHOA, MD[1,2]

In 2008, when the UK Prospective Diabetes Study (UKPDS) group presented their 30-year findings concerning the possible sustained effects of improved glycemic control after 10 years of extended follow-up in type 2 diabetic patients, a so-called "legacy effect" was reported to address the long-term emergent and/or sustained benefits of early improved glycemic control. Opposite results were obtained by the Hypertension in Diabetes Study (HDS) carried out in the frame of UKPDS, with no evidence of any legacy effect on cardiovascular (CV) outcomes for an initial 4-year period of tight blood pressure (BP) control. Thus, it was concluded that BP control has to be continued over time, since, although it had a short time-to-effect relationship in preventing stroke, BP control was associated with a short persistence of its clinical benefits once the intervention was discontinued. These findings are unique because, whereas most interventional trials in hypertension that included diabetic patients have shown a reduction in CV outcomes shortly after starting treatment, only the UKPDS-HDS specifically explored the possible persistence of clinical benefits after discontinuing intensive BP-lowering intervention. This article aims to provide a critical interpretation of the UKPDS findings of lack of BP legacy, in the context of the currently available evidence on the benefits of antihypertensive treatment. The importance of effective BP control in type 2 diabetic patients to prevent CV outcomes and other diabetes-related complications is underlined, with emphasis on early, tight, and continuous BP control to optimize patients' protection.

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Diabetic patients are characterized by a significantly higher risk of CV events compared with nondiabetic individuals, with diabetes itself being currently considered a CV disease equivalent (1–4). CV complications are responsible for 80% of total mortality in diabetic patients (1), partly because of the high prevalence of other CV risk factors in this population (4). Hypertension is a major comorbidity of diabetes and a recognized modifiable risk factor hastening the progression and development of microvascular and macrovascular complications (5,6). Observational data from the UK Prospective Diabetes Study (UKPDS) reported a continuous positive correlation between the level of systolic BP and the risk of developing macrovascular (coronary heart disease [CHD] and stroke) and microvascular (nephropathy, retinopathy, and neuropathy) complications in patients with type 2 diabetes, without any evidence of BP threshold level (5). In keeping with the known synergistic interaction of hypertension and diabetes as CV risk determinants, interventional studies demonstrated that optimal BP control is particularly important in hypertensive patients with coexisting diabetes (7). This notion was recently confirmed by secondary analyses of several major prospective interventional studies in diabetes, originally aimed at assessing the benefits of glycemic control (8–11).

The UKPDS was formally closed in 2007, i.e., 30 years after its outset, thus being one of the longest trials ever made in clinical sciences. The main study lasted over 20 years, from 1977 to 1997, with a subsequent 10 years of extended follow-up from 1997 to 2007. The main aim of this study was to establish whether, in patients with type 2 diabetes, intensive glycemic control might reduce the risk of vascular complications (12), and its results have profoundly influenced the management of type 2 diabetes (13,14). The Hypertension in Diabetes Study (HDS), embedded in the UKPDS in 1987 in recognition of the need to control both glycemia and BP (15), confirmed that hypertension is a major risk factor for CV disease in patients with type 2 diabetes (16–18) and addressed the importance of a tight BP control in hypertensive patients with type 2 diabetes (19), in line with the results of the Hypertension Optimal Treatment (HOT) trial (20). The outcomes were subsequently reassessed both in the main study and in UKPDS-HDS after a period of 10 years of extended follow-up under conditions of standard care, to study the possible long-term persistence of the beneficial effects of study interventions beyond the intervention period (9).

EARLY AND DELAYED BENEFITS OF IMPROVED GLYCEMIC CONTROL IN THE UKPDS AND OTHER STUDIES

—Out of a total number of 5,102 newly diagnosed type 2 diabetic patients enrolled in the UKPDS, 4,209 individuals were randomly assigned to receive either conventional (diet alone) or more intensive antidiabetic treatment (12) and 3,867 of them completed the follow-up period (median 10 years) (12,19). At this point, the effects of intensive glycemic control on microvascular

From the [1]Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy; and the [2]Department of Cardiology, S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy.
Corresponding author: Gianfranco Parati, gianfranco.parati@unimib.it.
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complications were fully apparent (relative risk [RR] reduction 25%, $P = 0.01$), whereas it had only a marginal effect on CV end points with a 16% reduction ($P = 0.052$) in the RR of myocardial infarction and no significant reductions in any other macrovascular outcomes (19,21). After a further 10 years of extended follow-up under the standard less intense community- or hospital-based diabetes care conditions (9), the reductions in the risk of microvascular disease were maintained in the initial intensive glycemic control group. Moreover, long-term benefits of previous intensive glycemic control also emerged for CV end points with a significant reduction in the risk of myocardial infarction (RR reduction of 15%, $P = 0.01$, for the sulfonylurea-insulin group, and RR reduction of 33%, $P = 0.005$, for the metformin group) and of all-cause mortality (RR reduction of 13%, $P = 0.007$). Based on these results, the concept of legacy effect was proposed in the UKPDS to refer to the long-term sustained (microvascular end points) and/or emergent (macrovascular end points) benefits of a period of intensive glycemic control implemented early in the disease course (9).

Before the UKPDS, the concept of glycemic legacy had been reported in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) trial, a study similar to UKPDS, but performed in 1,441 patients with type 1 diabetes randomized to either intensive or conventional glycemic control (22). Upon completing the active trial phase (mean duration 6.5 years), clear benefits for microvascular end points were reported for intensive glycemic control, with no differences in terms of major CV end points (22). After an additional 8 years of extended follow-up, the results were similar to those of the UKPDS with maintained reduction in the risk of microvascular complications and remarkable effect of early intensive glycemic control on CV outcomes rates, with a 42% reduction in the risk of any CV event ($P = 0.02$) and a 57% reduction in the combined end point of nonfatal myocardial infarction, stroke, or death from CV disease ($P = 0.02$) (10).

Three other major studies published recently assessed the possible early benefits of intensive glycemic control in terms of CV protection. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (23), 11,140 patients with type 2 diabetes where randomized to standard versus intensive glucose control based on gliclazide (modified release) and other drugs as required to achieve a target glycated hemoglobin ≤6.5%. After a median of 5 years of follow-up, the results were very similar to those reported in the UKPDS by the end of the randomized intervention: there was a significant 14% reduction in the risk of microvascular disease but no convincing reductions in the risk of macrovascular outcomes (23). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (24) randomized 10,251 type 2 diabetic patients to receive either intensive therapy (HbA_{1c} target <6.0%) or standard therapy (HbA_{1c} target from 7.0 to 7.9%). In this study, prematurely discontinued because of excess mortality in the intensive therapy group, a nonsignificant 10% reduction was observed in the primary composite end point of myocardial infarction, stroke, or death from CV causes (24). Finally, the Veterans Affairs Diabetes Trial (VADT) study randomized 1,791 type 2 diabetic patients to achieve either conventional (aiming for an HbA_{1c} of <9%) or intensive glycemic control (aiming for an HbA_{1c} of <6%). After a median follow-up of 5.6 years, there was only a nonsignificant reduction of 12% ($P = 0.14$) in the primary composite end point of any major CV event for intensive glycemic control, and there was only a borderline reduction of 38% ($P = 0.05$) in the progression of microalbuminuria (25).

Thus, the ADVANCE, ACCORD, and VADT trials confirmed the findings of the UKPDS and DCCT, that intensive glycemic control does not confer significant reductions in the risk of macrovascular events in the short term, while reducing the risk of microvascular complications (10,19,23–26). It should be noted that these three studies included older patients with an average duration of diabetes of 8–11 years, whereas the UKPDS and DCCT included younger newly diagnosed diabetic patients (Table 1).

SHORT- AND LONG-TERM EFFECTS OF TIGHT AND CONVENTIONAL BP CONTROL IN THE UKPDS-HDS

—Ten years after the outset of the UKPDS, 1,148 of

Table 1—*Results of intensive glycemic control in different studies in diabetes*

Trial	Mean HbA_{1c} (%) for intensive vs. conventional management	Median follow-up (years)	Number of patients	Years from diagnosis of diabetes at entry	Benefits in prespecified CV outcomes
At the end of randomized intervention					
ACCORD (24)	6.4 vs. 7.5	3.4	10,250	10	No
ADVANCE (23)	6.5 vs. 7.3	5.0	11,140	8	No
VADT (25)	6.9 vs. 8.4	5.6	1,700	12	No
PROactive (26)	7.0 vs. 7.6	2.9	5,238	8	No
UKPDS 33 (19)	7.0 vs. 7.9	10.0	4,209	Newly diagnosed	No
DCCT/EDIC* (22)	7.0 vs. 9.0	6.5	1,441	Newly diagnosed	No
At the end of extended follow-up (no randomized intervention)					
UKPDS 80 (9)	8.0 vs. 8.1	17.0	3,277	—	Yes (myocardial infarction)
DCCT/EDIC* (10)	7.9 vs. 7.8	17.0	1,394	—	Yes (any CV event and combined end point of nonfatal myocardial infarction, stroke, and CV death)

*Type 1 diabetic patients.

the main study participants (BP ≥160/90 mmHg or ≥150/85 mmHg in case of ongoing antihypertensive therapy) were enrolled into the HDS and randomly assigned to either tight BP control (aiming for a BP ≤150/85 mmHg with either captopril up to 50 mg twice daily, or atenolol up to 100 mg once daily) or less tight BP control group (aiming for a BP ≤180/105 mmHg, avoiding the use of ACE inhibitors or β-blockers). Additional therapies could be sequentially added if needed (12). Randomized intervention continued over 4 years, and when the interventional study closed in 1997, the median duration of follow-up since the beginning of the main UKPDS was 8.4 years (12). In the tight BP control group, systolic and diastolic BP decreased by 10 and 5 mmHg, respectively, and were significantly lower than in the less tight BP control group (143/82 vs. 154/88 mmHg, respectively, $P < 0.001$). At the end of the intervention period, there was a significant reduction of 37% ($P = 0.009$) in the RR of microvascular outcomes and a 44% reduction in the risk of stroke ($P = 0.01$), with no significant risk reduction in any other macrovascular end points, including myocardial infarction (19,21,27). After the period of randomized intervention, the survivor cohort of the HDS ($n = 884$) entered a posttrial follow-up to determine whether the risk reductions for microvascular and macrovascular outcomes achieved with tight BP control would be sustained after discontinuing the initial intensive antihypertensive treatment (8).

The extended posttrial follow-up in the HDS study had a median duration of 8 years for a total follow-up duration of 14.5 years from randomization. Between-group differences in BP levels were lost within 2 years after discontinuation of tight BP control strategy, and by the end of the HDS, the previously reported benefits in CV outcomes and microvascular disease were no longer present in the patients initially randomized to tight BP control. The absence of lasting and sustained benefits for the previously improved BP control in the HDS, once intensive treatment was discontinued, led to the conclusion that to maintain its benefits, tight BP control must be continued over time (8). Thus, the absence of a legacy effect in the HDS not only did not contradict the importance of tight BP control in type 2 diabetic patients, but it actually further emphasized its crucial role in the prevention of CV events and diabetes-related complications.

The absence of a legacy effect for tight BP control raises several questions on the physiological mechanisms of CV protection provided by antihypertensive treatment. In particular, based on the results of the HDS, one could argue that, at least in diabetic patients, BP lowering is characterized not only by a short time-to-effect relationship, but also by a similarly short persistence of its prognostic benefits, whenever intensive BP-lowering strategies are discontinued.

For a proper interpretation of the HDS results, however, it is important to consider to what extent some methodological aspects of this study might have affected its results.

Possible role of suboptimal BP lowering

Although prospective observational studies have shown that even small reductions in BP reduce the incidence of CV events (28), the BP target of ≤150/85 mmHg considered for the "tight" BP control group in the UKPDS (12) was by far above the current BP target of <130/80 mmHg recommended for patients with hypertension and diabetes in all major guidelines (29–32). When the UKPDS started, "acceptable" BP levels for individuals with diabetes were as high as ≤160/95 mmHg (33). Subsequent studies have assessed the benefit associated with achievement of lower BP targets, confirming the possibility of short-term risk reductions in CV outcomes. However, no extended follow-up was conducted in any of them to see if such benefits were sustained in the long term (34–38).

Influence of previous history of diabetes and delayed start of antihypertensive treatment

The HDS started 10 years after the original study; therefore, the participants in the HDS were not actually newly diagnosed patients with diabetes as were the patients randomized to intensive or conventional glycemic control at the beginning of the UKPDS (27). During these 10 years, additional irreversible organ damage (renal and vascular) has likely developed in the hypertensive diabetic patients of the HDS, leading to a higher level of CV risk. A recent systematic review comparing the reductions in the incidence of CV events achieved in trials on antihypertensive agents, including patients with different baseline levels of CV risk, showed that the duration of disease with regard to time treatment started may influence outcome (39). It also showed that once organ damage is advanced, a high incidence of CV events persists despite intense BP lowering ("ceiling effect"), suggesting that once high risk has been attained (as in the case of hypertensive patients with diabetes), the risk reduction in CV outcomes depends more on baseline risk than on achieved BP (39). Finally, the importance of an early start of antihypertensive treatment to optimize patient protection was suggested by the results of the Systolic Hypertension in Europe (Syst-Eur) study (see below).

Factorial design of the study and impossibility to control for the effects of background interventions

When posttrial follow-up started, the median value of HbA_{1c} at baseline was significantly higher in the group previously assigned to tight BP control (8.3 vs. 7.5% in the less tight BP control group, $P = 0.001$). Because the data from the main study and from HDS were analyzed independently following a factorial design, it was not possible to control for the effect of potential confounders, such as glycemic levels, on CV outcome.

Use of older less efficacious antihypertensive agents with adverse effects on glucose homeostasis

In the intensive BP-lowering group, values of glycated hemoglobin were higher than in the control group. This could be partly explained by the randomization of one arm of the tight BP control group to atenolol. Also, given that 61% of patients in the tight-BP control group were on two or more antihypertensive agents (compared with 36% in the less tight BP control group), a greater use of thiazide diuretics in the tight BP control group could also not be ruled out. Thus, it is likely that the adverse metabolic effects reported for both atenolol and thiazide diuretics in several studies (40,41) developed in individuals allocated to atenolol in the HDS by the end of the randomized intervention, as further suggested by the significant increases in mean glucose levels (1.0 vs. 0.7 mmol/L in the captopril group, $P < 0.01$) and in body weight (2.3 vs. 0.5 kg in patients allocated to captopril and 1.2 kg in patients allocated to less tight control, $P < 0.0001$). Besides, when posttrial follow-up started, individuals previously allocated to atenolol had a significantly higher mean body

weight (84.0 vs. 80.0 kg in the captopril group, $P = 0.01$), higher levels of total cholesterol ($P = 0.04$), and lower levels of HDL cholesterol ($P = 0.009$).

Role of a shorter median time of randomized intervention in HDS

Whereas intensive antidiabetic treatment in the main UKPDS was implemented for a median of 11 years, the randomized antihypertensive intervention in the HDS was only conducted during a median of 4 years. However, although this timeframe of intervention was enough for benefits in CV outcomes to appear in the short term, it was probably not long enough for tight BP control to further influence the progression of organ damage and hence to confer a protecting legacy against long-term complications.

Small differences in BP between tight and less tight BP control

Although the difference between BP targets considered at entry for tight (≤150/85 mmHg) and less tight (≤180/105 mmHg) BP control groups was wide (30/20 mmHg), the difference between mean BP levels achieved over the 4 years of the randomized intervention for the tight and less tight BP control was relatively small (143/82 vs. 154/88 mmHg, respectively, $P < 0.0001$) (21), and this might have contributed to the lack of differences in outcome at the end of the extended follow-up.

ABSENCE OF BP LEGACY OR ONLY A TIME-TO-EFFECT RELATIONSHIP BETWEEN BP CONTROL AND CV OUTCOME?

—BP reduction, per se, is the main determinant of the prognostic benefit of antihypertensive treatment in terms of major CV events (42). Most interventional trials in hypertension, including those on diabetic patients, have shown the occurrence of a short time-to-effect

Table 2—*Results of major trials on hypertension including diabetic patients*

Trial	Treatment comparison	Median follow-up (years)	Number of diabetic patients (total *n*)	Mean age (years), basal characteristics	Benefits in CV outcomes
		Trials comparing active treatment vs. placebo			
ADVANCE (38)	Perindopril + indapamide vs. placebo	4.3	11,140 (11,140)	66, DM	Benefits in the composite end point of macro- or microvascular events
SHEP* (43)	Chlorthalidone/atenolol vs. placebo	4.5	583 (4,736)	72, DM, elder, isolated systolic hypertension	Yes (major CVD events, MI, stroke)
MICRO-HOPE (44)	Ramipril vs. placebo	4.5	3,577 (9,297)	65, DM + CHD, CVD, or other CVD risk factor	Yes (MI, stroke, CV death)
PROGRESS* (45)	Perindopril ± indapamide vs. placebo	3.9	761 (6,105)	64, DM + cerebrovascular disease	Yes (recurrent stroke)
IDNT (46)	Amlodipine vs. placebo	2.6	1,136 (1,715)	59, DM + HBP + nephropathy	Yes (MI)
Syst-Eur* (47)	Nitrendipine vs. placebo	2.6	492 (4,695)	70, DM + HBP, >60 years	Yes (any CVD, stroke, cardiac events)
		Trials comparing intensive vs. less intensive BP-lowering regimens			
UKPDS-HDS 1998 (21)	Target BP ≤150/85 vs. ≤180/105 mmHg	8.4	1,148 (5,102)	56, DM + HBP	Yes (stroke)
HOT* (20)	Target diastolic blood pressure ≤80 vs. ≤85 vs. ≤90 mmHg	3.8	1,501 (18,790)	63, DM + HBP	Yes (major CV events)‡
ABCD (34)	Target diastolic blood pressure ≤75 vs. ≤90 mmHg	5.3	470 (480)	59, DM ± HBP	Yes (stroke)
		Trials comparing regimens based on different drug classes			
INVEST* (48)	Verapamil SR vs. atenolol	2.7	6,400 (22,576)	66, DM + HBP + CHD	No
INSIGHT* (49)	Nifedipine gastrointestinal transport system vs. hydrochlorothiazide + amiloride	4.0	1,302 (6,321)	66, DM + HBP + other CVD risk factor	Benefit in the secondary end point of all-cause mortality and death from vascular and nonvascular causes
STOP-2* (50)	Diuretics or β-blockers vs. calcium antagonists vs. ACE inhibitors	5.0	719 (6,614)	76, DM + HBP, elder	Yes (MI)†
		Trials conducting extended posttrial follow-up			
UKPDS-HDS 2008 (8)	Target BP ≤150/85 vs. ≤180/105 mmHg	14.5	884 (5,102)	64, DM + HBP	No

CVD, CV disease; DM, diabetes mellitus; HBP, high BP; MI, myocardial infarction. *Diabetic subgroup. †ACE inhibitor vs. calcium antagonists. ‡Target diastolic blood pressure group ≤80 vs. ≤90 mmHg.

relationship between BP control by antihypertensive treatment and the improvement in CV outcome (8,20,21,34,38, 43–50) (Table 2).

A comprehensive review of 14 randomized trials on antihypertensive drugs concluded that, in particular, the reductions in stroke and CHD appear rapidly after starting treatment (51). In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, reaching BP control by the 6th month of the study was associated with significant benefits for subsequent major CV outcomes. Moreover, this study also showed that the BP response predicted events and survival already after only 1 month of active treatment (52). Also, most interventional studies in diabetes and hypertension have confirmed that benefits of antihypertensive treatment on major CV outcomes usually appear in the short term (34–38,44). The effectiveness of tight BP control in patients with hypertension, including a subgroup with type 2 diabetes, was first shown by the HOT trial, a multicenter study where 18,790 patients with hypertension from 26 countries were randomly assigned to treatment groups with diastolic BP targets of ≤90, ≤85, or ≤80 mmHg (53). After a mean of 3.8 years of follow-up, a subgroup analysis of type 2 diabetic patients (n = 1.501) showed a significant decline in the rate of major CV events in relation to the target group (P for trend = 0.005). Type 2 diabetic patients randomized to a target diastolic BP ≤80 mmHg had a significant reduction of 51% in the RR of major CV outcomes when compared with the target group ≤90 mmHg (RR 2.06, 95% CI 1.24–3.44) (20), a result confirmed later by the HDS of the UKPDS (19,21,27).

The Heart Outcomes Prevention Evaluation (HOPE) study (54) embedded the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE substudy (44), which investigated the effects of the addition of an ACE inhibitor (10 mg/day ramipril) to the current medical regimen of high-risk patients with diabetes (n = 3,577). After a median of 4.5 years of follow-up, a significant reduction of 25% (95% CI 12–36, P = 0.0004) in the risk of the composite primary end point was reported, with a significant reduction in the risk of myocardial infarction by 22%, of stroke by 33%, and of CV death by 37% (44).

The ADVANCE study, besides focusing on the results of intensive glycemic control, also assessed the effects of routine administration of an ACE inhibitor/diuretic combination on vascular events in 11,140 individuals with type 2 diabetes (38). After a mean 4.3 years of follow-up, the relative risk for the combined end point of major macrovascular or microvascular events was significantly reduced in the ACE inhibitor/diuretic group by 9% (RR 0.91; 95% CI 0.83–1.00, P = 0.04). However, there were no significant reductions for macrovascular (RR 0.92; 95% CI 0.81–1.04, P = 0.16) or microvascular (RR 0.91; 0.80–1.04, P = 0.16) outcomes when separately considered. These modest reductions are easily explained by the fact that active treatment was added on top of previous antihypertensive therapy, and thus the difference in BP between the two groups was small (5.6 and 2.2 mmHg for systolic BP and diastolic BP, respectively).

Thus, there appears to be unequivocal evidence that in both hypertensive subjects with and without diabetes, benefits of antihypertensive treatment on major CV outcomes usually appear shortly after treatment implementation, in line with what was observed in the UKPDS. On the other hand, with regard to the long-term effects of an initial treatment, the evidence is rather limited. Strong data in favor of long-term benefits of an early start of antihypertensive treatment come from the Syst-Eur study. In this study, elderly patients with isolated systolic hypertension after 2 years of randomized treatment with nitrendipinde or placebo were invited to continue or to start open-label antihypertensive treatment (55). After 4 years of follow-up (6 years, counting from randomization), patients who received early antihypertensive treatment, as compared with patients who initially received placebo, had a significantly greater reduction in the risk of stroke (28%), CV complications (15%), and total mortality (13%). In the 492 diabetic patients enrolled, the additional benefits associated with early start of treatment were even more pronounced, with significant reductions in the risk of the abovementioned end points by 60, 51, and 38%, respectively (55).

These results are in clear contrast with results of the UKPDS-HDS. Thus, it is likely that the putative absence of a legacy effect of improved BP control reported in HDS was a result of several limitations of this study (discussed previously), and it does not reflect a real lack of long-term benefit of early BP lowering in diabetes.

CONCLUSIONS—The observations obtained over an extended period of posttrial follow-up in the UKPDS might indeed seem to demonstrate the absence of a legacy effect for an initial tight BP control, once intensive treatment is discontinued. However, these results need to be interpreted with caution, since other factors may contribute to explain the observed loss of CV benefits in the long-term follow-up of type 2 diabetic patients with hypertension included in this study. The most important of them is likely to be a delayed start of treatment, at a time when subclinical organ damage might already have been present, leading to an increased basal risk of CV events. In light of previous interventional trials, the interpretation of the results of the UKPDS-HDS, rather than focus on the possible lack of BP legacy, should emphasize the unquestionable finding that CV protection, especially when hypertension and diabetes coexist, is more likely to be effectively achieved if tight BP control is implemented early (39) and sustained over time. This strategy is supported by a recent critical analysis of several hypertension trials showing that the longer the disease duration before starting antihypertensive treatment, the smaller the benefits in terms of CV risk reduction and the larger the residual risk remaining, even if optimal preventive measures are taken (39). Therefore, an adequate antihypertensive treatment, possibly early in the course of the disease, remains a cornerstone in the modern approach to diabetes management.

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