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Cardiovascular outcomes at recommended blood pressure targets in middle-aged and elderly patients with type 2 diabetes mellitus and hypertension. — Source link

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Keywords:	Antihypertensive treatment, blood pressure, blood pressure target, cardiovascular disease, cardiovascular risk, diabetes mellitus, hypertension

BLOOD PRESSURE "Back-to-back" ORIGINAL ARTICLE I:

Cardiovascular outcomes at recommended blood pressure targets in middle-aged and elderly patients with type-2 diabetes mellitus and hypertension

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ABSTRACT

Purpose: Available data of event-based clinical outcomes trials show that little evidence supports the guidelines recommendations to lower blood pressure (BP) to < 130/80 mmHg in middle-aged and elderly people with type-2 diabetes mellitus (DM) and hypertension. We addressed this issue by post-hoc analyzing the risk of cardiovascular (CV) events in mostly elderly high-risk hypertensive patients with type-2 DM participating in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.

Material and methods: Patients (n=5250) were divided into 4 groups according to the proportion of on-treatment visits before the occurrence of an event (< 25% to ≥ 75%) in which BP was reduced to < 140/90 or < 130/80 mmHg.

Results: After adjustment for baseline demographic differences between groups, a reduction in the proportion of visits in which BP achieved < 140/90 mmHg accompanied a progressive increase in the risk of CV mortality and morbidity as well as of cause-specific events such as stroke, myocardial infarction and heart failure. A progressive reduction in the proportion of visits in which BP was reduced < 130/80 mmHg did not have any effect on CV risks.

Conclusion: In mostly elderly high-risk hypertensive patients with type-2 diabetes mellitus participating in the VALUE trial, achieving more frequently BP < 140/90 mmHg showed a marked protective effect on overall and all cause specific cardiovascular outcomes. This was not the case for a more frequent achievement of the more intensive BP target, i.e. < 130/80 mmHg.

KEYWORDS

Antihypertensive treatment; blood pressure; blood pressure target; cardiovascular disease; cardiovascular risk; diabetes mellitus; hypertension

Introduction

Randomized event-based clinical outcomes trials [1-4] show little evidence to support the recommendations of diabetes and hypertension guidelines [5-7] that in patients with type-2 diabetes mellitus (DM) and hypertension, blood pressure (BP) should be treated to < 130/80 mmHg rather than < 140/90 mmHg. While in patients with diabetes, BP reductions to 130-139 mmHg systolic and 80-89 mmHg diastolic have usually been accompanied by reductions in cardiovascular (CV) and renal events, but on-treatment BP values < 130/80 mmHg have usually shown no further protective effect as recently shown in a meta-analysis [8]. This has been found also in post-hoc analyses of trials showing that in diabetes BP reductions < 130/80 mmHg did not provide further CV or renal benefits than those obtained by reducing BP to < 140/90 mmHg. Indeed, in some instance a trend to an increased CV outcome appeared [9-11]. Thus, the optimal target BP has not been settled in patients with diabetes and hypertension, and this is particularly the case in the many elderly patients with the combinations of these diseases.

In the present study we investigated mostly elderly patients with type-2 DM and hypertension in the large database provided by the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [12]. We aimed to test the hypothesis put forward in recent guidelines [5-7] that achieving a target BP < 130/80 mmHg leads to a lower incidence of CV morbidity and mortality than achieving a target BP < 140/90 mmHg in this population.

Material and methods

Participants

The design and the main results of the VALUE trial have been reported in detail previously [12]. Briefly, VALUE was a multicenter, randomized, double-blind trial which compared the long-term effect of an antihypertensive treatment based on the angiotensin receptor blocker valsartan or the calcium antagonist amlodipine on cardiac morbidity and mortality in hypertensive patients of any ethnicity with an age ≥ 50 years and a high CV risk profile. The qualifying risk factors for recruitment were predefined combinations of male gender, age and other risk factors or the presence of ECG-based left ventricular hypertrophy (with or without a strain pattern), proteinuria, increased serum creatinine, diabetes or a verified but stable coronary, cerebrovascular or peripheral artery disease. Patients with renal artery stenosis, clinically relevant valvular disease, a recent (3 months) cerebrovascular event, coronary angioplasty or by-pass surgery, congestive heart failure requiring an ACE inhibitor and coronary disease requiring a beta-blocker were excluded from being randomized. Exclusion extended to pregnant women and individuals with severe hepatic disease.

Blood pressure measurements and treatment

Both treated and untreated hypertensive patients were considered for inclusion into the trial. Untreated patients were recruited if their systolic BP was between 160 and 210 mmHg and diastolic BP was < 115 mmHg. Treated patients were recruited if their systolic BP was < 210 mmHg or diastolic BP < 115 mmHg. The recruited patients were rolled-over into one or the other arm of the trial without a run-in phase. For valsartan treatment started with 80 mg daily and for amlodipine with 5 mg daily. The dose of either drug was doubled and hydrochlorothiazide (12.5 mg and 25 mg daily) and other antihypertensive drugs were added

in sequential steps if BP was not reduced < 140/90 mmHg. Angiotensin receptor blockers were excluded from the treatment algorithms and ACE inhibitors and calcium channel blockers only allowed if required for conditions other than hypertension. Patients were followed-up for 4-6 years with visits performed monthly during the initial 6 months of treatment and at 6 months intervals thereafter. Blood pressure was measured twice by a newly calibrated manual sphygmomanometer 24 hours post-dose with the patient being quietly seated for 5 min at each visit.

Outcomes

The primary endpoint of the study was time to first cardiac event, i.e. a composite of fatal or non-fatal myocardial infarction, sudden cardiac death and death from revascularization procedures or heart failure, heart failure requiring hospitalization and emergency procedures to prevent myocardial infarction. Secondary endpoints were all events, fatal and non-fatal stroke, myocardial infarction, hospitalized heart failure, and CV, non-CV and all-cause mortality. An endpoint committee, blind to treatment allocation, adjudicated events.

Data availability statement

The data that support the findings of this study are available from the corresponding author, S.E.K. upon reasonable request.

Statistical analyses

Because the primary endpoint was not significantly different between the two treatment groups data were pooled for all analyses of the patients with type-2 DM (n=5250). Four groups according to the percentage of on-treatment visits with BP < 140/90 mmHg up to the occurrence of an event: < 25%, 25 to 49%, 50 to 74% and ≥ 75% were considered as done in previous trials [13-14] including in the overall VALUE population [15]. The same four group

subdivision was used for the percentage of visits with BP < 130/80 mmHg, i.e. the target BP recommended by guidelines in a high CV risk condition [5-7]. On the assumption that the BP found at a given visit reflected the value existing during the preceding between-visit interval data were expressed as the percentage of time in which BP was reduced below the higher or lower value. For each group calculation was made of the incidence of the primary and secondary endpoints. The relative risk of each endpoint was quantified separately for the higher and lower BP target, using the Cox proportional hazard model and taking the group in which BP control covered ≥ 75% of the on-treatment time as reference. To reduce the impact of potential confounders hazard ratios were adjusted for baseline covariates (age, gender, systolic BP and diastolic BP, body mass index, high serum total cholesterol [240 mg/dl or 6 mmol/L], smoking, proteinuria, history of CV events and left ventricular hypertrophy). For baseline systolic BP and diastolic BP, the 5th degree polynomials were used to capture an extended range of possible relationships between BP and events. Two-sided p-values were calculated for trends versus the subgroup with ≥ 75% of the time with BP control. $P < 0.05$ was considered statistically significant without adjustment for multiplicity. Data are shown as means ± standard deviations (SDs) or estimates with 95% confidence intervals (CIs).

Results

Baseline characteristics in relation to time achieving target < 140/90 mmHg

Table 1 shows the baseline characteristics of the patients achieving BP < 140/90 mmHg over different proportions of the on-treatment period prior to the occurrence of the primary endpoint. Systolic BP and diastolic BP were progressively greater, and most CV risk and disease factors progressively more common, from the longest to the shortest time (≥ 75% to <

25%) with a BP < 140/90 mmHg, with an expected concomitant progressive increase of average on-treatment BP.

Fractions of smokers and fractions of study participants with coronary disease were inversed, while heart rate, baseline antihypertensive treatment, body mass index and fraction of patients with previous stroke or transient ischemic attack were unchanged. Results were similar when groups were stratified according to BP values prior to the occurrence of secondary endpoints (data not shown).

Event incidence and risk for BP < 140/90 mmHg

Both for the primary and for all secondary endpoints the *event incidence* increased progressively as the time with BP < 140/90 mmHg decreased (Figure 1, upper panel). The *risk* of any event also showed a steep progressive increase as the time with a BP below 140/90 mmHg decreased when adjusting the data for baseline covariates, including systolic BP and diastolic BP values (Figure 2, upper panel).

Baseline characteristics in relation to time achieving target < 130/80 mmHg

Table 2 shows the baseline characteristics of the patients achieving BP < 130/80 mmHg over different proportions of the on-treatment period prior to the occurrence of the primary endpoint. Although the between-group differences were less pronounced and not invariably significant, baseline systolic BP and diastolic BP values as well as prevalence of several CV risk and disease factors increased progressively from the group with the longest to the group with the shortest time at BP < 130/80 mmHg. There was an expected concomitant progressive increase of the on-treatment average BP values.

At variance from the findings shown in Table 1, fractions with antihypertensive treatment at baseline increased with BP control ≥ 75%. This was also the case for fractions of participants

with coronary disease but not for fractions of smokers, which was also at difference from the findings in Table 1. The results were similar when the groups were stratified according to BP values prior to the occurrence of secondary endpoints (data not shown).

Event incidence and risk for BP < 130/80 mmHg

From the longest to the shortest time with BP < 130/80 mmHg the *incidence* of stroke continued to show a progressive increase and non-CV mortality concomitantly exhibited a progressive reduction. The incidence of the primary and all other CV endpoints showed a J-curve pattern, i.e. an increase as the time under more intensive BP control decreased from ≥ 75% to 50 to 74%, with a decrease as control was achieved for times shorter than 50% (Figure 1, lower panel). However, importantly the *risk* of all the various events did not show any consistent trend from the longest to the shortest time with a BP < 130/80 mmHg when adjusting the data for baseline covariates, including systolic BP and diastolic BP values (Figure 2, lower panel).

Discussion

The risk of CV morbidity and mortality as well as myocardial infarction, heart failure and stroke in mostly elderly patients with the combination type-2 DM and hypertension showed a progressive steep increase as the rate of BP control < 140/90 mmHg decreased from ≥ 75% to < 25% of the on-treatment time. There was a concomitant steep increase in the risk of these events when adjusting for between-group differences in a large number of demographic and clinical baseline variables. This was not the case for the different rates of BP control < 130/80 mmHg. For patients below these BP values, the adjusted overall morbidity and mortality risk, as well as the risk of cause-specific events of cardiac disease and stroke, were unaffected by

the frequency of BP control. Thus, while more frequent BP reductions < 140/90 mmHg were highly protective, no further protection was achieved by more frequent BP reductions < 130/80 mmHg. Our findings provide evidence in support of BP target < 140/90 mmHg but also against the need of pursuing an intensive BP target in middle-aged and elderly patients averaging about 67 years with type-2 DM and hypertension, as presently recommended by international guidelines [5-7].

Several other results of our study are noteworthy. One, in the present large subgroup of 5250 DM hypertensive patients the relationship of the higher and lower BP targets with the incidence and adjusted risk of CV morbidity and mortality was principally similar to that of the entire VALUE population, i.e. CV protection was achieved by reducing BP <140/90 mmHg with no further protection < 130/80 mmHg. We discuss the comparison of the DM patients with the entire population of high-risk hypertension in VALUE in more details in a companion article [16].

Two, in a large trial of DM patients systolic BP reduction < 120 mmHg did not show beneficial effects on CV morbidity and mortality except for stroke, the risk of which was reduced by 41% compared to patients remaining at SBP > 130 mmHg [4]. In post-hoc analyses of other large scale trials including hypertensive or normotensive patients, treatment-induced progressive systolic BP reduction to 120 mmHg or less was accompanied by no effect or even an increase of CV events and myocardial infarction, again with a progressive reduction in the incidence of stroke [9-11].

Three, only about one third of our patients with DM achieved BP < 140/90 mmHg for ≥ 75% of the overall treatment duration, and in more than half of the patients this highly protective target BP remained unachieved for half of the treatment time. This confirms that consistent BP control is a difficult goal to reach even in the context of a randomized clinical trial, i.e.

when the patients are care taken by expert investigators and the follow-up is more adequate than in regular clinical practice. Given the evidence that visit-to-visit BP variability may be an independent CV risk factor [17-19] the inconsistency of BP control may be one of the factors responsible for the persistently high residual risk exhibited by treated hypertensive patients [20].

Four, it is remarkable that non-CV mortality risk is highly significantly related to improved BP control over time when target BP is < 140/90 mmHg. This finding suggests that in our patients with DM and high-risk hypertension, there is an extensive misclassification of CV death into non-CV death. In fact, the finding mirrors the relationship between time-dependent BP control and CV mortality with similar finding also for all-cause mortality.

Five, fractions of smokers and fractions of study participants with coronary disease were increasing with ≥ 75% of controls at BP target <140/90 mmHg. Further, fractions of participants with coronary disease but not fractions of smokers also increased with ≥ 75% of controls at BP target <130/80 mmHg. We report these findings in middle-aged and elderly patients with DM and hypertension, but we have not elucidated these findings in detail. Possibly, coronary patients with DM and hypertension receive the utmost attention for BP control with BP lowering medication.

Study limitations

Our study had some limitations. One, only a limited number of patients achieved BP < 130/80 mmHg at rates greater than 50% or 75% of the treatment duration, which means that this target comparison involved groups of different sizes. This was particularly the case for the DM patients, in whom the low rate of intensified BP control for 50% or more of the overall treatment duration may have favored chance findings such as the lack of relationship between

the BP reduction and the risk of stroke compared to the overall trial population. Two, because in post-hoc analyses comparisons involve non-randomized groups, the possibility that our results did not depend on the achievement rates of higher or lower BP values but rather on differences in baseline characteristics cannot be excluded. However, our estimates of CV risk were adjusted for a large number of baseline variables, including markers of asymptomatic hypertension mediated organ damage (left ventricular hypertrophy and proteinuria), that have an important impact on CV risk. Three, the effect of more properly achieving higher and lower BP targets was different, although baseline differences between groups were qualitatively similar in either case. Four, unaccounted baseline differences are unlikely to explain the effect of BP reductions < 140/90 mmHg on the various CV events. Thus, although interpretation of post-hoc data requires caution, it seems reasonable to conclude that baseline confounders did not play a major role in our results.

Implications

Our data suggest that in middle-aged and elderly patients with type-2 diabetes mellitus and hypertension a more consistent achievement of blood pressure target < 140/90 mmHg leads to a major reduction in the risk of coronary events, heart failure, and stroke, protective effects extending to lower cardiovascular and all-cause mortality and even to non-cardiovascular mortality. This does not occur for a more frequent control of blood pressure < 130/80 mmHg. Thus, guidelines should not recommend using this intensive blood pressure target in middle-aged and elderly patients with diabetes and hypertension. Our findings are in line with a recent Cochrane analysis (21).

Disclosure statement

S.E. Kjeldsen has received honoraria from Merck GBaA, Sanofi and Takeda. R. Mo has received honoraria from Novartis. B. Holzhauer and D. Zappe are employees of Novartis Pharma. The other authors report no relevant conflicts of interest.

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References

1. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet. 1998;351:1755–1762.
2. Holman RR, Paul SK, Berthel MA, et al. Long-term follow-up after tight control of blood pressure in type-2 diabetes. N Eng J Med. 2008;359:1565-1576.
3. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370:829–840.
4. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–1585.

5. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and Hypertension: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40:1273-1284
6. Williams B, Mancia G, Spiering W, et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Blood Press. 2018;27:314-340.
7. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/ AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269-1324.
8. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ. 2016;352:i717.
9. Cooper DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA. 2010;304:61–68.
10. Redon J, Mancia G, Sleight P, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). JACC. 2012;59:74–83.
11. Sim JJ, Shi J, Kovesdy CP, et al. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. JACC. 2014;64:588–597.
12. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022–2031.
13. Mancia G, Messerli F, Bakris G, et al. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. Hypertension. 2007;50:299–305.
14. Mancia G, Schumacher H, Redon J, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation. 2011;124:1727-1736.

15. Mancia G, Kjeldsen SE, Zappe DH, et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. Eur Heart J. 2016;37:955-964.
16. Olsen E, Holzhauer B, Julius S et. al. Cardiovascular outcomes at recommended blood pressure targets in middle-aged and elderly patients with type-2 diabetes mellitus compared to all middle-aged and elderly hypertensive study participants with high cardiovascular risk. Submitted.
17. Mehlum MH, Liestøl K, Kjeldsen SE, et al. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. Eur Heart J. 2018;39:2243-2251.
18. Mehlum MH, Liestøl K, Wyller TB, et al. Blood pressure variability in hypertensive patients with atrial fibrillation in the VALUE trial. Blood Press. 2019;28:77-83.
19. Mehlum MH, Liestøl K, Kjeldsen SE, et al. Blood pressure–lowering profiles and clinical effects of angiotensin receptor blockers versus channel blockers. Hypertension. 2020;75:1584-1592.
20. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 3. Effects in patients at different levels of cardiovascular risk. Overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2305–2314.
21. Saiz LC, Gorricho J, Garjón J, et al. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database Syst Rev. 2020 Sep 9;9:CD010315. doi: 10.1002/14651858.CD010315.pub4. PMID: 32905623.

Legends to figures

Figure 1

Incidence of morbid and fatal events in *groups of diabetic patients* divided according to the proportion of the overall treatment duration (< 25% to ≥ 75%) in which BP was reduced < 140/90 mmHg (upper panel) or < 130/80 mmHg (lower panel) prior to the occurrence of an event. N refers to the number of patients in each group. CV: cardiovascular; MI: myocardial infarction; CHF: congestive heart failure.

Figure 2

Percent (and 95% CI) change in the risk of events according to the proportion of time in which BP was reduced < 140/90 mmHg (upper panel) or < 130/80 mmHg (lower panel) in *groups of diabetic patients*. The group in which these BP targets were achieved for ≥ 75% of the time is taken as reference and shown by the empty circle (minor variations in "n" as some endpoints were composite and primary and other endpoints secondary). Data were adjusted for both baseline covariates and achieved average systolic BP and diastolic BP. P values refer to trend. Other symbols as in Figure 1.

Fig. 1 and Fig. 2 follow after Table 1 and Table 2

Table 1 – Baseline characteristics of the 4 groups of *diabetic* patients in which treatment reduced BP below 140/90 mmHg for different proportions (from < 25% to ≥ 75%) of the overall duration of treatment.

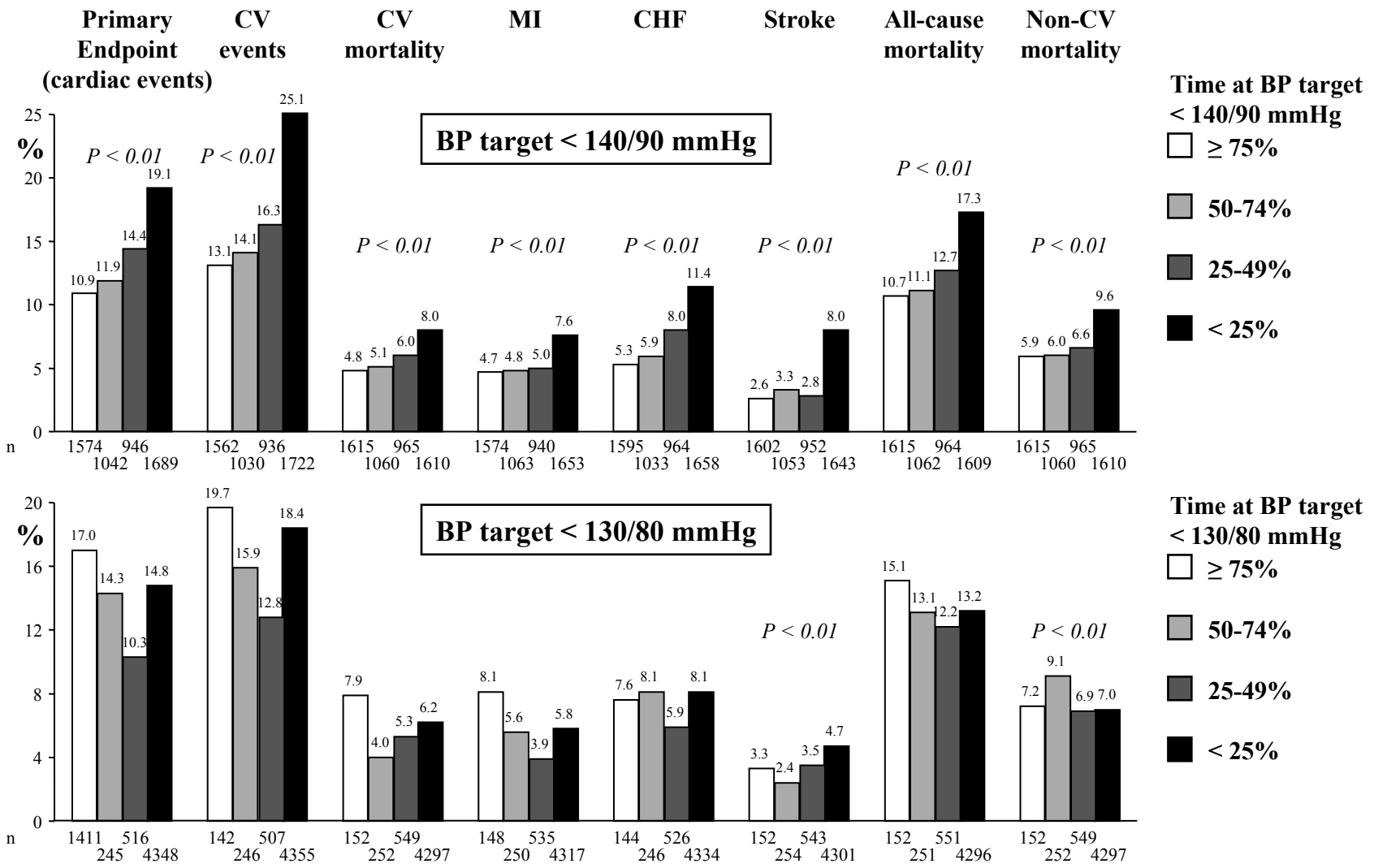
	< 25%	25% - 49%	50% - 74%	≥ 75%	P (trend)
n	1688	946	1042	1574	
Females (%)	47.0	46.7	42.7	40.7	<0.0001
Age (years)	67.6 ± 7.7	68.0 ± 8.0	67.0 ± 7.8	66.1 ± 8.0	<0.0001
Caucasians (%)	89.2	87.4	86.2	81.2	<0.0001
SBP (mmHg)	166.0 ± 17.6	158.0 ± 17.0	153.0 ± 16.7	146.0 ± 17.1	<0.0001
DBP (mmHg)	88.8 ± 10.9	87.1 ± 10.6	86.6 ± 10.6	85.0 ± 10.4	<0.0001
Heart rate (beats/min)°	73.0 ± 13.8	72.7 ± 13.6	72.5 ± 13.8	72.3 ± 13.7	0.523
Antihypertensive treatment (%)	93.9	93.3	93.7	94.2	0.728
Body mass index (kg/m^2)	30.1 ± 5.4	30.1 ± 5.3	29.9 ± 5.6	29.7 ± 5.5	0.088
Smoking (%)	17.5	19.0	19.6	24.7	<0.0001
Proteinuria (%)	32.8	28.8	26.1	24.0	<0.0001
High serum creatinine (%)	4.9	5.3	3.2	1.9	<0.0001
High total cholesterol (%)	32.6	29.0	28.9	25.0	<0.0001
Left ventricular hypertrophy (%)*	7.5	5.5	4.4	3.1	<0.0001
Coronary disease (%)	35.7	38.7	39.6	45.6	<0.0001
Stroke / TIA (%)	15.0	17.1	17.7	15.7	0.508
Peripheral artery disease (%)	13.7	14.3	11.2	10.0	<0.0003
On-treatment mean SBP (mmHg)	156.2 ± 11.0	143.4 ± 4.0	137.9 ± 3.7	131.0 ± 5.6	<0.0001
On-treatment mean DBP (mmHg)	84.2 ± 8.3	80.4 ± 6.5	79.4 ± 5.9	77.5 ± 5.6	<0.0001

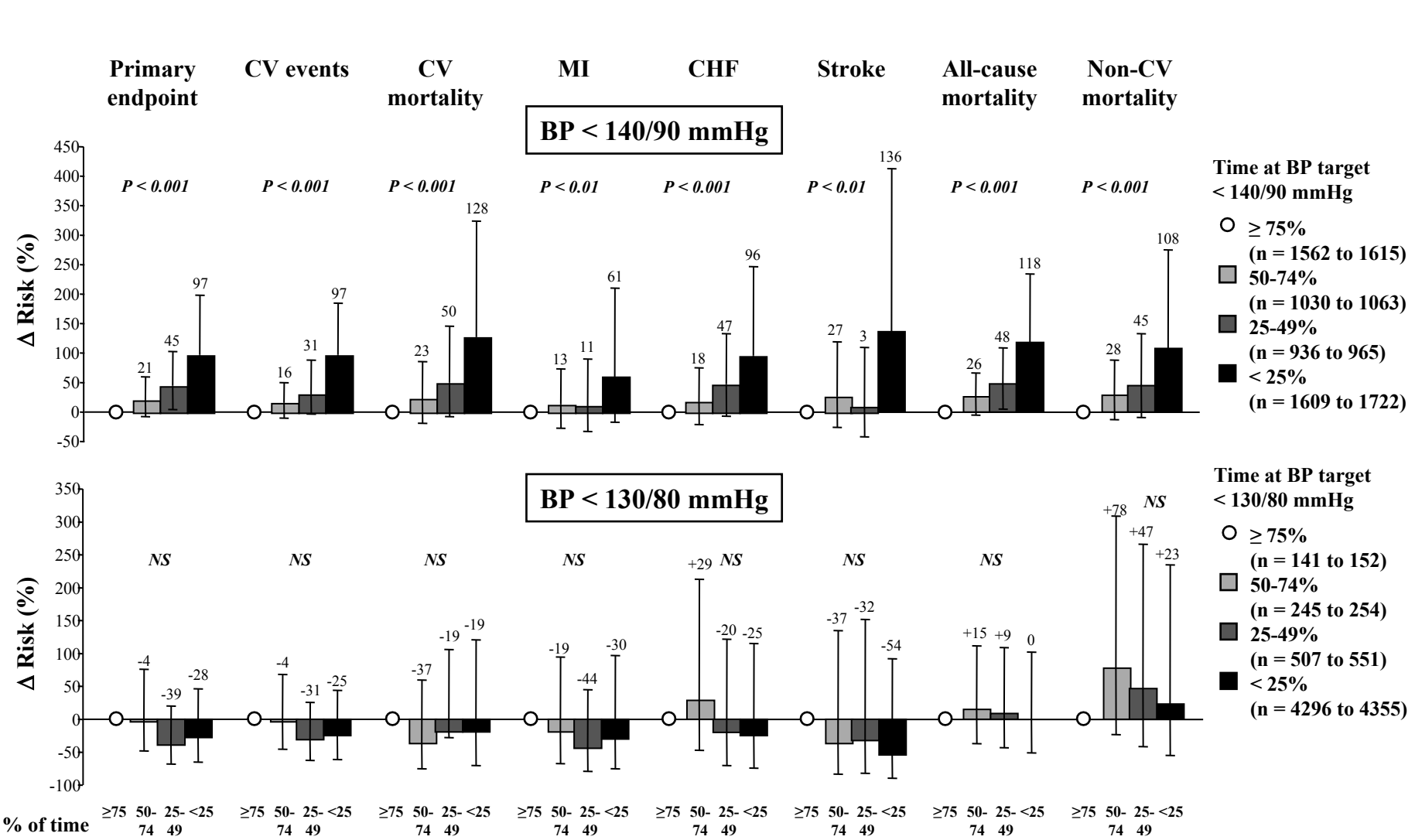
Data are shown as means ± SD or %. °by EKG; * EKG, strain pattern; Data from all randomized patients without GCP deficiencies and missing BP values; S: systolic; D: diastolic; TIA: transient ischemic attack; High serum creatinine: ≥ 150 µmol/L; High total cholesterol: ≥ 240 mg/dL (6 mmol/L)

Table 2 – Baseline characteristics of the 4 groups of *diabetic* patients in which treatment reduced BP below 130/80 mmHg for different proportions (from < 25% to ≥ 75%) of the overall duration of treatment.

	< 25%	25% - 49%	50% - 74%	≥ 75%	P (trend)
n	4348	516	245	141	
Females (%)	44.8	40.7	43.3	35.5	0.017
Age (years)	67.2 ± 7.9	66.8 ± 8.0	66.7 ± 7.7	66.8 ± 8.4	0.57
Caucasians (%)	86.8	82.0	83.7	74.5	<0.0001
SBP (mmHg)	159.0 ± 18.0	147.0 ± 16.9	143.0 ± 17.7	134.0 ± 16.6	<0.0001
DBP (mmHg)	88.0 ± 10.5	83.0 ± 10.6	81.6 ± 10.8	77.8 ± 11.0	<0.0001
Heart rate (beats/min)°	72.8 ± 13.7	71.8 ± 13.8	72.4 ± 13.6	71.3 ± 13.3	0.25
Antihypertensive treatment (%)	93.3	96.1	95.9	97.9	0.0005
Body mass index (kg/m^2)	29.9 ± 5.4	30.0 ± 5.8	30.2 ± 5.8	29.5 ± 5.7	0.67
Smoking (%)	20.2	20.0	22.9	22.0	0.49
Proteinuria (%)	28.8	27.1	21.2	23.4	0.014
High serum creatinine (%)	4.0	3.5	0.4	2.8	0.029
High total cholesterol (%)	30.2	25.2	20.8	19.1	<0.0001
Left ventricular hypertrophy (%)*	5.3	5.0	4.9	3.5	0.49
Coronary disease (%)	37.6	47.9	52.7	60.3	<0.0001
Stroke / TIA (%)	15.7	19.2	15.9	17.7	0.096
Peripheral artery disease (%)	12.3	11.8	11.4	12.8	0.74
On-treatment mean SBP (mmHg)	145.7 ± 11.7	132.0 ± 4.1	127.0 ± 3.6	120.5 ± 5.3	<0.0001
On-treatment mean DBP (mmHg)	81.9 ±7.1	75.8 ± 5.2	73.8 ± 4.6	70.6 ± 5.0	<0.0001

Symbols and explanations as in Table 1.


Primary Endpoint (cardiac events)
CV events
CV mortality
MI
CHF
Stroke
All-cause mortality
Non-CV mortality
BP target < 140/90 mmHg
%
P < 0.01
10.9 11.9 14.4 19.1
13.1 14.1 16.3 25.1
4.8 5.1 6.0 8.0
4.7 4.8 5.0 7.6
5.3 5.9 8.0 11.4
2.6 3.3 2.8 8.0
10.7 11.1 12.7 17.3
5.9 6.0 6.6 9.6
n
1574 946 1042 1689
1562 936 1030 1722
1615 965 1060 1610
1574 940 1063 1653
1595 964 1033 1658
1602 952 1053 1643
1615 964 1062 1609
1615 965 1060 1610
Time at BP target < 140/90 mmHg
≥ 75%
50-74%
25-49%
< 25%
BP target < 130/80 mmHg
17.0 14.3 10.3 14.8
19.7 15.9 12.8 18.4
7.9 4.0 5.3 6.2
8.1 5.6 3.9 5.8
7.6 8.1 5.9 8.1
3.3 2.4 3.5 4.7
15.1 13.1 12.2 13.2
7.2 9.1 6.9 7.0
1411 516 245 4348
142 507 246 4355
152 549 252 4297
148 535 250 4317
144 526 246 4334
152 543 254 4301
152 551 251 4296
152 549 252 4297
Time at BP target < 130/80 mmHg
≥ 75%
50-74%
25-49%
< 25%


Primary endpoint
CV events
CV mortality
MI
CHF
Stroke
All-cause mortality
Non-CV mortality
BP < 140/90 mmHg
P < 0.001
P < 0.001
P < 0.001
P < 0.01
P < 0.001
P < 0.01
P < 0.001
P < 0.001
Δ Risk (%)
450
400
350
300
250
200
150
100
50
0
-50
21
45
97
16
31
97
23
50
128
13
11
61
18
47
96
27
3
136
26
48
118
28
45
108
Time at BP target < 140/90 mmHg
≥ 75% (n = 1562 to 1615)
50-74% (n = 1030 to 1063)
25-49% (n = 936 to 965)
< 25% (n = 1609 to 1722)
BP < 130/80 mmHg
NS
Δ Risk (%)
350
300
250
200
150
100
50
0
-50
-100
-4
-39
-28
-4
-31
-25
-37
-19
-19
-19
-44
-30
+29
-20
-25
-37
-32
-54
+15
+9
0
+78
+47
+23
Time at BP target < 130/80 mmHg
≥ 75% (n = 141 to 152)
50-74% (n = 245 to 254)
25-49% (n = 507 to 551)
< 25% (n = 4296 to 4355)
% of time
≥75
50-74
25-49
<25