Diastolic Pressure in Type 2 Diabetes

Can target systolic pressure be reached without "diastolic hypotension"?

ETTY OSHER, MD[1,2]
NAFTALI STERN, MD[1,2]

The practicality of vigorous lowering of systolic pressure in diabetes to <130 mmHg remains uncertain. Baseline blood pressure data from several recent trials indicate that, in diabetic subjects, there is nearly a fourfold excess in systolic pressure (the difference between baseline pressure and target pressure) over diastolic pressure with respect to the recommended systolic/diastolic target pressure of <130/80 mmHg. Additionally, systolic pressure was 2–3 mmHg higher and diastolic pressure was 1–3 mmHg lower in diabetic hypertensive than in nondiabetic hypertensive individuals, which adds ~4 mmHg to pulse pressure and also to the difference between the excess systolic and excess diastolic pressure. We attempted to force (titrate both systolic and excess diastolic pressure) systolic and diastolic blood pressure to <130/85 mmHg based on Joint National Committee VI guidelines in the setting of a clinical practice in 257 diabetic patients. Although target systolic pressure was attained in a third of this cohort, in 57% of the patients, the attained diastolic pressure was ≤70 mmHg. Patients with final diastolic pressure <70 mmHg were older, had a higher prevalence of coronary artery disease, and had higher initial systolic and pulse pressures. Review of achieved blood pressure in studies such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) indicates that a significant fraction of the diabetic subjects' diastolic pressure was also driven down to <70 mmHg or even <60 mmHg. Thus, attempted lowering of blood pressure to target systolic pressure is associated with inordinate lowering of diastolic pressure in a significant number of patients. Whether the benefits of tight systolic control to <130 mmHg outweigh the risks of excessive diastolic reduction, especially in older diabetic subjects or diabetic patients with coronary artery disease, remains unresolved.

Diabetes Care 31 (Suppl. 2):S249–S254, 2008

The gradual shift in the treatment of hypertension in diabetes from the classic target pressure of <140/90 mmHg to tighter blood pressure control has been influenced by several large clinical trials that provided unequivocal evidence that more intensive lowering of arterial pressure in diabetes is both feasible (1) and effective in reducing cardiovascular morbidity (1–3). The U.K. Prospective Diabetes Study may have been the first to discern the unique advantage offered to diabetic subjects by effective antihypertensive treatment, by showing that the rate of stroke and death related to diabetes was lower in diabetic individuals whose blood pressure was reduced to 144/82 mmHg compared with patients subjected to less tight blood pressure control, whose achieved blood pressure was 154/87 mmHg (3). The Hypertension Optimal Treatment (HOT) study provided evidence that the treatment target in diabetes should indeed be moved downward, since the lowest rate of major cardiovascular events was observed in treated hypertensive diabetic patients in whom the goal diastolic pressure was <80 mmHg (2). Although these studies supported the intensification of antihypertensive therapy in diabetes, the feasibility of attaining the guideline actual target blood pressure of <130/85 or 130/80 mmHg has hardly been studied, especially with regard to systolic goals. Only in recent years, after the results of several observational studies in which systolic blood pressure was a stronger predictor of cerebro- and cardiovascular morbidity than diastolic blood pressure (5–7), has the treatment paradigm of hypertension shifted to systolic blood pressure (4). This new focus on systolic pressure was reinforced by the large World Health Organization/International Society of Hypertension meta-analysis (Blood Pressure Lowering Treatment Trialists' Collaboration), which indicated that achieved systolic blood pressure in clinical trials was the strongest predictor of the actual reduction in the rate of stroke and coronary events (8). Although the implications for diastolic pressure of tighter systolic control (e.g., <130 mmHg) in diabetic hypertensive patients are largely unstudied, the prediction that diastolic pressure might be reduced beyond the range seen in traditional standard practice appears reasonable. Such excessive diastolic pressure lowering may not be entirely inconsequential, in light of recent data from the Framingham study indicating that in the middle-aged and elderly, who comprise the majority of the type 2 diabetic population, risk for coronary heart disease increases with lower diastolic pressure at any level of systolic pressure >120 mmHg (9). This contention follows the footsteps of earlier reports linking low diastolic pressure in treated hypertensive patients with increased risk for myocardial infarction (10,11). In one report, the relative risk for myocardial infarction at an achieved diastolic pressure of 60 mmHg was twofold higher than that at 100 mmHg (11). In a recent secondary analysis of the International Verapamil-Trandolapril Study (INVEST), which focused on hypertensive subjects with coronary artery disease, risk for first occurrence of all-cause death and nonfatal myocardial infarction was clearly increased for patients in whom the on-treatment diastolic pressure was <70 mmHg (12). Achieved diastolic pressure of 60–70 mmHg led to nearly twofold higher risk, and the risk tripled for

From the [1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and the [2]Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel.
Address correspondence and reprint requests to Naftali Stern, MD, Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv-Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel. E-mail: stern@tasmc.health.gov.il.
The authors of this article have no relevant duality of interest to declare.
This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.
Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; INVEST, International Verapamil-Trandolapril Study.
DOI: 10.2337/dc08-s262

Table 1—*Baseline systolic and diastolic blood pressure in hypertension clinical trials: comparison between diabetic and nondiabetic subjects*

Study (diabetes/ no diabetes)	Systolic blood pressure, no diabetes (mmHg)	Systolic blood pressure, diabetes (mmHg)	Diastolic blood pressure, no diabetes (mmHg)	Diastolic blood pressure, diabetes (mmHg)	Mean age difference (years) (diabetes–no diabetes)
CAPPP (10,413/572)	160.6 ± 20.0	163.6 ± 18.8	99.0 ± 10.0	97.2	3.4
INSIGHT (5,019/1,302)	171.9	175.2	99	97.2	
Syst-Eur (4,695/492)	173 ± 9.9	175.3 ± 10.5	85.6 ± 5.8	84.5 ± 6.3	0.5
INVEST (16,176/6,400)	149	150.8	86.9	85.4	
ALLHAT (18,411/13,101)	146	146.5 ± 15.4	84.7	82.9 ± 10	−0.5
LIFE (7,998/1,195)	174 ± 14	177 ± 14	98 ± 9	96 ± 10	

Data are means ± SD. CAPPP, Captopril Prevention Project; Syst-Eur, Systolic Hypertension in Europe.

achieved diastolic pressure of ≤60 mmHg (12). The same trend was also noted in a subanalysis of the diabetic subjects in the INVEST trial, in whom coronary event rate tended to increase once diastolic pressure dropped to <60 mmHg. These latter findings were limited, however, by the small number of subjects identified at the lowest diastolic pressure range (13).

In the present report, we first analyze current data on diastolic pressure in diabetic hypertensive subjects. We then review the results of our own experience in attempted forced titration of both systolic and diastolic blood pressure to the Joint National Committee VI target level of <130/85 mmHg in diabetes. Finally, we place the outcome of this field intervention in the perspective of achieved diastolic pressure in recent large hypertension clinical studies, in which the final on-treatment blood pressure was closer to the recommended target pressure compared with earlier trials. Even with suboptimal control of systolic blood pressure, marked lowering of diastolic pressure to <70 mmHg appears an inevitable outcome in a significant fraction of intensively treated hypertensive diabetic patients.

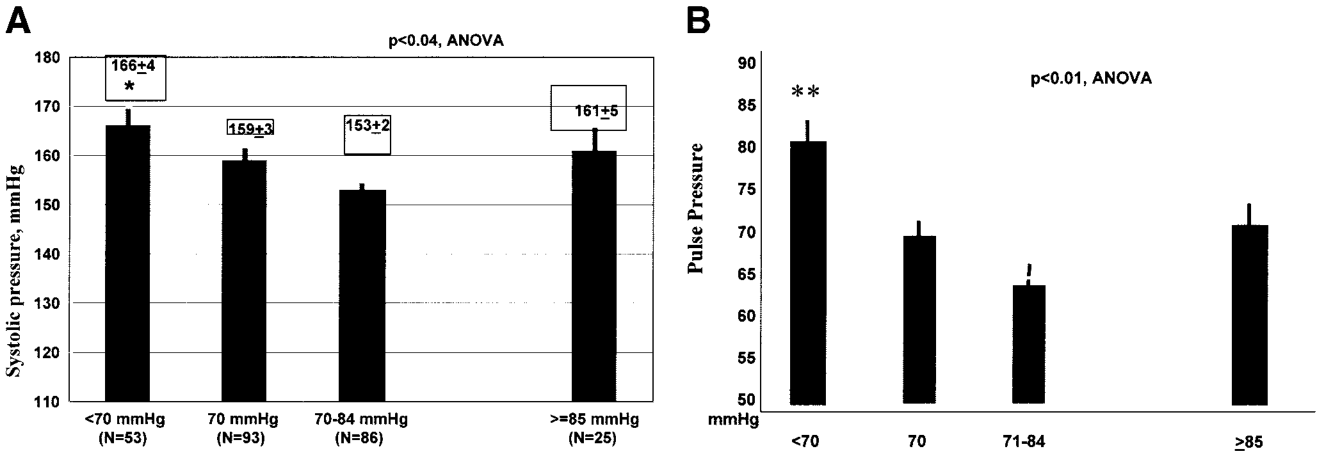
DIASTOLIC PRESSURE IN TYPE 2 DIABETES

— In the general population, systolic blood pressure increases progressively with age, whereas diastolic blood pressure rises until ~60 years of age, after which it starts to decline (14,15). The age-related decline in diastolic pressure is presumed to result from early recoil of the pressure wave, which, because of increasing arterial stiffness and lack of proper large artery compliance, occurs earlier (i.e., during the systole rather than later on during the diastole, as seen in the young). Such shift of the initial reflection wave from the diastole to the systole increases systolic and decreases diastolic pressure. A recent cross-sectional case-control study showed that type 1 diabetic subjects had a higher systolic blood pressure than nondiabetic control subjects in all age-groups, whereas diastolic blood pressure was higher in individuals <40 years of age but lower in individuals >45 years of age (16). These findings in older type 1 diabetic subjects are consistent with the concept that, whereas aging affects systolic and diastolic pressure in a parallel manner in subjects with and without diabetes, the changes in systolic and diastolic pressure induced by arterial stiffening take place at a younger age in diabetes. Because the pathogenesis of large artery disease likely results, at least in part from hyperglycemia per se (17), one might anticipate similar alterations in systolic and diastolic pressure in type 2 diabetes as well. Consistent with this notion is our previous cross-sectional study of 2,227 subjects with type 2 diabetes, showing that whereas the prevalence of systolic hypertension rises steadily with age in type 2 diabetes, the prevalence of diastolic hypertension does not (18).

Table 1 depicts baseline systolic and diastolic pressure from several large clinical trials in hypertension that recruited both diabetic (mostly type 2) and nondiabetic hypertensive subjects. There are several lessons to be drawn from these reported baseline data, compiling a total of 21,188 hypertensive diabetic and 62,712 nondiabetic individuals with high blood pressure.

First, there is a larger excess in systolic pressure than in diastolic pressure with respect to the recommended pressure goal of <130/80 mmHg. The "systolic gap," i.e., the difference between baseline systolic pressure and the target pressure of 129 mmHg (the highest acceptable <130 mmHg target value), was 34.6, 46.2, 46.3, 22, 17.5, 48, and 7 mmHg in the diabetic subjects participating in Captopril Prevention Project (CAPPP), Intervention as a Goal in Hypertension Treatment (INSIGHT), Systolic Hypertension in Europe (Syst-Eur) Trial, INVEST, ALLHAT, Losartan Intervention For Endpoint Reduction in Hypertension (LIFE), and Appropriate Blood Pressure Control in Diabetes (ABCD) (13,19–26), respectively, but the corresponding gap between the pretreatment diastolic pressure and the target pressure of 79 mmHg was only 18.2, 18.2, 5.5, 6.4, 4, and 5 mmHg, yielding an average (non-weighted) systolic over diastolic excess ratio of ~4. Because the desirable reduction in systolic pressure so markedly exceeds that of the required diastolic pressure lowering, and because selective drugs affecting systolic but not diastolic pressure are not available, forced downward titration of systolic to <130 mmHg can be expected to lower diastolic pressure to much less than 79 mmHg, at least in some patients.

One additional key finding reflected in Table 1 is that in most of the included studies, systolic pressure was 2–3 mmHg higher and diastolic pressure was 1–3 mmHg lower in diabetic hypertensive individuals than in nondiabetic hypertensive individuals. Although there are major differences among the trials with respect to age, ethnic and geographic spread, the presence of comorbidities, previous blood pressure lowering therapy, and patient selection, the finding of lower baseline diastolic pressure and higher systolic pressure is fairly consistent across these trials. This adds ~4 mmHg to pulse pressure and also to the difference between the systolic and diastolic gap in diabetic versus nondiabetic subjects, thus provid-



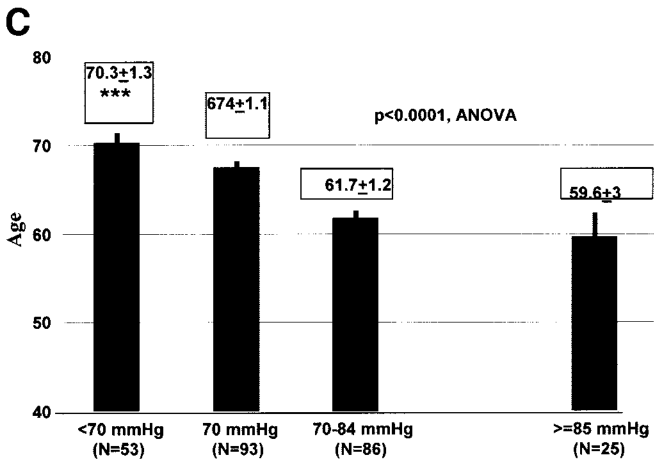


Figure 1—*Relation between achieved final diastolic pressure and initial (baseline) systolic pressure* (A), *initial pulse pressure* (B), *and patients' age. Patients are divided into groups by the final diastolic pressure (<70 mmHg, 70 mmHg, 71–84 mmHg, and ≥85 mmHg). Patients with the lowest achieved diastolic pressure had higher baseline systolic* (A; ***P < 0.04, ANOVA) and higher initial pulse pressure* (B; ***P < 0.01) and were older* (C; **P < 0.0001, ANOVA) than the other patients who achieved goal diastolic pressure. DP, diastolic pressure.*

ing further opportunity to induce exaggerated diastolic decline in diabetes in the course of drug treatment driven by a systolic goal paradigm.

ATTEMPTED FORCED TITRATION OF BLOOD PRESSURE TO <130/85 MMHG IN TYPE 2 DIABETIC HYPERTENSIVE SUBJECTS— We have previously reported the results of systematic implementation of Joint National Committee VI guidelines in clinical practice by forced titration of both systolic and diastolic pressure in 257 consecutive patients with type 2 diabetes and hypertension to <130/85 mmHg (27). The initial mean blood pressure for the entire cohort was 159/86 mmHg, reflecting the fact that the majority of patients were already receiving blood pressure–lowering therapy at baseline and that the diastolic gap (extent of diastolic reduction required to achieve the target of 79 mmHg) was much lower than the systolic gap. Indeed, the latter was quite in line with baseline data in the large clinical trials reviewed above. We used individually tailored treatment, driven only by target levels, generally accepted preference principles, patients' ability to comply, and the appearance of clinical or biochemical adverse effects. Treatment was unbound to specific drug class or sequence, except for the use of ACE inhibitors whenever possible. Additionally, we did not further increase medication once diastolic blood pressure has reached 50 mmHg. After treatment, diastolic target pressure was achieved in 90% of patients (232/257). However, goal systolic pressure of <130 mmHg was reached in only one-third of this cohort (86/257) and the desirable systolic and diastolic pressure was observed in just 32% of the treated subjects. Nevertheless, despite this apparent high failure rate with respect to systolic target, the mean achieved systolic pressure in the entire cohort was 132 ± 1 mmHg. Because systolic control so clearly lagged behind diastolic control, attempts to reach target systolic level in the presence of already normalized diastolic pressure resulted in lowering of diastolic pressure to ≤70 mmHg in 57% (146/257) of our patients (mean achieved diastolic pressure: 66 ± 0.5 mmHg) and to <70 mmHg in about one-fifth of the cohort (53/257; mean achieved diastolic pressure: 60 ± 1 mmHg). Of particular importance was the finding that patients with the lowest achieved diastolic pressure (<70 mmHg) had a nearly twofold higher prevalence of preexisting ischemic heart disease (52 vs. 27% in patients with on-treatment diastolic pressure of ≥70 mmHg. Low achieved diastolic pressure (<70 mmHg) was also associated with older age and high initial systolic pressure and initial pulse pressure (Fig. 1). Additionally, in a forward multiple stepwise regression analysis, 52% of the variation in the attained reduction in diastolic pressure could be explained by the combination of initial systolic blood pressure (20%; β coefficient 0.789; $P < 0.0001$), age (18%; β coefficient 0.857; $P < 0.0001$), weight (2%; β coefficient −0.1; $P < 0.013$), preexisting ischemic heart disease (1%; β coefficient 2.72; $P < 0.03$), and the interaction between age and initial pulse pressure (11%; β coefficient −0.01; $P < 0.0001$). Neither the attained diastolic pressure nor the actual decline in diastolic pres-

Table 2—*Achieved final systolic and diastolic blood pressure in several large trials that included diabetic hypertensive subjects*

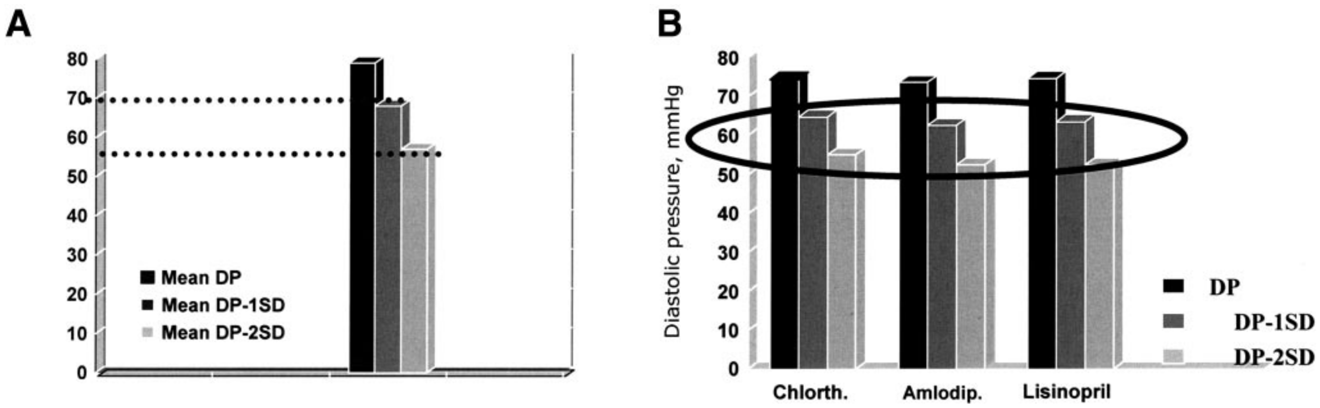
	BP (mmHg)	Mean age (years)	Trial drug(s)
HOT (2)	143/82	61.5	Penedil
IDNT (29)	141/83	58	Irbesartan
RENAAL (30)	140/74	60	Losartan
UKPDS (3)	144/86	56.4	Atenolol
ABCD (26)	133/78	58	Enalapril
Syst-Eur (22)	162/82	60	Nitendip
Micro-HOPE (31)	140/77	56.4	Ramipril
LIFE (25)	146/79	58	Losartan
ALLHAT (24)	135/74	60	Chlorthalidone
ALLHAT	136/74	65	Amlodipine
ALLHAT	138/75	67	Lisinopril
ASCOT-BPLA (28)*	136/77	67	Amlodipine
ASCOT-BPLA†	138/79	67	Atenolol

Numbers in parentheses refer to the corresponding reference number from which the data were extracted. *Entire population, including 26.6% (2,567) diabetic subjects. †Entire population, including 27% (2,578) diabetic subjects. HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; IDNT, Irbesartan in Diabetic Nephropathy Trial; RENAAL, Reduction of End Points in Type 2 Diabetes with the Angiotensin II Antagonist Losartan; Syst-Eur, Systolic Hypertension in Europe; UKPDS, U.K. Prospective Diabetes Study.

sure was associated with the use of any specific antihypertensive drug class or a definable combination of drugs. These results support the concept that excessive lowering of diastolic pressure appears an inevitable outcome of attempts to approach the target systolic pressure.

RECENT EVIDENCE FOR DIASTOLIC COST IN LARGE CLINICAL TRIALS OF HYPERTENSION IN TYPE 2 DIABETIC SUBJECTS

— The continuous failure to approach recommended systolic target values (Table 2) appears to be changing in recent trials, such as ALLHAT (24) and the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) (28), probably because of the inclusion of multiple dose adjustments and the combined use of multiple drugs. The resulting on-treatment systolic blood pressure in these studies has moved to the mid-130 mmHg zone, and not surprisingly, the attained mean diastolic pressure has inevitably shifted from the mid-80s all the way to 74 mmHg in ALLHAT. One overlooked aspect of this lower on-treatment mean diastolic pressure, which is best exemplified in ALLHAT, is depicted in Fig. 2. If 1 SD is subtracted from the achieved mean diastolic pressure observed in the fifth and final year of ALLHAT, the derived (mean − 1 SD) diastolic value is 65 mmHg for the chlorthalidone arm and 64 mmHg for either the amlodipine or the lisinopril arm. The parallel diastolic values reflecting 2 SDs below the mean would be 53–54 mmHg. Although less extreme, similarly low attained −1 SD/−2 SD diastolic pressure levels are obtained, even for the LIFE and ASCOT-BPLA studies (Fig. 2). Because a non-negligible part of treated hypertensive diabetic subjects in these studies must



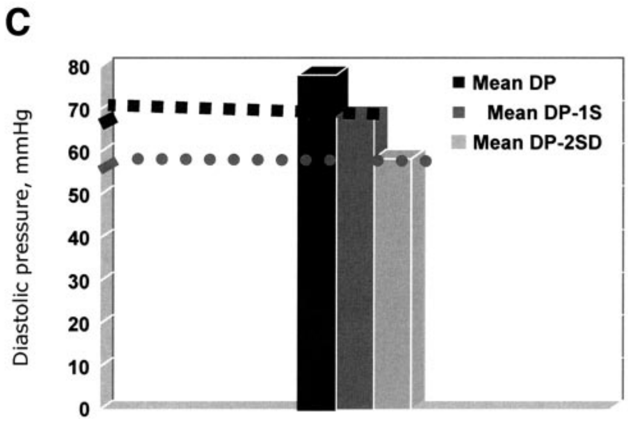


Figure 2—*Achieved final mean diastolic pressure, as well as mean diastolic pressure minus 1 and 2 SD derived from the reported results of three large trials: LIFE (25; A), ALLHAT (24; B), and ASCOT-BPLA (28; C). The data in A and B represent mean diastolic levels as well as diastolic pressure at 1 and 2 SD below the reported mean for the diabetic patients included in these studies. C represents the diastolic mean as well as 1 and 2 SD below the mean for the entire study population, since data on diabetic subjects have not been reported separately. Amlodip., amlodipine; Chlorth., chlorthalidone; DP, diastolic pressure.*

have fallen within the diastolic zone ranging between −1 SD and −2 SD, it follows that diastolic lowering to <70 mmHg and even to 50–60 mmHg was recorded in a significant fraction of patients. This conclusion is certainly in line with our own experience in clinical practice summarized above. To our knowledge, the only instance in which target systolic pressure has been indeed achieved without excessive diastolic lowering is one of the ABCD trials (26), conducted in diabetic subjects with mild hypertension, whose mean baseline blood pressure was 135/84 mmHg.

CONCLUSIONS — Therapeutically induced "diastolic hypotension" in diabetes may pose a previously unrecognized clinical challenge simply because the potential to implement current guidelines is increasing because of the effectiveness of current multi-drug combination therapy (32,33). Since it is generally accepted that most intramural coronary perfusion occurs in the diastole, patients with coronary artery disease appear particularly vulnerable to reduction in perfusion pressure during the diastole (low diastolic pressure). Because coronary disease in diabetes is not only extremely common but also often undiagnosed, our finding that excessive diastolic lowering is more common in subjects with coronary artery disease may be of great concern.

The choice between leaving systolic pressure above the desirable range and lowering diastolic pressure to ~60 mmHg or less may not be restricted to diabetic patients, but with the exception of renal failure, the requirement in existing guidelines to lower systolic pressure to <130 mmHg is presently limited to diabetes. As the prevalence of diabetes rises with age, the elderly diabetic subject and/or the diabetic patient with coronary artery disease emerge as the most likely candidates to exhibit very low diastolic pressure in the course of aggressive systolic pressure lowering to target.

We believe that until more information on the risk ratio of leaving systolic pressure >130 mmHg versus lowering diastolic pressure to <70 or <60 mmHg is available, qualifications concerning the attained diastolic pressure should be considered in future guidelines for target blood pressure in older diabetic subjects, particularly in the presence of coronary artery disease.

References

1. Estacio RO, Jeffers BW, Gifford N, Schrier RW: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23 (Suppl. 2):B54–B64, 2000
2. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: 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* 51:1755–1762, 1998
3. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 317:703–713, 1998
4. Black HR: The paradigm has shifted to systolic blood pressure. *J Hum Hypertens* 18 (Suppl. 2):S3–S7, 2004
5. Onat A, Ceyhan K, Erer B, Basa O, Uysal O, Sansoy V: Systolic, diastolic and pulse pressures as coronary risk factors in a population with low cholesterol levels: a prospective 10-year evaluation. *Clin Cardiol* 26:91–97, 2003
6. Psaty BM, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, O'Leary DH, Bryan RN, Anderson M, Lumley T: Association between blood pressure level and the risk of myocardial infraction, stroke, and total mortality: the cardiovascular health study. *Arch Intern Med* 161:1183–1192, 2001
7. Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L: Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. *Arch Intern Med* 162:506–508, 2002
8. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 362:1527–1535, 2003
9. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 100:354–360, 1999
10. McCloskey LW, Psaty BM, Koepsell TD, Aagaard GN: Level of blood pressure and risk of myocardial infarction among treated hypertensive patients. *Arch Intern Med* 152:513–520, 1992
11. D'Agostino RB, Belanger AJ, Kannel EB, Cruickshank JM: Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *Br Med J* 303:385–389, 1991
12. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ: Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 144:884–893, 2006
13. Bakris GL, Gaxiola E, Messerli FH, Mancia G, Erdine S, Cooper-DeHoff R, Pepine CJ, INVEST Investigators: Clinical outcomes in the diabetes cohort of the INternational VErapamil SR-Trandolapril study. *Hypertension.* 44:637–642, 2004
14. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, Brown C, Roccella EJ: Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. *Hypertension* 26:60–69, 1995
15. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D: Hemodynamic patterns of age-related changes in blood pressure. *Circulatio*n 96: 308–315, 1997
16. Ronnback M, Fagerudd J, Forsblom C, Pettersson-Fernholm K, Reunanen A, Groop PH: Finnish Diabetic Nephropathy (FinnDiane) Study Group Altered age-related blood pressure pattern in type 1 diabetes. *Circulation* 110:1076–1082, 2004
17. Stern N, Marcus Y: Hypertension in diabetes mellitus: role of the vasculature. *Curr Hypertens Reports* 6:90–97, 2004
18. Kabakov E, Norymberg C, Osher E, Koffler M, Greenman Y, Tordjman K, Stern N: Prevalence of hypertension in type 2 diabetes mellitus: impact of the tightening definition of high blood pressure and associated confounding risk factors. *J Cardio Metab Syndr* 1:95–101, 2006
19. Niklasona A, Hednera T, Niskanenb L, Lanke J: Development of diabetes is retarded by ACE inhibition in hypertensive patients: a subanalysis of the Captopril Prevention Project (CAPPP). *J Hypertens* 22:645–652, 2004
20. Niklasona A, Hednera T, Niskanenb L, Lanke J: Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/β-blocker–based treatment regimen. *Diabetes Care* 24:2091–2096, 2001
21. Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G, Ruilope LM: Outcomes With Nifedipine GITS or Co-Amilozide in Hypertensive Diabetics and Nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 41:431–436, 2003
22. Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 340:677–684, 1999
23. Pepine CJ, Handberg EM, Cooper-DeHoff

RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW: A calcium antagonist vs. a non–calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril Study (INVEST): a Randomized Controlled Trial. *JAMA* 290:2805–2816, 2003

24. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U: Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 165:1401–1409, 2005
25. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint Reduction in Hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359:1004–1010, 2002
26. Mehler PS, Coll JR, Estacio R, Esler A, Schrier RW, William R, Hiatt WR: Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 107:753–756, 2003
27. Osher E, Greenman Y, Tordjman K, Kisch E, Shenkerman G, Koffler M, Shapira I, Stern N: Attempted forced titration of blood pressure to <130/85 mm Hg in type 2 diabetic hypertensive patients in clinical practice: the diastolic cost. *J Clin Hypertens (Greenwich)* 8:29–34, 2006
28. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: ASCOT Investigators: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 366:895–906, 2005
29. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *Engl J Med* 345:851–860, 2001
30. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
31. Gerstein HC, Yusuf S, Mann JFE, Hoogwerf B, Zinman B, Held C, Fisher M, Wolffenbuttel B, Bosch J, Richardson L, Pogue J, Halle JP: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy: Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253–259, 2000
32. Smuyllan H, Safar ME: The diastolic blood pressure in systolic hypertension. *Ann Intern Med* 132:233–237, 2000
33. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB: The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med* 159: 2004–2009, 1999