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Nifedipine GITS/Candesartan Combination Therapy Lowers Blood Pressure Across Different Baseline Systolic and Diastolic Blood Pressure Categories: DISTINCT Study Subanalyses

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Abstract

DISTINCT was an 8-week, double-blind, randomized study to investigate the antihypertensive efficacy and safety of various nifedipine gastrointestinal treatment system (GITS)/candesartan cilexetil (N/C) dose combinations, vs respective monotherapies or placebo, in patients with diastolic blood pressure (DBP) ≥95 to <110 mm Hg. The current prespecified analysis compared BP reduction in participants with mild vs moderate baseline hypertension (ie, systolic [S]BP <160 mm Hg vs ≥160 mm Hg and DBP <100 mm Hg vs ≥100 mm Hg). A total of 1362 patients were analyzed by descriptive statistics. In all patient subgroups investigated, the NC combinations (ie, N: 20, 30, or 60 mg; C: 4, 8, 16, or 32 mg daily) provided greater SBP and DBP lowering and higher rates of BP control (defined as BP <140/90 mm Hg) than respective monotherapies or placebo, with greatest absolute BP reductions observed in the moderately elevated SBP or DBP subgroups. A trend to dose-response relationship was observed in each subgroup. In each SBP and DBP subgroup, treatment-related vasodilatory events (flushing, headache, or edema) were less frequent for patients receiving NC combination therapy than N monotherapy. These analyses support the use of calcium antagonist and angiotensin receptor blocker combination therapy in patients with both mild and moderate hypertension, for whom effective BP normalization and good drug tolerance would greatly reduce the risk of cardiovascular events.

Keywords

candesartan cilexetil, combination therapy, DISTINCT study, essential hypertension, nifedipine GITS, vasodilatory side effects

A large number of studies have shown that the magnitude of blood pressure (BP) response to antihypertensive treatment is related to baseline BP values; ie, the higher the initial BP, the higher is the BP-lowering effect of any treatment regimen;[1–3] however, this does not translate into a greater rate of BP control. For example, an analysis of the Framingham participants that classified patients according to baseline systolic BP (SBP) reported that higher baseline SBP was associated with lower likelihood of reaching goal BP (defined as SBP <140 mm Hg and diastolic BP [DBP] <90 mm Hg).[4] Compared to participants with SBP <140 mm Hg at baseline, those with SBP between 140 and 159 mm Hg at baseline were half as likely to be controlled at follow-up, and those with SBP ≥160 mm Hg were only one-quarter as likely to be controlled. Similarly, logistic regression analysis of patients grouped by baseline SBP deciles in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that higher baseline SBP predicted lower rates of BP control.[5]

Individual clinical trials and meta-analyses have also documented that combinations of antihypertensive drugs lower BP more effectively than escalating-dose monotherapy[2,6] and thus have the potential for greater reduction in cardiovascular (CV) risk.[7] Management guidelines[8–10] support this view, with the latest guidelines from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recommending initial 2-drug combination therapy for patients at high CV risk or with markedly high BP.[8] One combination therapy approach recommended by guidelines[8] that provides both BP and CV benefits

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is a calcium channel blocker (CCB)/renin-angiotensin system (RAS) blocker. Medications used as monotherapies in the CCB and the RAS blocker classes provide effective BP lowering together with specific benefits of reductions in stroke and all-cause death (with CCBs) and heart failure (RAS blockers).[11,12] A CCB and RAS blocker in combination has been shown to offer benefit in terms of CV event reduction relative to placebo and other medication classes investigated in patients with isolated systolic hypertension[13] and in those with multiple CV risk factors, including previous CV events, diabetes, and left ventricular hypertrophy.[14,15]

DISTINCT (reDefining Intervention with Studies Testing Innovative Nifedipine GITS–Candesartan Therapy) was an 8-week randomized, double-blind, placebo-controlled trial to examine the efficacy and safety of various dose combinations of nifedipine GITS and candesartan cilexetil as initial therapy compared with respective monotherapies (including very low doses) in patients with mild to moderate hypertension. Nifedipine and candesartan cilexetil are both effective monotherapies for lowering BP.[16–19] The nifedipine GITS formulation offers, in addition, the advantage of controlled drug release, making it suitable for once-daily administration, and an observational study suggests that candesartan reduces the risk of cardiovascular disease and heart failure in comparison with another angiotensin receptor blocker (ARB), losartan.[16,18] A placebo arm was included in DISTINCT in accordance with the International Conference on Harmonisation guideline for evaluation of fixed-dose combination products for the treatment of hypertension and similar to other multifactorial trials of combination antihypertensive therapies.[20–23] DISTINCT demonstrated that initial combination therapy with nifedipine GITS/candesartan cilexetil was more effective in lowering BP and meeting target BP goals (SBP <140 and DBP <90 mm Hg) vs respective monotherapies at the same doses in participants with hypertension. DISTINCT additionally showed an improved side-effect profile, including reduced vasodilatory effects, for combination therapy compared with nifedipine GITS monotherapy.[24]

The current prespecified subgroup analysis of the DISTINCT study investigated the relationship between baseline BP and the magnitude of BP reduction and level of BP control with different dose combinations of nifedipine GITS/candesartan cilexetil, compared with respective monotherapies. Because both SBP and DBP are prognostic for CV outcomes,[25] although with different impacts at different patient ages,[26] the relationship between baseline BP and effect of therapy was analyzed independently for SBP and DBP. In accordance with recommendations current at the time of study, reduction in DBP was the primary endpoint in DISTINCT.

Methods

Trial Design

The DISTINCT study protocol was reviewed and approved by each center's independent ethics committee or institutional review board, and the study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines on good clinical practice. All participants provided written, informed consent.

DISTINCT was an 8-week multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multifactorial study (ClinicalTrials.gov identifier: NCT01303783) to determine the BP-lowering responses to various dose combinations of nifedipine GITS and candesartan cilexetil compared with the respective component monotherapies. Details of the study design have been published previously.[24] Briefly, participants with mild to moderate essential hypertension were randomized in equal ratios to 1 of 16 double-blind treatment groups to receive nifedipine GITS (N) 20 mg (n = 85), 30 mg (n = 83), or 60 mg (n = 80) or candesartan (C) 4 mg (n = 84), 8 mg (n = 87), 16 mg (n = 84), or 32 mg (n = 84), or combination N/C 20/4 (n = 87), 20/8 (n = 88), 30/8 (n = 86), 20/16 (n = 87), 30/16 (n = 88), 60/16 (n = 82), 30/32 (n = 87), 60/32 mg (n = 84), or placebo (n = 86) for 8 weeks. There was a forced-dose titration period of 1 week for subjects randomized to the highest dose of combination therapy (N/C 60/32 mg). Patients were not stratified by hypertension grade at study entry.

Participants

The study included men or women aged ≥18 years with World Health Organization (WHO) grade 1 or 2 hypertension (mean seated DBP ≥95 mm Hg to <110 mm Hg measured by a calibrated electronic BP device) who provided written informed consent prior to inclusion. Female subjects had to be postmenopausal for 1 year, surgically sterile, or using an effective contraceptive method other than hormonal contraceptives. Key exclusion criteria included grade 3 or secondary hypertension; hypertensive retinopathy or encephalopathy; a cerebrovascular ischemic event within the previous 12 months; a history of intracerebral or subarachnoid hemorrhage; heart failure in the previous 6 months; type 1 or uncontrolled type 2 diabetes mellitus (glycated hemoglobin >9%); uncorrected hypokalemia or hyperkalemia; gastrointestinal or liver disease; renal insufficiency (glomerular filtration rate <50 mL/min); severe coronary heart disease; or clinically significant cardiac valvular disease.

Subgroup Analysis Endpoints

Subgroup analysis was performed on 4 subgroups of participants categorized with mild or moderate

Table 1. Demographics and Baseline Characteristics According to Baseline SBP and DBP Subgroups

Parameter[a]	SBP Subgroup		DBP Subgroup		Total Population
	<160 mm Hg (n = 830)	≥160 mm Hg (n = 532)	<100 mm Hg (n = 796)	≥100 mm Hg (n = 566)	(N = 1362)
Age, years	51.9 (10.5)	57.4 (8.9)	54.6 (10.5)	53.3 (9.9)	54.0 (10.3)
Sex, n (%)					
Female	364 (43.9)	210 (39.5)	343 (43.1)	231 (40.8)	574 (42.1)
Male	466 (56.1)	322 (60.5)	453 (56.9)	335 (59.2)	788 (57.9)
Ethnic group, n (%)					
White	596 (71.8)	396 (74.4)	586 (73.6)	406 (71.7)	992 (72.8)
Black	147 (17.7)	72 (13.5)	120 (15.1)	99 (17.5)	219 (16.1)
Asian	74 (8.9)	47 (8.8)	69 (8.7)	52 (9.2)	121 (8.9)
Other	13 (1.6)	17 (3.2)	21 (2.6)	9 (1.6)	30 (2.2)
Prior antihypertensive use, n (%)	492 (59.3)	393 (73.9)	507 (63.7)	378 (66.8)	885 (65.0)
Body mass index, kg/m^2	31.1 (5.8)	30.8 (5.6)	31.1 (5.8)	30.9 (5.5)	31.0 (5.7)
SBP, mm Hg	149.1 (7.1)	168.0 (5.3)	154.5 (11.6)	159.4 (10.2)	156.5 (11.3)
DBP, mm Hg	99.1 (3.3)	100.3 (3.8)	97.0 (1.5)	103.1 (2.4)	99.6 (3.5)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Data are mean (standard deviation) unless otherwise stated.

hypertension: those who had a baseline SBP of <160 mm Hg or ≥160 mm Hg and those who had a baseline DBP of <100 mm Hg or ≥100 mm Hg (grade 2). The efficacy endpoints were change from baseline in mean seated DBP and SBP, and control rate at week 8, defined as the proportion of participants achieving the predetermined BP target of <140/90 mm Hg. Safety endpoints were the incidence, severity, and relation to study drug of adverse events (AEs). Vasodilatory events including flushing, headache, and edema were of special interest.

Statistical Analysis

Descriptive efficacy subgroup analyses were performed on the full analysis set (FAS), which included all randomized participants who received at least 1 dose of study medication and had a baseline and at least 1 valid postbaseline BP measurement. Missing values were imputed by a last observation carried forward approach. The change in BP from baseline to week 8 was analyzed using the response surface model to build the dose response of nifedipine and candesartan.[27] Safety analyses were performed on all randomized participants who took at least 1 dose of study drug.

Results

Baseline Characteristics

All 1362 patients in the FAS were included in this subgroup analysis of baseline BP.

Demographic and baseline characteristics of patients categorized by SBP and DBP subgroups are shown in Table 1. The populations in each baseline BP subgroup were comparable in terms of age, sex, ethnic group, and body mass index. Approximately two thirds of the total study population (65%) had received prior antihypertensive treatment. Higher proportions of patients had received prior antihypertensive treatment in the SBP ≥160 mm Hg than in the <160 mm Hg subgroup.

Study Outcomes

BP Reduction. Response surface modeling showed that nifedipine GITS/candesartan combinations provided greater SBP and DBP lowering after 8 weeks of treatment compared with respective component monotherapies or placebo in all SBP and DBP subgroups, consistent with the main study results[24] (Figure 1). For example, mean ± SE reductions in SBP in the N60C32, N60, C32, and placebo treatment groups were 29.8 ± 2.5, 23.0 ± 2.7, 20.3 ± 2.8, and 8.0 ± 2.7 mm Hg, respectively, in the SBP ≥160 mm Hg subgroup and were 20.0 ± 2.1, 13.1 ± 2.0, 14.3 ± 1.9, and 35 ± 1.9 mm Hg, respectively, in the SBP <160 mm Hg subgroup. Mean ± SE reductions in DBP in the same treatment groups were 17.8 ± 1.6, 14.8 ± 1.7, 13.8 ± 1.6, and 6.7 ± 1.6 mm Hg, respectively, in the DBP ≥100 mm Hg subgroup and 15.6 ± 1.3, 101 ± 1.3, 12.3 ± 1.3 and 6.8 ± 1.3 mm Hg, respectively in the DBP <100 mm Hg subgroup.

A similar dose-response relationship was observed in each subgroup (similar to the main study results), although small patient numbers in each BP/treatment subgroup limit detailed interpretation. Low-dose combination therapy (eg, N20C4) was equivalent to higher doses of monotherapy for BP reduction in all BP subgroups. As would be expected, BP reductions with active treatments were generally greater in subgroups with more severe hypertension at baseline, ie, for SBP ≥160 mm Hg vs SBP <160 mm Hg and DBP ≥100 mm Hg vs DBP <100 mm Hg (Figure 2).

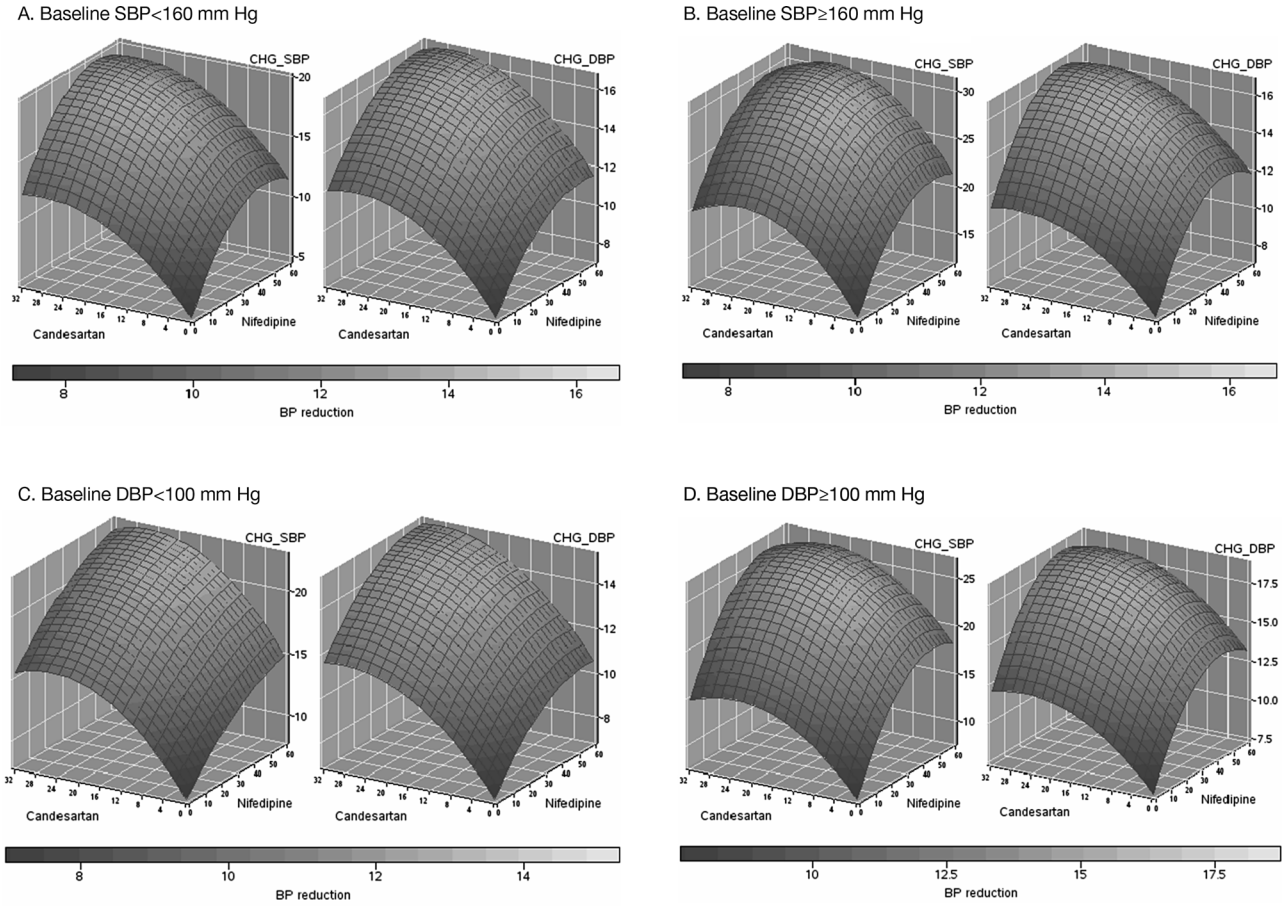

Figure 1. Response surface modeling plots for least-squares mean change in BP from baseline to week 8 according to baseline SBP and DBP subgroups. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Time course analyses for change in SBP and DBP in each pooled treatment group indicated a sharp reduction in BP in the first 2 weeks of treatment, followed by a plateau of treatment effect in subsequent weeks (Figure 3). Consistent across all treatment subgroups, the greatest BP reductions were observed for combination therapy compared with respective monotherapies or placebo, regardless of the treatment time points. Patients with higher BP at baseline (ie, SBP ≥160 mm Hg or DBP ≥100 mm Hg) also displayed greater BP reductions across time relative to patients with lower baseline BP (Figure 3B,D vs 3A,C).

BP Control Rate. Rates of BP control (defined as BP <140/90 mm Hg) at week 8 were higher with combination therapy than respective monotherapies in all SBP and DBP subgroups (Figure 4). In patients with SBP <160 mm Hg at baseline, control rates ranged from 31.7% to 58.5% with monotherapy and from 50.0% to 73.4% with combination therapy at different doses. For patients with SBP ≥160 mm Hg, respective rates were 6.1% to 35.3% and 36.4% to 56.4%. A similar pattern was seen in the DBP subgroups. A trend toward a dose-response relationship was also observed in each subgroup, similar to the main study results, although small patient numbers in each BP/treatment subgroup limit detailed interpretation.

Overall, rates of BP control were lower in patients with higher BP at baseline (ie, SBP ≥160 mm Hg or DBP ≥100 mm Hg) compared to patients with lower baseline BP. For example, in patients with baseline DBP <100 mm Hg, the highest control rate was 74.5% (with N60C32); by comparison, in the DBP ≥100 mm Hg subgroup, the highest control rate achieved was 65.7% (with N20C16). Highest control rates in the respective SBP subgroups were 73.4% and 56.4%, both with combination therapy.

Across all groups, patients achieved similar or better control rates with low-dose combination compared with the highest doses of monotherapy.

Safety. Treatment-emergent AEs were seen with a similar frequency in the 4 baseline BP subgroups (SBP <160 mm Hg, 37.8%; SBP ≥160 mm Hg, 40.3%; DBP <100 mm Hg, 39.4%; DBP ≥100 mm Hg, 38.0%). In each SBP and DBP subgroup, rates of

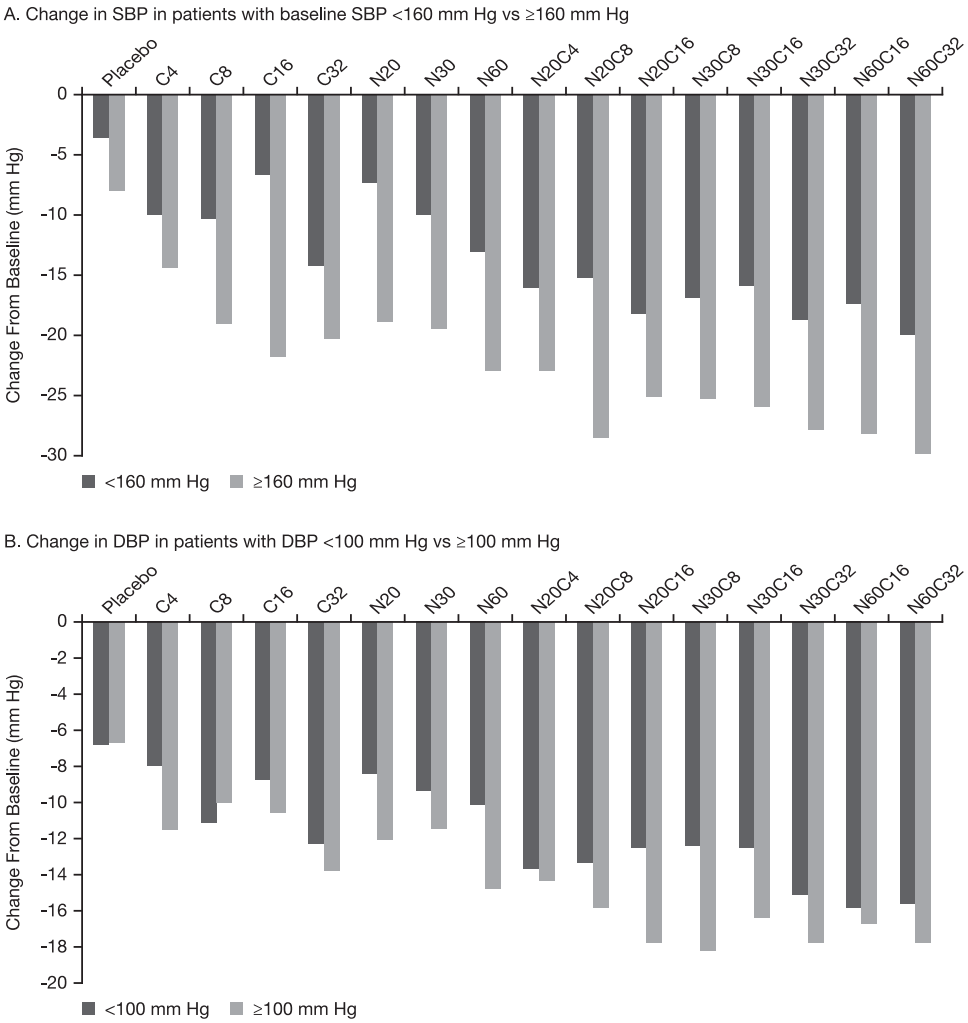

Figure 2. Mean change in SBP and DBP according to baseline SBP and DBP subgroup. C, candesartan; DBP, diastolic blood pressure; N, nifedipine GITS; SBP, systolic blood pressure.

treatment-related vasodilatory events (ie, flushing, headache, or edema) were less frequent in the pooled nifedipine GITS/candesartan combination therapy group (SBP <160 mm Hg, 17.1%; SBP ≥160 mm Hg, 20.5%; DBP <100 mm Hg, 18.5%; DBP ≥100 mm Hg, 18.1%) than in the pooled nifedipine GITS monotherapy group (21.3%; 26.9%; 25.5%; and 21.0%, respectively) (Table 2). These results are consistent with the main study outcomes. Dose-response relationships were not assessed. There was no difference in the incidence of vasodilatory AEs in patients with higher baseline BP (SBP ≥160 mm Hg or DBP ≥100 mm Hg) than in those with lower BP.

Six serious AEs were reported, with low numbers in each subgroup (SBP <160 mm Hg group, n = 2; SBP ≥160 mm Hg group, n = 4; DBP <100 mm Hg group, n = 3; DBP ≥100 mm Hg group, n = 3). A total of 34 patients discontinued treatment because of AEs, again with broadly equal proportions in all subgroups (SBP <160 mm Hg, 2.3%; SBP ≥160 mm Hg, 2.8%; DBP <100 mm Hg, 2.9%; DBP ≥100 mm Hg, 1.9%).

Discussion

This prespecified analysis of the DISTINCT study data provides information on the relationship between baseline BP and the extent of BP reduction after treatment with nifedipine GITS/candesartan combinations or respective monotherapies for 8 weeks. In each SBP and DBP subgroup, nifedipine GITS/candesartan combination therapy provided greater reductions in BP and greater rates of BP control (defined as BP <140/90 mm Hg) than the respective component monotherapies. In addition, a dose-response trend was identified for both BP reduction and BP control.

Results of this subgroup analysis of DISTINCT are consistent with the results from the overall analysis, which showed that all combinations provided

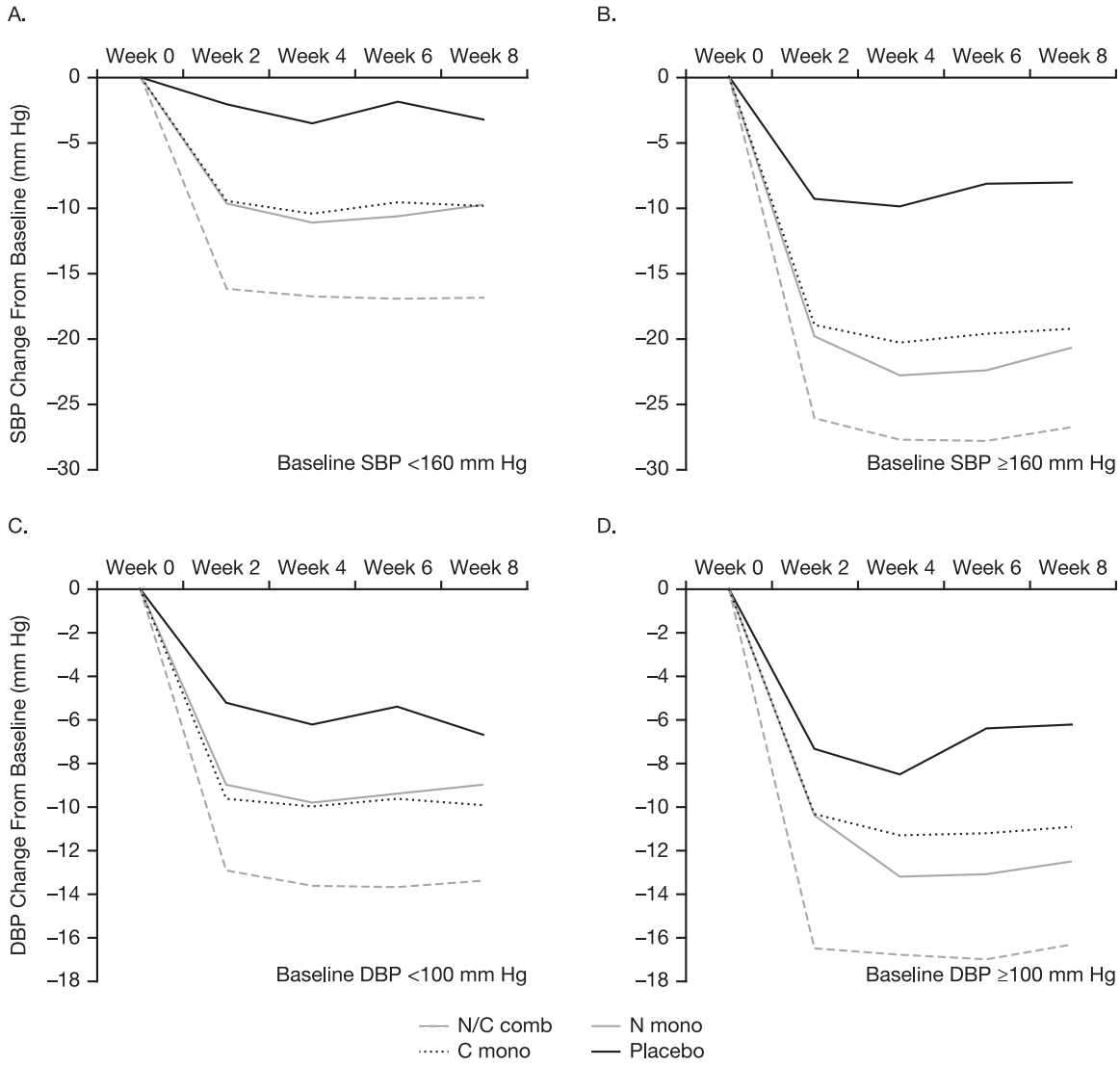

Figure 3. Time course analyses for change in SBP and DBP in pooled treatment groups. (A) Baseline SBP <160 mm Hg. (B) Baseline SBP ≥160 mm Hg. (C) Baseline DBP <100 mm Hg. (D) Baseline DBP ≥100 mm Hg. C, candesartan; DBP, diastolic blood pressure; N, nifedipine GITS; SBP, systolic blood pressure.

statistically better BP reductions from baseline compared with the respective monotherapies.[24] The superior BP reductions of combination therapy were maintained throughout the 8-week study. The results are also consistent with previous studies of combination therapy consisting of a CCB and an ARB.[28–31] Importantly, a greater and earlier effect on BP control via combination therapy has the potential to provide greater CV benefit, as suggested by meta-analysis[2] and by review of major clinical trials with CCB/RAS blocker therapies.[32]

As would be expected, in this analysis absolute BP reductions were generally greater in participants with more severe baseline hypertension, ie, SBP ≥160 mm Hg vs SBP <160 mm Hg and DBP ≥100 mm Hg vs DBP <100 mm Hg. Greater treatment effects in patients with more severe baseline hypertension have also been reported for other CCB/ARB combinations. Subanalysis of data from the COACH study showed that amlodipine/olmesartan combination therapy produced greater SBP reductions in patients with stage 2 hypertension (–25.1 to –32.7 mm Hg) than those with stage 1 hypertension (–17.7 to –23.7 mm Hg) after 8 weeks of treatment.[31] In addition, a large observational study of hypertensive patients in daily practice reported a significant correlation between BP reduction and the BP at baseline among patients receiving a fixed-dose combination of amlodipine and olmesartan, with BP reductions most pronounced in patients with grade 3 hypertension.[33] These results provide support for

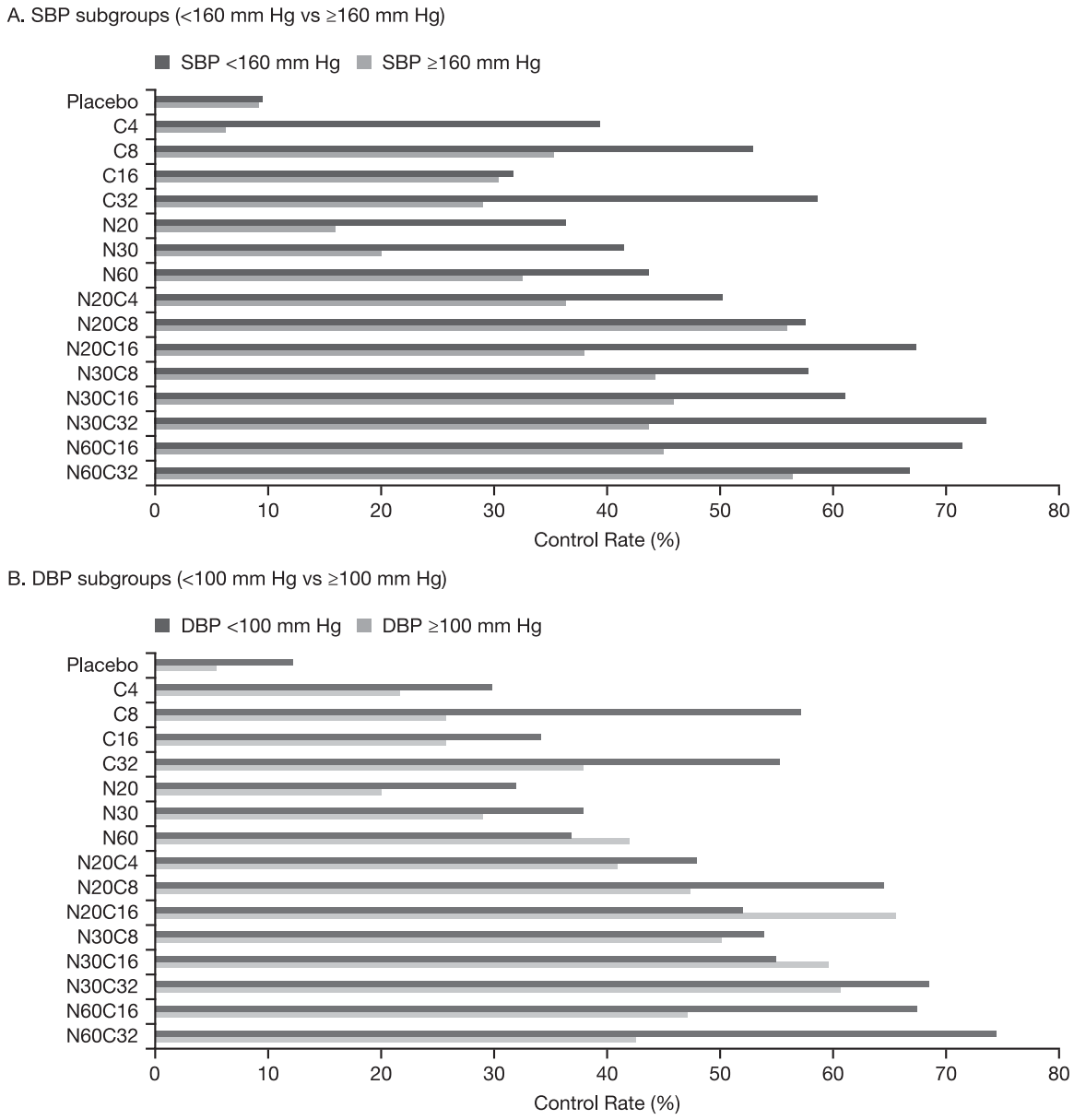

Figure 4. Control rates (BP <140/90 mm Hg) at week 8 according to baseline SBP and DBP subgroups. BP, blood pressure; C, candesartan; DBP, diastolic blood pressure; N, nifedipine GITS; SBP, systolic blood pressure.

initiating treatment with CCB/ARB combination therapy in patients with high baseline BP who need to achieve large BP reductions.

Despite the larger numerical decrease in BP seen in those with higher baseline BP, rates of BP control in this study were generally lower in patients with higher BP at baseline. With combination therapy, rates reached 73.4% for patients with SBP <160 mm Hg compared with 56.4% for those with SBP ≥160 mm Hg. This finding is consistent with large-scale, long-term randomized trials in which treatment of patients with particularly high baseline BP has resulted in relatively low rates of SBP control.[34] In up to 50% of patients in these trials, SBP remained above 140 mm Hg even when patients received multiple antihypertensive therapies from different drug classes, emphasizing that SBP control is difficult to achieve even if DBP has been normalized. However, the current analysis and previous studies[2] suggest that better control rates may be achieved even with low-dose combination therapy than with higher doses of monotherapy.

Overall rates of AEs were similar in all baseline BP groups and were unrelated to dose. Rates of vasodilatory events were lower for nifedipine GITS and candesartan combinations than for nifedipine GITS monotherapy in all baseline BP subgroups, and the

Table 2. Treatment-Emergent Vasodilatory Side Effects According to Baseline SBP and DBP (Safety Population)

		SBP Group		DBP Group	
Adverse Events n (%)		<160 mm Hg (n = 843)	≥160 mm Hg (n = 538)	<100 mm Hg (n = 807)	≥100 mm Hg (n = 574)
Any	Placebo	5/55 (9.1)	5/33 (15.2)	6/51 (11.8)	4/37 (10.8)
Vasodilatory AE	C mono	23/204 (11.3)	18/142 (12.7)	21/207 (10.1)	20/139 (14.4)
	N mono	32/150 (21.3)	28/104 (26.9)	38/149 (25.5)	22/105 (21.0)
	N/C comb	74/434 (17.1)	53/259 (20.5)	74/400 (18.5)	53/293 (18.1)
Flushing	Placebo	0/55 (0.0)	0/33 (0.0)	0/51 (0.0)	0/37 (0.0)
	C mono	0/204 (0.0)	0/142 (0.0)	0/207 (0.0)	0/139 (0.0)
	N mono	1/150 (0.7)	0/104 (0.0)	1/149 (0.7)	0/105 (0.0)
	N/C comb	4/434 (0.9)	2/259 (0.8)	4/400 (1.0)	2/293 (0.7)
Headache	Placebo	4/55 (7.3)	2/33 (6.1)	5/51 (9.8)	1/37 (2.7)
	C mono	9/204 (4.4)	3/142 (2.1)	6/207 (2.9)	6/139 (4.3)
	N mono	20/150 (13.3)	8/104 (7.7)	18/149 (12.1)	10/105 (9.5)
	N/C comb	25/434 (5.8)	13/259 (5.0)	15/400 (3.8)	23/293 (7.8)
Edema	Placebo	1/55 (1.8)	3/33 (9.1)	1/ 51 (2.0)	3/37 (8.1%)
	C mono	15/204 (7.4)	15/142 (10.6)	15/207 (7.2)	15/139 (10.8)
	N mono	16/150 (10.7)	20/104 (19.2)	23/149 (15.4)	13/105 (12.4)
	N/C comb	49/434 (11.3)	40/259 (15.4)	58/400 (14.5)	31/293 (10.6)

Abbreviations: AE, adverse event; C, candesartan; DBP, diastolic blood pressure; N, nifedipine GITS; SBP, systolic blood pressure.

incidence of these events was similar across the 4 subgroups. This finding is consistent with other studies of CCB/RAS blocker combination therapies, which show that RAS blockers predictably attenuate the vasodilatory side effects associated with CCBs through decreasing postcapillary resistance.[20,28,35] As noted by other reviewers, CCB-associated peripheral edema may be more common in clinical practice than is recorded in clinical trials, and these distressing effects are a common reason for lack of compliance with CCB therapy, especially among patients who require high doses to gain BP control.[35,36] Therapy with a combination such as nifedipine GITS/candesartan is therefore likely to be of particular benefit for individuals with high baseline BP, who may be able to achieve significant reductions in BP while avoiding unwanted side effects associated with higher CCB doses. Notably, incidences of adverse events including hypotension, syncope, renal deterioration, and hyperkalemia were not increased by the nifedipine GITS/candesartan combination, as has been reported for dual vs single RAS blockade.[37]

Compliance is likely to be further enhanced by the use of a simplified therapeutic regimen that incorporates a fixed-dose combination of the CCB and RAS blocker.[32,35] Increased compliance through these means is likely to improve antihypertensive efficacy and reduce hypertension-associated morbidity and mortality.

Conclusions

The DISTINCT study previously demonstrated that initial nifedipine GITS/candesartan combination therapy is more effective in lowering BP and meeting target BP goals (SBP <140 and DBP <90 mm Hg) than respective monotherapies at the same doses in participants with hypertension. The current analyses demonstrate that this combination therapy is more beneficial in terms of BP reduction and BP control than the respective monotherapies in all patients investigated in DISTINCT, regardless of their baseline severity of hypertension. Combination therapy also reduced the incidence of vasodilatory side effects, which is particularly important in patients with more severe hypertension who might otherwise receive high-dose monotherapy. This subanalysis supports the use of CCB/ARB combination therapy in preference to respective monotherapies in patients with both mild and moderate hypertension, in whom BP normalization with high drug tolerability would greatly reduce the risk of CV events.

Disclosures

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G.C. and G.V. declare no conflicts of interest.

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