Efficacy and Safety of Dual Calcium Channel Blockade for the Treatment of Hypertension: A Meta-Analysis

Carlos L. Alviar1,6, Santhosh Devarapally2, Girish N. Nadkarni1, Jorge Romero3, Alexandre M. Benjo1,4, Fahad Javed1, Bryan Doherty1, Hyuensok Kang5, Sripal Bangalore6 and Franz H. Messerli1

BACKGROUND
Dual calcium-channel blocker (CCB) with a dihydropyridine (DHP) and a nondihydropyridine (NDHP) has been proposed for hypertension treatment. However, the safety and efficacy of this approach is not well known.

METHODS
A MEDLINE/EMBASE/CENTRAL search for randomized clinical trials published on this topic from 1966 to February 2012 was performed. Efficacy outcomes of decrease in systolic (SBP) and diastolic (DBP) blood pressures from baseline, changes in heart rate (HR), and adverse effects were compared between dual CCB therapy vs. DHP or NDHP. SBP, DBP, and HR were expressed as weighted mean deviation (WMD).

RESULTS
A total of 6 studies with 153 patients were included. Dual CCB produced a significantly greater reduction in SBP (21.6 ± 9.2 mmHg) from baseline than DHP (10.3 ± 6.3 mmHg (WMD = 10.9 mmHg, P < 0.0001)) or NDHP (8.9 ± 4.2 mmHg (WMD = 14.1 mmHg, P = 0.002)). Dual CCB therapy reduced DBP from baseline more than either monotherapy (dual CCB = 17.5 ± 10.2 mmHg vs. DHP = 11.6 ± 8.7 mmHg, WMD = 5.5 mmHg, P < 0.001; and NDHP = 10.5 ± 5.6 mmHg, WMD = 5.3 mmHg, P = 0.03). Dual CCB therapy had significantly lower HR compared to DHP (P < 0.001) but was comparable to NDHP (P = 0.12) (Delta change dual CCB = –4.0 ± 3.5 vs. DHP = –2.0 ± 1.5 and NDHP = –6.0 ± 5.0 beats/min). Dual CCB therapy did not increase adverse effects.

CONCLUSIONS
Dual CCB therapy lowers blood pressure significantly better than CCB monotherapy, without an increase in adverse events. However, given the lack of long-term outcome data on efficacy and safety, dual CCB therapy should be used with restraint, if at all. Large-scale long-term trials are needed to further evaluate such a strategy.

Keywords: blood pressure; calcium channel blockers; combination; dihydropyridine; dual therapy; hypertension; nondihydropyridine.

doi:10.1093/ajh/hps009

Combinations of 2 or more different pharmacological agents are increasingly used in the treatment of stage 2 hypertension.1 There is strong evidence to suggest that combination therapy is more efficacious than monotherapy up titration. The antihypertensive effect has been reported to be up to 5 times greater with combination of 2 drugs from different classes when compared with doubling the dose of 1 pharmacological agent.2 Although most of the data on combination therapy are on 2 drugs of different classes, same-class drug combinations, such as dual calcium-channel blockers (CCBs) (dihydropyridines (DHPs) and nondihydropyridines (NDHPs)) have also been proposed as a treatment option for patients with hypertension, especially in resistant hypertension and/or when blockers of the renin angiotensin system are not tolerated.3-5 CCBs are as effective as diuretics, β-blockers, or angiotensin-converting enzyme inhibitors for blood pressure (BP) reduction with no adverse metabolic effects (glucose/lipid profile), and have well documented benefits for stroke prevention, cardiovascular mortality, and angina control.6 The American Heart Association consensus group for resistant hypertension,8 the American Kidney society,5,7 and others have alluded in their guidelines to the use of same-drug combinations, such as CCB dual therapy with DHP and NDHP, as an appropriate therapeutic option to achieve blood pressure goals.3-5,8,10 However, the data on efficacy and safety of this approach is scant. Our objective was to test the efficacy and safety of dual CCB therapy when compared with either monotherapy in patients with hypertension.

METHODS
A comprehensive search was performed to identify randomized clinical trials in MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE in...
any language between 1966 and February 2012, using the search terms dihydropyridines, nondihydropyridines, calcium channel blockers, dual therapy, combination therapy, and using the names of individual medications. Data were searched through cross-references and experts were questioned, bibliographies of retrieved articles were searched for relevant studies, and major scientific meetings, including but not limited to the American Heart Association, American College of Cardiology, American Society of Hypertension, National Kidney Foundation and European Society of Cardiology, were monitored for the results of trials that were still ongoing at the time of the MEDLINE and COCHRANE CENTRAL search. Similarly, scientific media websites and online resources for clinicians and researchers were also monitored for publications on this topic.

Study selection

Two investigators (J. R. and C. A.) independently evaluated and selected the studies for the analysis. Any disagreements were resolved by discussion and consensus. Inclusion criteria were as follows: (i) prospective, randomized clinical trials; (ii) assignment of participants to either dual therapy, DHP monotherapy group, or NDHP monotherapy group, comparing blood pressure reduction from baseline; (iii) use of equivalent dosages in all 3 groups (if maximum dosages were used in 1 group, they must have also been used in the other 2 groups); (iv) available data on change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (efficacy); and (v) follow-up time of at least 1 week.

Outcome measures

The efficacy outcome was the change in SBP and DBP from baseline between the study groups, comparing dual CCB therapy with monotherapy (DHP or NDHP). Safety outcomes included the risk of adverse effects, including edema, headache, constipation, and flushing between the comparator groups. In addition, we also analyzed the effect of dual CCB therapy on heart rate (HR) compared with monotherapy with DHP and NDHP given the theoretical concerns of bradycardia and heart block in patients with CCB therapy.11

Statistical analysis

Efficacy outcomes were assessed by estimating the weighted mean deviation (WMD) of SBP and DBP. This was calculated from the change in SBP and DBP from baseline with dual therapy compared with the change with DHP or NDHP monotherapy, by using the before and after means as well as standard deviations. We chose to use WMD as compared to the standardized mean difference because the WMD is an average that takes in account the weight of some studies in the final analysis compared to others. This is of particular importance when the results of some studies make a greater contribution to the final totalized results than others. The studies that are more precise, and thus have narrower confidence intervals, are given more weight. We chose to use the WMD because it is the preferred methodology used when combining or comparing data for continuous outcomes measured on the same scale. Safety outcomes were evaluated by comparing the rates of adverse effects between groups, and were expressed as relative risk (RR). In addition, for heart rate comparison, we used WMD. As patient characteristics, medication dosages, and length of follow-up differed across studies, the RR for each study was assumed to have a random offset from the population mean RR (i.e., a random-effects model). The primary result was presented as the Mantel–Haenszel pooled RR and 95% confidence interval (CI), calculated from the random effects model. The I² statistic was calculated to assess the degree of heterogeneity among the trials, and we considered a value of ≤25% to indicate a low degree of heterogeneity. Therefore, although the studies had different characteristics, pooling estimates of the RRs and WMDs were judged to be reasonable. Sensitivity analyses were conducted to further explore the robustness of the results. This was done to identify any study that may have exerted a disproportionate influence on the summary treatment effect by deleting 1 study at a time and repeating the analyses. Results obtained with a fixed effects model were also compared with those obtained with a random-effects model. Funnel plots of the effect size vs. the standard error of the log-transformed effect were generated for each outcome in the safety analysis to assess for publication bias. All statistical analysis and calculations were performed using Stata IC version 10 (StataCorp, College Station, TX).

RESULTS

Studies characteristics

A total of 29 potentially eligible trials were identified, from which 6 trials satisfied the inclusion criteria and were included in this analysis (Figure 1). The trial by Bory et al. was excluded, as the doses used in the combination group were lower for both DHP and NDHP when compared with the monotherapy group.12 Another 2 clinical trials were excluded, as they were designed for the evaluation of the acute effects of dual CCB therapy vs. DHP and NDHP monotherapy in settings not associated with the treatment of hypertension, including coronary artery spasm provoked by exercise and intraoperative-induced hypotension in nonhypertensive patients.13,14 Additionally, 2 other trials were excluded from the analysis, as they did not report data on final achieved DBP and SBP.15,16 However, the findings from these 2 trials were included in the safety analysis, as both of these studies provided data on adverse effects. Finally, the 1 other trial was excluded due to lack of comparison with either DHP monotherapy or with baseline blood pressure.17

Table 1 summarizes the trials included in this analysis. The 6 trials included a total of 153 patients.18–23 The mean age from all studies was 55.5 ± 4.9 years, with 78% men. In terms of benzothiazepines, 2 studies combined diltiazem with nifedipine, 1 with nitrendipine, and 1 with felodipine. For the phenylalkylamine family, 1 study combined verapamil with lacidipine, 1 with nitrendipine, and 1 with nifedipine. The type of formulation for each agent (short acting vs. long acting) is described in Table 1. The duration of treatment ranged from 1 to 18 weeks with a mean of 4.9 ± 5.3 weeks.
Effect on systolic blood pressure

The mean change in SBP from baseline with dual CCB therapy was 21.6 ± 9.2 mmHg, while that with DHP was 10.3 ± 6.3 mmHg, and 8.9 ± 4.2 mmHg with NDHP monotherapy. This translated into an additional SBP reduction of 10.9 mmHg more with dual CCB than the reduction with a DHP alone (P < 0.01) (Figure 2A) or by 14 mmHg more than the reduction with a NDHP alone (WMD = 14.1, P = 0.002) (Figure 2B). There was, however, significant heterogeneity for both analyses (I² = 85.7% and 75.5%, respectively).

Effect on diastolic blood pressure

The mean change in DBP from baseline with Dual CCB therapy was 17.5 ± 10.2 mmHg, while that with DHP monotherapy was 11.6 ± 8.7 mmHg and 10.5 ± 5.6 mmHg with NDHP. This translated into an additional DBP reduction of 5.5 mmHg more with dual CCB than with a DHP alone (P < 0.001) (Figure 3A) or by 5.3 mmHg more than with a NDHP alone (P = 0.03) (Figure 3B). There was, however, modest to significant heterogeneity for both analyses (43.6% and 89.8%, respectively).

Dual therapy and adverse effects

Information about patients lost at follow-up is described in Table 2. There were 3 trials reporting the effect of dual therapy on heart rate. The mean change from baseline was ~4.0 ± 3.5, 2.0 ± 1.5, and -6.0 ± 5 beats/min with CCB dual therapy, DHP, and NDHP, respectively. Thus, we found that dual therapy additionally reduced HR by 6 beats/min more than with DHP alone (P < 0.001). Conversely, when compared with NDHP, dual therapy reduced HR by 4 beats/min less than DHP, but this difference was not statistically significant (P = 0.115) (Figure 4). There was no significant increase in edema, headache, or flushing rates with the use of dual CCB therapy when compared with either monotherapy (Table 3). However, the incidence of constipation was lower in the dual CCB group when compared to NDHP (RR = 0.35 (0.14–0.83); P = 0.01).
Table 1. Studies characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Sample Size</th>
<th>Agents Used</th>
<th>Dual Therapy Daily Dose</th>
<th>Monotherapy Daily Dose</th>
<th>Mean Age</th>
<th>Men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrevey N(^{18})</td>
<td>1999</td>
<td>48 (48 at baseline, 24 in each monotherapy group, 16 in dual therapy group)</td>
<td>diltiazem (short acting) and nifedipine (short acting)</td>
<td>diltiazem 120mg/d, Nitrendipine 20mg/d</td>
<td>Diltiazem 60–120mg, Nitrendipine 10–60mg</td>
<td>52 (SD not provided)</td>
<td>79.2</td>
</tr>
<tr>
<td>Comerio G(^{19})</td>
<td>1993</td>
<td>13 (13 at baseline, 13 in monotherapy, 13 in dual therapy)</td>
<td>verapamil (long acting) and lacidipine (no data about long vs. short acting)</td>
<td>verapamil 240mg lacidipine 4 mg</td>
<td>verapamil 240mg lacidipine 4 mg</td>
<td>47 ± 9</td>
<td>62</td>
</tr>
<tr>
<td>Frishman WH(^{20})</td>
<td>1988</td>
<td>24 (24 at baseline, 24 in monotherapy, 24 in dual therapy)</td>
<td>diltiazem (short acting) and nifedipine (short acting)</td>
<td>diltiazem 360mg/d, nifedipine 120mg/d</td>
<td>diltiazem 360mg/d, nifedipine 120mg/d</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nalbantgil I(^{21})</td>
<td>1993</td>
<td>40 (40 at baseline, 20 in each monotherapy group, 40 in dual therapy group)</td>
<td>verapamil (long acting) and nifedipine (short acting)</td>
<td>verapamil 120mg nitrendipine 10mg</td>
<td>verapamil 120mg nitrendipine 10mg</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pucci PD(^{22})</td>
<td>1991</td>
<td>12 (12 at baseline, 12 in each monotherapy, 12 in dual therapy)</td>
<td>diltiazem and felodipine (no data about long vs. short acting)</td>
<td>diltiazem 60mg felodipine 10mg</td>
<td>diltiazem 60mg felodipine 10mg</td>
<td>56.6 ± 8</td>
<td>92</td>
</tr>
<tr>
<td>Saseen J(^{23})</td>
<td>1996</td>
<td>16 (16 in each phase: baseline, monotherapy, and dual therapy)</td>
<td>diltiazem and nifedipine (long acting), verapamil (long acting) and nifedipine (long acting)</td>
<td>verapamil 180mg or diltiazem 180mg + nifedipine 30mg</td>
<td>verapamil 180mg or diltiazem 180mg nifedipine 30mg</td>
<td>48 ± 8.8</td>
<td>75</td>
</tr>
</tbody>
</table>

Abbreviations: N/A, not available; SD, standard deviation.

DISCUSSION

In the present study, we have attempted to analyzed efficacy and safety of dual CCB therapy for the treatment of hypertension by compiling the available evidence in a form of a meta-analysis. We found that dual CCB therapy significantly decreases both systolic and diastolic blood pressures when compared to monotherapy with either subclass of CCB. Similarly, dual CCB does not increase the rate of adverse effects when compared with dihydropyridines or nondihydropyridines alone, during short-term follow-up period.

Previously published guidelines have suggested the use of same-drug-class combination therapy with DHP and NDHP with limiting evidence available.\(^{5,7}\) The use of this combination was initially documented by case reports\(^{15,36}\) and by a compilation of small prospective studies with limited data and short follow-up.\(^{27}\) Of note, the American Heart Association statement for resistant hypertension clarifies that "it is premature from a purely blood pressure perspective to recommend the use of same-class combinations over use of agents from different classes."

Conversely, the National Kidney Foundation Hypertension and Diabetes Executive Committee Working Group recommends that outpatients with chronic kidney disease with or without diabetes who present with a BP greater than 150/100 mmHg should be treated with 2 different antihypertensive agents, and included dual CCB therapy among their recommend approach. They specifically stated that "a nondihydropyridine and dihydropyridine calcium antagonist have additive and even synergistic blood pressure–reducing capabilities." According to their therapeutic algorithm they recommend to "add other sub-group of CCB (i.e. amiodipine-like) if verapamil or diltiazem are already being used to a long acting calcium channel blocker." In a similar way, Bakris et al. have proposed this combination as an alternative approach in patients with diabetes and hypertension,\(^{9}\) based on the additive effects on BP reduction reported in a single study.\(^{23}\) Similarly, 2 review articles on this topic have been previously published with analogous conclusions.\(^{10,27}\)

The effects of this dual CCB combination on blood pressure reduction has been proposed to be secondary to both a synergistic effect between 2 different mechanisms of action (e.g., the negative ino/chronotropic effect from the NDHP and a vasodilatory effect from the DHP) and to different pharmacodynamic and pharmacokinetic interactions, that potentiate the antihypertensive effect from each subclass.\(^{23,28-31}\) However, the evidence gathered supporting this combination is weak and based mostly on nonrandomized studies with only few randomized clinical trials exclusively evaluating blood pressure control and adverse effects. No cardiovascular outcome data on dual CCB therapy have been put forward. Also, it is not entirely known if the differences between DHP and NDHP make them complementary, and the additional beneficial effect in blood pressure control might be due to an additive effect more than a true potentiating mechanism that could have been achieved by adding any other medication from a different class. In fact, there is little evidence whether the differences of the 2 subclasses of
CCB are different enough to provide complementary effects. Again, the additional BP effect of the 2 drugs might be simply additive and might have been achieved by increasing the dose of either.

Our study demonstrates that dual CCB therapy significantly decreases SBP and DBP when compared with monotherapy, with an acceptable safety profile during a short-term evaluation. These results correlate with previously published studies. We also evaluated the short-term safety of this combination by comparing the incidence of adverse effects and dropout rates of patients receiving dual therapy versus monotherapy. Unfortunately, the studies had

Figure 2. Effect of CCB dual therapy on the change of SBP from baseline compared with DHPs (A) and NDHPs (B). CCB dual therapy decreased SBP 10.93 mmHg more than DHPs alone and 14.11 mmHg more than NDHP from baseline. Abbreviations: CCB, calcium-channel blocker; CI, confidence interval; DHPs, dihydropyridines; NDHPs, nondihydropyridines; SBP, systolic blood pressure; WMD, weighted mean deviation.
a limited follow-up time, with the longest being 20 weeks, and neither morbidity nor mortality data were available in any study. However, we found that dual CCB therapy was not associated with an increased incidence of adverse effects in either group. To the contrary, there was a reduction in constipation with dual CCB therapy compared with monotherapy. Conceivably, this decrease in constipation rates may have occurred due to an idiosyncratic effect in calcium homeostasis related to an improved vascular selectivity of the calcium channel blockade in the combination group.32,33

The potential advantages of dual CCB therapy over other combination therapies such as using a renin-angiotensin system antagonist and a CCB or diuretic could be justified by a potentially safer adverse effect profile. For instance, CCBs are usually not associated with electrolyte abnormalities (as is the case for diuretics), and they are not associated with angioedema or hyperkalemia. However, despite the logical approach of combining drugs from different pharmacological groups in order to reduce the risk of adverse events, in the case of dual CCB, this concept might not be applied in the same way than in other combination therapies. This relies on the fact that DHP and NDHP could be considered of different classes if they are compared only by their chemical structure (benzothiazepines and phenylalkylamines). Nonetheless, they might as well be classified as being from the same pharmacological group, as both DHP and NDHP

Figure 3. Effect of CCB dual therapy on the change of DBP from baseline compared with DHPs (A) and NDHPs (B). CCB dual therapy decreased DBP 5.52 mmHg more than DHPs alone and 5.28 mmHg more than NDHPs from baseline. Abbreviations: CCB, calcium-channel blocker; CI, confidence interval; DBP, diastolic blood pressure; DHPs, dihydropyridines; NDHPs, nondihydropyridines; WMD, weighted mean deviation.
Table 2. Studies design and quality analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Study Site</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Study Duration</th>
<th>Lost to Follow-Up No (%)</th>
<th>Outcome Assessment</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreyev N</td>
<td>RCT, DB (2 wk baseline, 4 wk monotherapy, 2 wk washout, 4 wk dual therapy)</td>
<td>Latvia</td>
<td>grade 2 essential hypertension</td>
<td>secondary hypertension as evidenced by routine clinical evaluation, CHF, left bundle branch block, and patients receiving digitalis or antiarrhythmic drugs</td>
<td>12 weeks</td>
<td>0 (0.0)</td>
<td>SBP and DBP, HR</td>
<td>3</td>
</tr>
<tr>
<td>Comerio G</td>
<td>RCT, DB (2 wk baseline, 6 wk monotherapy, 6 wk dual therapy)</td>
<td>Italy</td>
<td>after a 2-wk run-in period, patients with DBP 105–119 mmHg</td>
<td>secondary hypertension, heart failure, renal or hepatic insufficiency, atrioventricular block, diabetes mellitus</td>
<td>14 weeks</td>
<td>not provided</td>
<td>casual systolic and diastolic blood pressure taken 5, 7, and 10 min after sitting; 24-h BP monitoring; HR</td>
<td>2</td>
</tr>
<tr>
<td>Frishman WH</td>
<td>RCT, SB, CxOver (2 wk baseline, 3 wk DHP monotherapy, 2 wk washout, 3 wk NDHP monotherapy, 1 wk washout, 3 wk dual therapy)</td>
<td>United States</td>
<td>mild hypertension</td>
<td>MI or cardiac surgery within 3 months, CHF; moderate–severe hypertension; SBP &lt;90 mmHg; LVH by ECG, severe bradycardia (&lt;50 beats/min at rest); atrioventricular block; sick sinus syndrome; significant valvular or congenital heart lesions; need for concomitant therapy with antiarrhythmic agents (including digitals); anemia, diabetes mellitus requiring insulin, renal failure, hepatic failure; asthma, emphysema, peripheral vascular disease; hypersensitivity to calcium-blocking drugs</td>
<td>14 weeks</td>
<td>7 (29.1)</td>
<td>BP and HR determinations were made at same time of day for each patient: 2–5 h after ingestion of medication, when peak blood drug levels usually seen</td>
<td>3</td>
</tr>
<tr>
<td>Nalbantgil I</td>
<td>RCT, DB (2 wk baseline, 6 wk monotherapy, 6 wk dual therapy, 6 wk crossover monotherapy)</td>
<td>Turkey</td>
<td>patients with essential hypertension</td>
<td>secondary hypertension as evidenced by plasma electrolytes, catecholamine excretion, and intravenous pyelography</td>
<td>20 weeks</td>
<td>0 (0.0)</td>
<td>through SBP and DBP, HR</td>
<td>2</td>
</tr>
<tr>
<td>Pucci PD</td>
<td>RCT, DB (1 wk baseline, 1 wk monotherapy, and 1 wk dual therapy)</td>
<td>Italy</td>
<td>stage 1 essential hypertension</td>
<td>unstable angina, MI 3 mo before enrollment, BP &gt;150/100, significant valvular disease</td>
<td>4 weeks</td>
<td>0 (0.0)</td>
<td>SBP and DBP identified with 1st and 5th Korotkoff sounds and measured lying and standing, HR</td>
<td>3</td>
</tr>
<tr>
<td>Saseen J</td>
<td>RCT, DB, CxOver (2 wk baseline, 2 wk monotherapy with DHP, 2 wk dual therapy with dilazem and DHP, 2 wk dual therapy with verapamil and DHP)</td>
<td>United States</td>
<td>patients who passed a qualification phase with no antihypertensive medications and with BP ≤200/115</td>
<td>serious medical conditions (hepatic disease, malnutrition, immunodeficiencies, alcohol abuse, heart failure, unstable angina, conduction abnormalities, CAGB in last 3 mo, smokers and the use of non-antihypertensive medications</td>
<td>8 weeks (2 weeks/group)</td>
<td>0 (0.0)</td>
<td>SBP and DBP, HR checked always at same time of day at 8 timed intervals after dosing, after being supine for 5 min and after standing for 2 min</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CxOver, crossover; DB, double blind; DBP, diastolic blood pressure; DHP, dihydropyridine; ECG, electrocardiogram; HR, heart rate; LVH, left ventricular hypertrophy, MI, myocardial infarction; NDHP, nondihydropyridine; No, number; RCT, randomized clinical trial.
Table 3. Side effects comparison between dual CCB therapy and individual monotherapy with DHPs and NDHPs

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Dual CCB vs. DHP (RR and 95% CI)</th>
<th>No of Studies Included</th>
<th>Dual CCB vs. NDHP (RR and 95% CI)</th>
<th>No of Studies Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>1.11 (0.32–3.91); P = 0.87</td>
<td>3</td>
<td>3.67 (0.68–19.72); P = 0.13</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>0.69 (0.40–1.20); P = 0.19</td>
<td>3</td>
<td>1.70 (0.51–5.67); P = 0.39</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.06 (0.49–8.68); P = 0.33</td>
<td>2</td>
<td>0.35 (0.14–0.83); P = 0.01</td>
<td>2</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.63 (0.26–1.55); P = 0.31</td>
<td>3</td>
<td>3.49 (0.56–21.78); P = 0.18</td>
<td>3</td>
</tr>
</tbody>
</table>

There were no differences between the incidence of side effects, except for constipation that was significantly less common in dual CCB therapy when compared with NDHPs.

Abbreviations: CI, confidence interval; CCB, calcium-channel blocker; DHPs, dihydropyridines; NDHPs, nondihydropyridines; No, number; RR, relative risk.

Figure 4. Effect of CCB dual therapy on HR compared with DHPs (A) and NDHPs (B). Dual CCB therapy was associated with an additional HR reduction of 5 beats/min from baseline when compared with DHPs alone. Dual CCB therapy was associated with a higher HR by 5 beats/min more than observed with NDHPs. Abbreviations: CCB, calcium-channel blocker; CI, confidence interval; DHPs, dihydropyridines; HR, heart rate; NDHPs, nondihydropyridines; WMD, weighted mean deviation.

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share similar intracellular targets, with the only pharmacodynamic difference being their predilection for different tissues. Moreover, in terms of adverse events profiles, CCB could be associated with different side effects in each class (e.g., edema for DHP and bradycardia for NDHP) or share the same adverse events (e.g., constipation for both DHP and NDHP). This makes it even more difficult to justify if they would be associated with an actual safer profile when used in combination. Thus, based on our results, it is difficult to predict if dual CCB therapy really decreases adverse events, and further clinical trials are warranted in order to answer this question.

Similarly, there might be an inherent advantage of using this combination in specific populations, such as black patients or patients with chronic kidney disease. In such subgroups in which other medications might be contraindicated (e.g., angiotensin-converting enzyme inhibitors, aldosterone antagonists, or angiotensin-receptor blockers in patients with hyperkalemia and renal failure), or simply less effective (e.g., thiazide diuretics in patients with decreased glomerular filtration rate or angiotensin-converting enzyme inhibitors in black patients), dual CCB therapy could be contemplated as a therapeutic option. Nonetheless, these advantages are all theoretical and based purely on speculative considerations, and as proven in the present study, there are no studies evaluating long-term efficacy and safety of dual CCB therapy that would delineate a definite advantage of this combination over the others. Moreover, in the current literature, there is not enough data to perform a subgroup analysis in different ethnic groups or in patients with chronic kidney disease, at least for the studies included in our analysis.

Given the theoretical negative chronotropic action of some DHPs, we included HR as an endpoint to assess if the effect of NDHP on atrioventricular nodal conduction was increased, and clinically significant, leading to bradyarrhythmias. Reassuringly, we found that dual therapy had a significantly higher HR when compared to NDHP and a lower HR when compared to DHP. This could be explained by the fact that the atrioventricular nodal–blocking effect exerted by NDHP might be mitigated by the reflex tachycardia from DHP. Our results, therefore, suggest that dual CCB may be superior in terms of HR regulation during the treatment of hypertension compared with either monotherapy. Of note, none of the studies included in this meta-analysis used efonidipine or azelnidipine, which are the 2 DHPs that have been associated with a negative chronotropic effect in vivo. Nonetheless, as both CCB subclasses depress sinus node activity and slow atrioventricular conduction to a lesser or greater extent, our observations could reflect a real potential benefit of dual CCB therapy in patients with this feature.23 Finally, the lack of information from the studies used for this meta-analysis, it was not possible to perform a subgroup analysis in terms of gender, ethnicity, associated medical conditions, hypertension stages, and so forth to assess for the benefit of dual CCB in such populations. For instance, only 1 study from the ones included in this meta-analysis and only 1 study from the ones initially screened but then excluded due to lack of BP data had information about the ethnicity of the patients. In the same way, the effect of dual CCB therapy in patients who are already resistant to 1 of either subclass (DHP or NDHP) cannot be extrapolated from our results, as only 1 study included and reported patients with this feature.23 Finally, the lack of information on dropout rates in the studies analyzed in our manuscript makes it difficult to compare outcomes among the groups.

CONCLUSIONS

Dual CCB therapy significantly decreased BP when compared to monotherapy with either DHP or NDHP, and did
not increase the rate of adverse effects during short-term evaluation. However, given the lack of outcome data, as well as the short follow-up period and the small number of subjects included in the overall analysis, our results should be interpreted with caution, and dual CCB therapy should not be an alternative treatment in patients with resistant hypertension as previously recommended.13,14 Large-scale, prospective randomized clinical trials with appropriate follow-up may be needed to further assess the efficacy and safety of dual CCB therapy on a long-term basis.

ACKNOWLEDGMENTS

We thank Zheng Lin for helping to interpret the 2 Chinese articles and Aleksandr Korniyenko for helping with the Russian translation.

DISCLOSURE

Franz H. Messerli has received speaker’s fees from Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, Sankyo, and Sanofi, and research grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics. All other authors declared no conflicts of interest. None of the authors received any compensation for their work on this manuscript.

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