Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents

A Meta-Analysis

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Abstract—Two or more antihypertensive agents are increasingly used to control blood pressure (BP) in hypertensive patients. However, it is unclear whether fixed-dose combinations (FDCs) of 2 antihypertensive agents in a single tablet provide greater benefits than the corresponding free-drug components given separately. A meta-analysis was performed to assess compliance, persistence, BP control, and safety associated with FDCs in comparison with their free-drug components. Fifteen included studies (n=32331) reported on ≥1 of the evaluated outcomes. In 3 cohort studies and 2 trials reporting on drug compliance (n=17 999), the use of FDCs was associated with significantly better compliance (odds ratio: 1.21 [95% CI: 1.03 to 1.43]; $P=0.02$) compared with its corresponding free-drug combinations. In 3 cohort studies (n=12 653), there was a nonsignificant improvement in persistence with therapy (odds ratio: 1.54 [95% CI: 0.95 to 2.49]; $P=0.08$), and in 5 trials (n=1775) the odds ratio for adverse effects for FDC use compared with free-drug combination use was 0.80 (95% CI: 0.58 to 1.11; $P=0.19$). In 9 trials (n=1671) with BP data, use of an FDC was associated with nonsignificant changes in systolic and diastolic BPs of 4.1 mm Hg (95% CI: −9.8 to 1.5; $P=0.15$) and 3.1 mm Hg (95% CI: −7.1 to 0.9; $P=0.13$), respectively. In these BP-lowering comparisons, there was heterogeneity associated with differences in study design but no publication bias. In conclusion, compared with free-drug combinations, FDCs of antihypertensive agents are associated with a significant improvement in compliance and with nonsignificant beneficial trends in BP and adverse effects. **(*Hypertension*. 2010;55:399-407.)**

Key Words: hypertension ■ antihypertensive agents ■ fixed-dose combination ■ treatment ■ drug combination ■ compliance ■ blood pressure

Raised blood pressure (BP) is currently the biggest single contributor to global mortality,[1] and extensive randomized trial data are consistent in showing that BP reduction substantially reduces cardiovascular morbidity and mortality.[2] However, despite these facts and the widespread availability of effective antihypertensive medications, the vast majority of >1 billion hypertensive patients worldwide remain with uncontrolled BP.[3] Even among hypertensive patients who receive treatment, in most countries at least half of them fail to reach currently recommended BP targets.[3]

Recent clinical trials have demonstrated that adequate BP control is possible among the majority of patients if combinations of ≥2 antihypertensive medications are used for treatment.[4–6] Accordingly, recent American and European guidelines now advocate the use of a combination of 2 drugs as an initial therapy for the majority of hypertensive patients to achieve better BP control.[7,8] In addition to the potential benefits attributable to possible synergistic pharmacological and physiological actions, this strategy of using a combination of 2 different drugs classes among drug-naive patients may, if provided in a single pill, also improve patient compliance and adherence.[9,10] On the other hand, there are concerns about increased adverse effects, particularly postural hypertension, among drug-naive patients treated initially with 2 antihypertensive agents.

The increased use of single-pill combinations of 2 antihypertensive agents, commonly called fixed-dose combinations (FDCs), may be a way to achieve better BP control by improving compliance compared with supplying 2 separate antihypertensive agents given separately (free-drug combination). Although numerous studies have been performed comparing FDCs with a single agent,[11] the data comparing FDCs with free-drug combinations of antihypertensive agents are limited.

Herein, we systematically review the current literature to assess compliance, BP control, and safety associated with the use of FDCs of antihypertensive agents compared with the use of free-drug combinations in the treatment of hypertension.

Methods

Selection of Studies

A literature search of PubMed (1966 to February 2008), Web of Science (1970 to April 2008), and the Cochrane Controlled Trial

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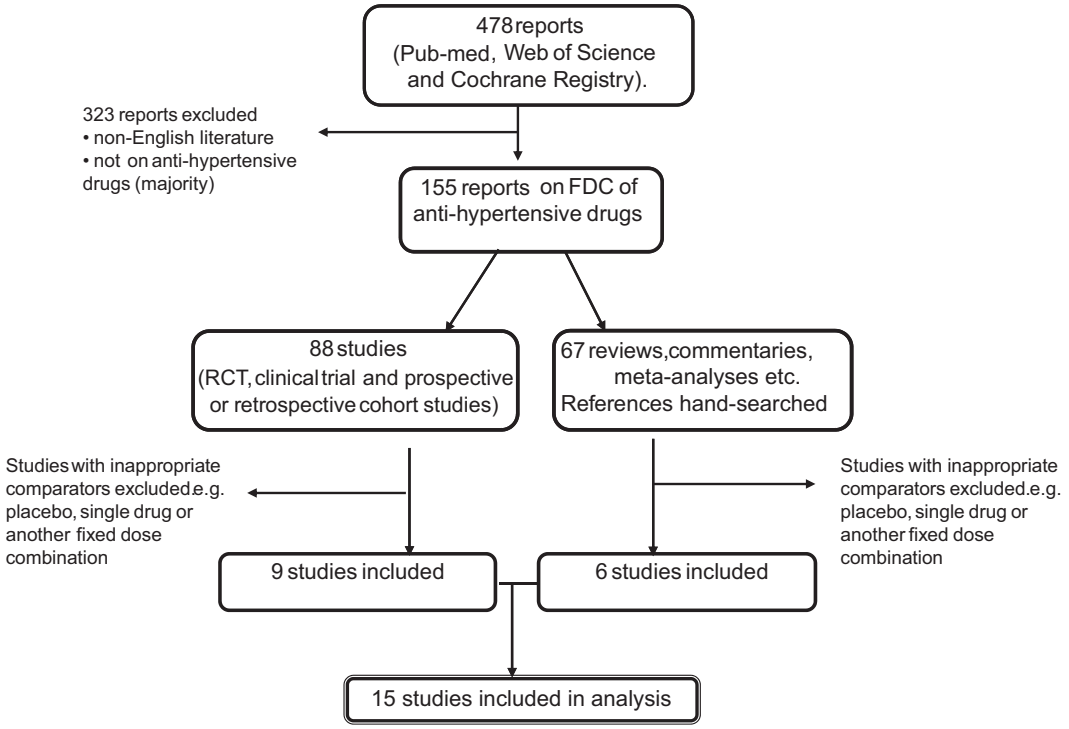

Figure 1. Selection of included studies. AHT indicates antihypertensive; RCT, randomized controlled trials.

Registry (1800 to April 2008) was undertaken to identify relevant studies using key words such as "fixed-dose combinations," "hypertension," "antihypertensive agents," "compliance," "adherence," "persistence," and "adverse effects." Among those identified, clinical trials or cohort studies were included if they were published in English and compared an FDC of antihypertensive agents with a free-drug combination of its components (eg, 1 FDC tablet containing candesartan and hydrochlorothiazide compared with candesartan and hydrochlorothiazide given as 2 separate tablets in equivalent doses) and reported extractable data pertaining to ≥1 outcome of interest: compliance (or adherence), persistence, BP-lowering efficacy, and adverse effects. Additional studies were identified reviewing the back references of included studies and other relevant articles identified during the literature search. All of the studies thus identified were assessed for inclusion using the aforementioned criterion. Authors of some of the identified studies with inadequate information were contacted for numeric values to allow derivation of a summary statistic.

Study Procedure

For all of the included studies, details of study design, definitions of outcome(s), mean ages of studied populations, results either as a percentage of response or absolute values, and limitations of study design were abstracted. In the case of randomized crossover–designed studies, results pertaining to the first phase were abstracted.[12] Compliance was defined using either pill counting or medicine possession ratio on the basis of the number of days of available medication between consecutive prescriptions. However, because both measures are reasonable and similar indicators of compliance (or adherence) to treatment, these measures were combined in analyses. Persistence with therapy was defined on the basis of the gap between the renewal of the prescription (refill gap), for example, a refill gap between 2 prescriptions of <120% of the previous prescription's supply.[13] All 6 of the retrospective cohort studies used similar data on medication use (either using medicine possession ratio or refill gap) to define compliance or persistence with therapy, respectively. Therefore, in keeping with a previous analysis of FDCs in the context of several disease areas,[14] we combined the results for compliance and persistence to improve the precision of our assessment.

Among included studies, only trials reported BP-lowering efficacy as either BP normalization ratios or as BP difference achieved at the end of treatment or both. We combined studies that reported similar BP treatment efficacy outcome measure(s). All of the studies reported patient-specific incidence of adverse effects, that is, the number (or percentage) of patients having adverse effects rather than the total number of adverse effects experienced (event specific); hence, there was no problem in combining the effect size of each of these studies.

Quality assessment of all of the included studies was done using either the Newcastle-Ottawa scale (cohort studies) or the Delphi list (clinical trials), and the studies were accordingly categorized into the following 4 categories: poor, fair, good, and excellent. All stages of the processes involved in this meta-analysis were verified by 2 persons independently to ensure proper adherence to the protocol.

Statistical Analysis

We used reported summary statistics or otherwise derived them manually on the basis of reported results. Appropriate summary statistics included mean BP difference (both systolic and diastolic BPs) from baseline and odds ratios (ORs) and CIs were calculated and tabulated for each of the outcomes studied. All of the analyses were done using Stata 9 software (Stata Corp) using the METAN program. Heterogeneity was examined visually and by using the I-square statistic, and, if needed, the reason(s) for heterogeneity was investigated by meta-regression using variables such as study design, mean age of study population, publication year, and sex. Fixed-effect models were used if there was no evidence of heterogeneity; otherwise, a random-effects model to report the pooled results was used. Publication bias was assessed using funnel graphs and other tests, such as Beggs or Eggers, as appropriate.

Results

Of 478 potential studies identified on the initial literature search, only 15 studies compared FDCs with the same free drug (or class) components and had extractable data on ≥1 of the outcomes analyzed (Figure 1).

Characteristics of Studies

Characteristics of the included studies are summarized in the Table. Nine of the 15 studies were clinical trials,[15–23] and 6 were retrospective cohort studies.[9,13,24–26] One trial used a randomized parallel design, and 8 clinical trials, 4 of which were randomized, used a crossover design. One of the retrospective cohort studies by Dezii[24] included a comparison of 2 distinct FDCs and their free-drug combinations, and, hence, the results of the 2 comparisons are reported and analyzed separately. On quality assessment, the study methodology of all of the included cohort studies was categorized as good or better; however, only 3 trials were categorized as having a good study design and process, with others being categorized as fair.

Patient Characteristics

A total of 32 331 hypertensive patients, including those on an FDC (n=20 267) and on the corresponding free-drug combination (n=13 242), were evaluated in 15 studies that met the inclusion criterion (some patients were "double counted," because they were included in both limbs of nonrandomized crossover studies). Overall, there was a similar proportion of men and women included in the database, with an age range of 18 to 79 years. The duration of follow-up varied from a few months to 5 years (Table).

Compliance and Persistence With Therapy

Three cohort studies[9,25,26] (n=17 642) and 2 trials[18,20] (n=357) reported data on compliance among 17 999 hypertensive patients (Figure 2).

In the cohort studies, the use of an FDC was associated with a 21% increase in compliance with medications as compared with the use of the free-drug combination (OR: 1.21 [95% CI: 1.00 to 1.47]). These results were similar to those obtained from the 2 trials (Figure 2A). Combining the results of all 5 of the studies, compliance with medication was significantly greater with the use of an FDC compared with a free-drug combination (OR: 1.21 [95% CI: 1.03 to 1.43]). There was no heterogeneity among these analyses.

Three other cohort studies[13,24] reported data on persistence with therapy among 12 653 patients (Figure 2B). The use of FDCs as compared with the use of the free-drug combination was associated with more than a 50% increase in persistence with therapy, but this difference was not statistically significant (OR: 1.54 [95% CI: 0.95 to 2.49]).

Analysis of the results of all 6 of the retrospective studies[9,13,24–26] including data on 30 295 patients showed that the use of an FDC as compared with the free-drug combination was associated with a 29% significant increase in compliance and persistence with therapy (OR: 1.29 [95% CI: 1.11 to 1.50]) (Figure 2C). No sign of heterogeneity or publication bias (Begg test $P=0.091$) was apparent in this analysis.

BP-Lowering Efficacy

Nine trials reported BP-lowering efficacy outcomes among 1671 antihypertensive patients. Of these, 3 also reported on normalization of systolic and diastolic BPs.

Assessment of the mean change in BP among 1671 hypertensive patients in 9 trials revealed a nonsignificant reduction of 4.1 mm Hg (95% CI: −9.8 to 1.5 mm Hg; $P=0.15$) in systolic and 3.1 mm Hg (95% CI: −7.1 to 0.9 mm Hg; $P=0.13$) in diastolic BP, associated with the use of an FDC as compared with its free-drug combination (Figure 3A and 3B). There was strong evidence of heterogeneity in both systolic and diastolic BP analyses but no evidence of publication bias in any of these analyses. On meta-regression, the type of study design including randomization status was found to be a significant determinant of heterogeneity ($P=0.05$).

Analysis of the results of the 3 studies[17,18,23] reporting on BP normalization show that the use of an FDC as compared with the equivalent free-drug combination is associated with a 30% increase in achieving BP control, although this difference failed to reach statistical significance (OR: 1.30 [95% CI: 0.98 to 1.71]; $P=0.07$; Figure 3C).

Adverse Effects

Adverse effects were reported in 5 trials including a total of 1775 hypertensive patients.[15,18,19,22,23] All except 1 reported a decreased incidence of adverse effects with FDCs compared with the corresponding free-drug combination. Meta-analysis of the results of these studies showed a 20% nonsignificant decrease in adverse effects associated with the use of an FDC as compared with the free-drug combination (OR: 0.80 [95% CI: 0.58 to 1.11]; Figure 4). There was no evidence of heterogeneity or publication bias (Beggs test $P=0.24$) in these analyses.

Discussion

This review evaluated whether the use of an FDC of 2 antihypertensive agents has additional benefits in terms of drug compliance, persistence, and BP lowering over the free-drug combination of its components when given separately. This question is particularly important because most hypertensive patients require ≥2 agents to achieve BP control, and recent data reveal that, in England, for example, most patients on treatment for hypertension are on ≥2 drugs.[27] Our analyses on the basis of cohort studies and trials show that the use of FDCs of antihypertensive agents was associated with a substantial and significant improvement in compliance and persistence with therapy among hypertensive patients. In addition, on the basis of trial data only, our review indicates that the use of FDCs was associated with a nonsignificant trend toward a reduction in BP levels and in reported adverse effects. These findings together are potentially of great clinical importance because if the levels of BP reduction observed are real, then the use of FDCs instead of free agents among treated hypertensive patients can reasonably be expected to result in a significant and important reduction in cardiovascular outcomes.[2] Whether the apparent improvements in BP levels and control (albeit insignificant) associated with the use of FDCs observed in our analyses are a consequence of improved compliance and/or persistence with therapy is difficult to confirm. However, significant improvement in BP control associated with improved compliance and adherence with therapy has been noted previously.[28] Furthermore, whether the apparently beneficial effects on BP levels would translate into a reduction in cardiovascular outcomes is not certain. However, given the compelling trial evidence for

Table. Characteristics of Included Studies

Included Studies	Study Design	FDC, Doses If Known	Free-Drug Combination, Doses If Known	No. of FDC/Free-Drug Combinations (Total)*
Bengtsson et al[16]	Trial CO‡	Oxprenolol 80 mg/chlorthalidone 10 mg	Diuretic and β-blocker	28/28 (34)
Ebbutt and Elsdon-Dew[17]	Trial CO‡ MC§	Oxprenolol 160.00 mg/ cyclopenthiazide 0.25 mg	Oxprenolol and cyclopenthiazide	30/30 (47)
Solomon and Dawes[21]	Trial CO‡ R‖DB¶	Bendrofluazide 2.5 mg/ propranolol 80.0 mg	Bendrofluazide 2.5 mg and propranolol 80.0 mg	14/14 (20)
Forrest[15]	Trial CO‡	Oxprenolol hydrochloride 160.00 mg/ cyclopenthiazide 0.25 mg	Diuretic plus β-blocker	1050/1050 (1117)
Nissinen and Tuomilehto[19]	Trial CO‡ R‖DB¶	Atenolol 100 mg/chlorthalidone 25 mg	Atenolol 100 mg and chlorthalidone 25 mg	23/23 (23)
Asplund et al[20]	Trial CO† R‖ MC§	Pindolol 10 mg/clopamide 5 mg	Pindolol 10 mg and clopamide 5 mg	80/80 (160)
Olvera et al[22]	Trial CO‡ R‖	Lisinopril 20.0 mg/thiazide 12.5 mg	Lisinopril 20.0 mg and thiazide 12.5 mg	14/14 (29)
Dezii[24]	Ret Cohort	Lisinopril/HCTZ	Lisinopril and diuretic	1644/624 (2268)
Dezii[24]	Ret Cohort	Enalapril maleate/HCTZ	Enalapril maleate and diuretic	969/705 (1674)
Taylor and Shoheiber[25]	Ret Cohort	Amlodipine besylate/benazepril HCl	DHP CCB and ACEi	2754/2978 (5732)
Gerbino and Shoheiber[9]	Ret Cohort	Amlodipine besylate/benazepril HCl	DHP CCB and ACEi	2839/3367 (6206)
Mancia and Omboni[23]	Trial R‖MC§	Candesartan cilexetil 16.0 mg/ HCTZ 12.5 mg	Previous medication and HCTZ 12.5 mg	195/203 (409)
Jackson et al[13]**	Ret Cohort	Valsartan/HCTZ	Valsartan and HCTZ	8150/561 (8711)
Schweizer et al[18]	Trial CO‡ MC§	Valsartan 160 mg/HCTZ 25 mg	Candesartan 32 mg and HCTZ 25 mg	138/197 (197)
Dickson and Plauschinat[26]	Ret Cohort	Amlodipine besylate/benazepril HCl	DHP CCB and ACEi	2336/3368 (5704)

Ret indicates retrospective; SD, study design; CCB, calcium channel blocker; ACEi, angiotensin-converting enzyme inhibitor; HCTZ, hydrochlorothiazide; SBP, systolic BP; DBP, diastolic BP; DHP, dihydropyridine; AE, adverse effect.

*Total numbers "n" is for all of those patients randomized/included in the study, whereas numbers as reported in study (excluding the dropouts) are used for FDC and free-drug combination.

†Quality of study design (poor, fair, good, and excellent) were categorized based on quality assessment scores.

‡Data show a crossover (CO) design.

§Data were multicenter (MC).

‖Data were randomized (R).

¶Data were double blinded (DB).

#MPR indicates the medication possession ratio.

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the cardiovascular benefits of BP lowering[2] and the observational data that show improved health outcomes associated with better adherence and compliance with medication,[29,30] this possibility seems like a reasonable expectation.[31,32] However, these potential BP and cardiovascular benefits need cautious interpretation, because, importantly, the effects on BP levels, BP normalization rates, and adverse effects did not reach statistical significance in this meta-analysis. Although this may reflect type II errors (given the small, often poor-quality database involved), the potential importance of these results reinforces the critical need for more and better quality data.

The heterogeneity noted in BP-lowering analyses was in part associated with, among other things, study design; for example, the only randomized trial[23] that reported a large significant BP difference associated with the use of an FDC was conducted recently and was the only parallel-designed trial; the other 4 randomized trials were crossover-designed studies and were conducted more than a decade ago.

Our finding of a 29% significant increase in compliance or persistence with therapy associated with the use of FDCs for hypertension is similar to the results of a recent meta-analysis of the use of FDC medications for various chronic diseases, such as diabetes mellitus, hypertension, and HIV.[14] We

Table. Continued

Duration of Follow-Up	Men, %	Mean Age (Range)	Outcomes Assessed, Definitions and Quality of Study Design (SD)†
16 k	53.6	56.3 (33.0 to 79.0)	Change in BP; fair-quality SD†
12 mo	36.7	59	BP control <160/95 mm Hg; fair-quality SD†
14 wk	50	44 (28 to 63)	Change in BP; AE; compliance (pill count); good-quality SD†
8 wk	34.7	56.5	Change in BP; AE; fair-quality SD
16 wk	65.2	47.9 (31.0 to 62.0)	Change in BP; AE; good-quality SD
8 mo	61.2	51	Change in BP; compliance (pill count); AEs; fair-quality SD
14 wk	Male and female	(30 to 70)	Change in BP; AEs; fair-quality SD
1 y	. . .	. . .	Persistence (renewed prescription within ×3 the No. of days supplied by previous prescription); good-quality SD
1 y	. . .	. . .	Persistence (renewed prescription within ×3 the No. of days supplied by previous prescription); good-quality SD
2 y	50	53 (18 to 64)	Compliance (MPR%#: total days' supply of drugs/length of follow-up); good-quality SD
1 y	. . .	. . .	Adherence (MPR%#: total days supply of drugs/total No. of days from first to last prescription refill date); excellent-quality SD
12 wk	64	55.5 (26.0 to 79.0)	Change in BP; BP normalization (DBP <90 mm Hg and/or SBP <140 mm Hg); good-quality SD
1 y	. . .	(>18)	Persistence (refill gap <120% of previous prescription day's supply); good-quality SD
6 mo	47.6	58.15 (22.0–79.0)	Changes in BP; AEs; compliance (intake >80% of prescribed doses); fair-quality SD
5 y	17.4	76	Compliance (MPR#); good-quality SD

extended the scope of these previous analyses by assessing compliance and persistence separately. Our separate results for compliance (21% improvement: $P=0.02$) and persistence (54% improvement: $P=0.07$) with FDCs of antihypertensive medications are in keeping with the findings of other less-specific reviews.[14,28]

The 20% reduction in adverse events associated with the use of an FDC reported in our review is perhaps surprising but is consistent with studies published previously[33,34] and a meta-analysis[11] of 82 studies comparing FDCs of 2 antihypertensive agents with various first-line antihypertensive agents as monotherapy. This earlier meta-analysis[11] showed that the use of FDCs had a comparable or even better safety profile than single agents. In another meta-analysis, the adverse effects associated with the use of combinations of 2 drugs were reported to be less than those associated with the additive effects of the 2 drugs given independently.[35]

A real and important limitation of our meta-analysis is the suboptimal quality of the design and conduct of the studies included. Although some of the studies had limited power, others used heterogeneous definitions or unclear and inadequate measurements for the ascertainment of outcomes, such as compliance and BP-lowering efficacy, which in some of the trials were reported on a per-protocol basis. Although the small number of dropouts in these trials was not big enough to affect the reported results, the possibility of bias remains. Similarly, the BP measurements made in the nonrandomized crossover studies may have been biased, because the patients in these studies were first evaluated on free-drug combinations and, thereafter, shifted to the FDC usually without any intervening washout period. In some of the included studies, free-drug combinations were described in terms of drug classes instead of specific drugs (eg, angiotensin-converting enzyme inhibitor plus a diuretic). However, most of these studies were retrospective cohorts assessing either compliance or persistence with FDC therapy and, thus, their reported results are unlikely to be affected by this lack of detail. Another limitation of our analyses is the lack of adjustment for possible confounders in some of the included observational studies and nonrandomized trials. In addition, none of the included studies adjusted for the presence of comorbidities and concomitant medications, both of which may affect all of the outcomes analyzed in this review.

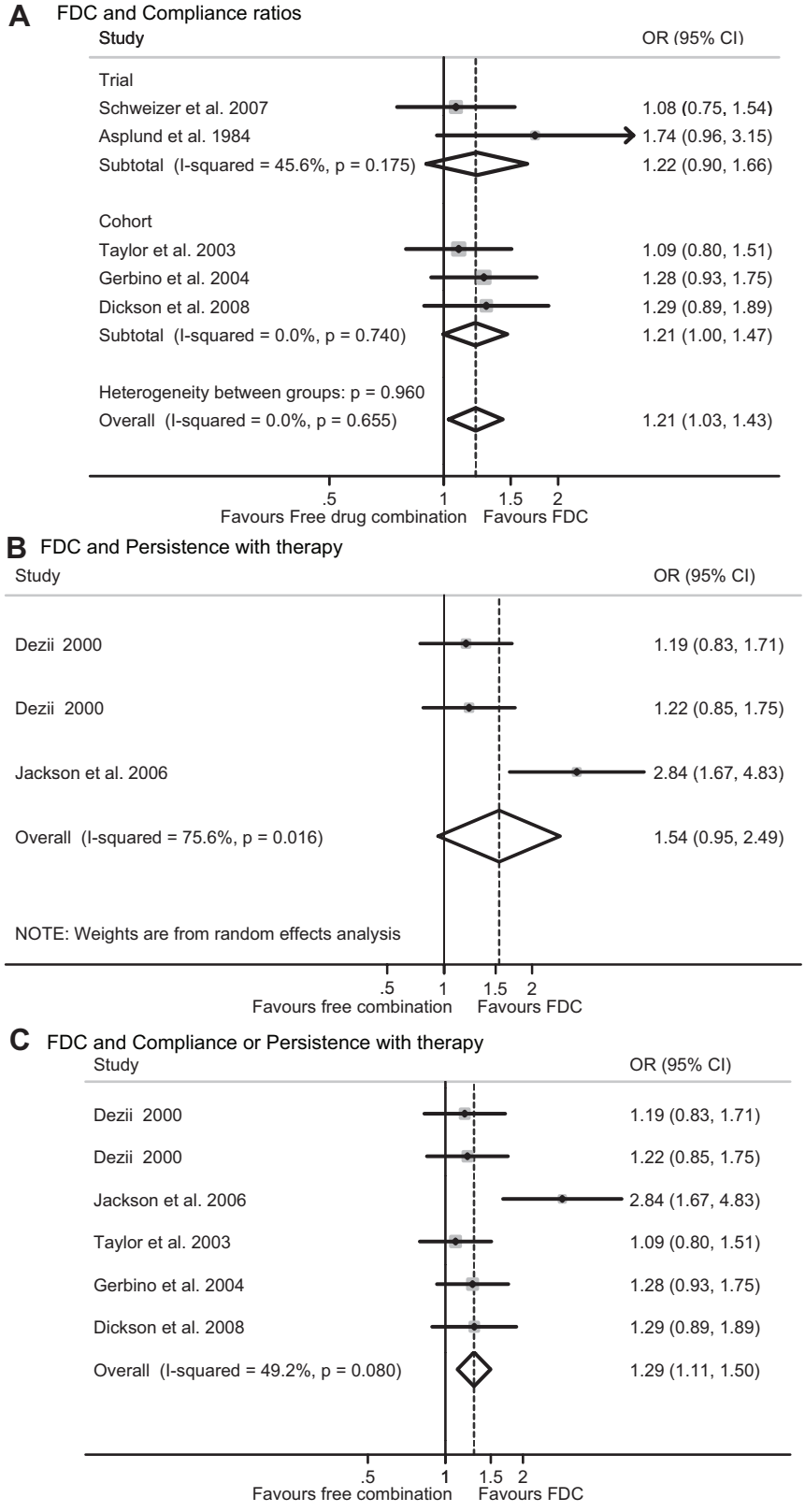

Figure 2. Compliance and persistence with therapy associated with the use of an FDC of 2 antihypertensive agents as compared with its corresponding free-drug combination. Fixed-effect model used where there is no evidence of heterogeneity (A and C).

We have tried to reduce the possibility of publication bias by searching for all of the relevant literature, including what was published only as abstracts or conference proceedings, and by contacting potential sources of relevant unpublished data. We analyzed our results for the possibility of publication bias, but given the limited number of studies available, these analyses cannot completely exclude the presence of some publication bias.

FDCs are commonly and routinely used in gynecology, infectious diseases, oncology, diabetes mellitus, and asthma.

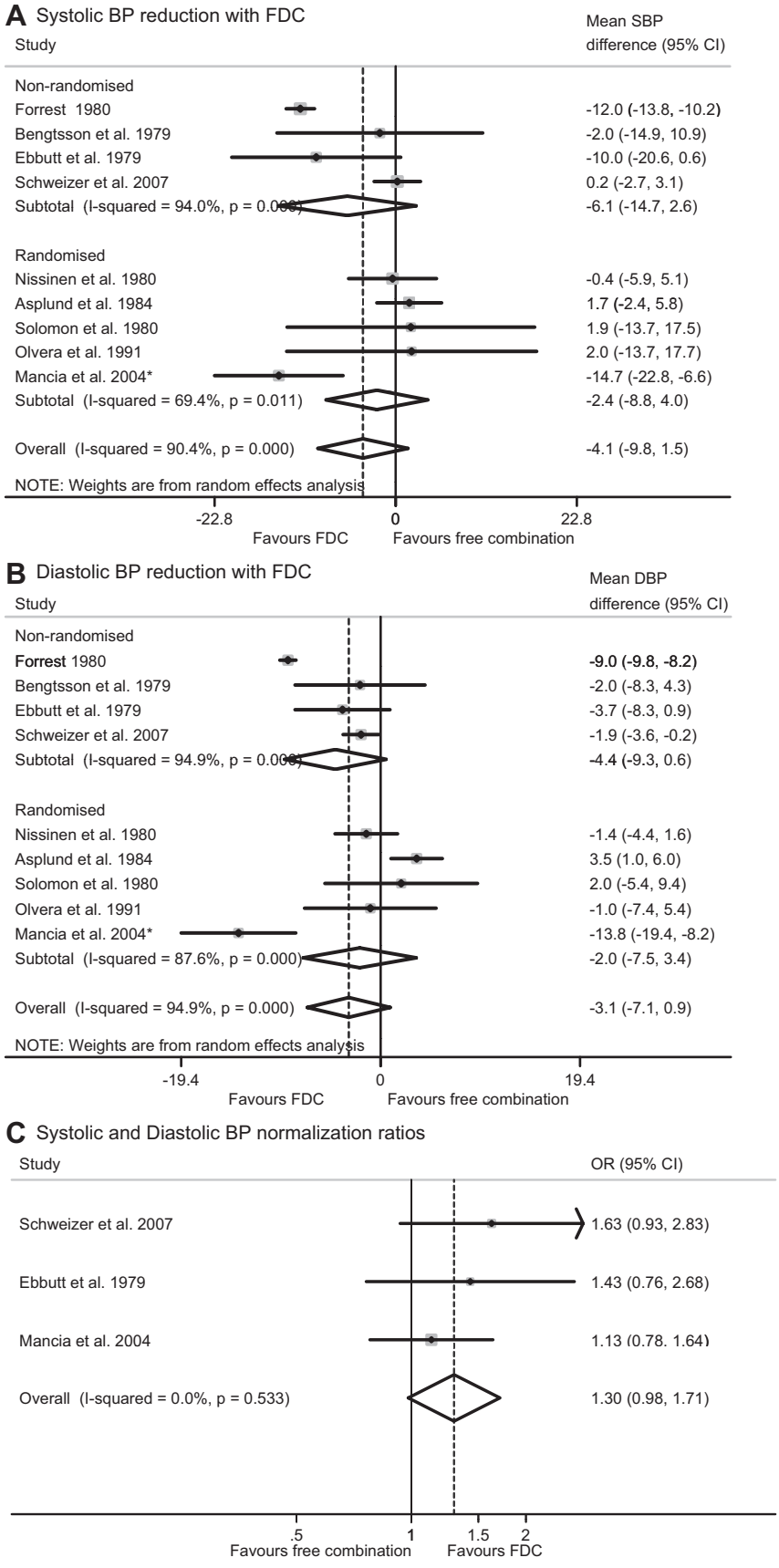

Figure 3. Systolic (A) and diastolic BP (B) reduction and BP normalization ratios (C) with use of an FDC as compared with its free-drug combination. Results were reported according to use of randomization in the included trials, because of the presence of heterogeneity. Random-effect model as used for A and B, and fixed-effect model was used for the analysis in C. * indicates that results pertaining to Mancia et al[23] are for a subgroup comparing FDC of candesartan and a diuretic with its corresponding free-drug combination, that is, angiotensin receptor blocker and a diuretic given separately.

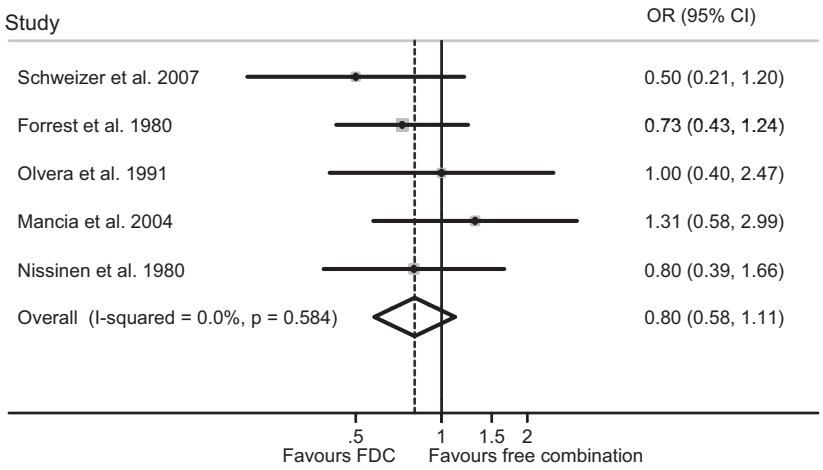

Figure 4. Adverse effects associated with the use of an FDC as compared with its free-drug combination. Fixed-effect model was used for the analysis, because there is no evidence of heterogeneity.

However, the use of FDCs in the treatment of hypertension is less common and variable; for example, in the United Kingdom, FDCs are rarely used for hypertension treatment. This seems illogical, because hypertensive patients are frequently on complex treatment regimens, which is associated with poor compliance,[10,28,36] and, hence, it would seem a suitable area for the use of FDCs. The rationale for this inconsistent approach to treating different disease areas is unclear, but one perception is that FDCs for hypertension are more expensive than the costs of the component parts. This is, to an extent, implied in the latest British Hypertension Society guidance,[37] which states that, "When there is no cost disadvantage to their use, the BHS [British Hypertension Society] recommends the use of fixed-dose combinations as a sensible way of reducing the number of medications and thereby potentially improving adherence with therapy." We have shown that adherence (compliance) does indeed improve with the use of FDCs, but we have not provided any supportive health-economic data. Nevertheless, more often than not the costs of the most commonly used combinations of agents used in hypertension (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus thiazide diuretics),[27] when provided as FDCs, are cheaper than the costs of the individual components (the diuretic usually being incorporated at no extra cost over the angiotensin-converting enzyme inhibitor or the angiotensin receptor blocker). Hence, direct costs are frequently reduced by using FDCs in hypertension, and it maybe that these reduced costs may positively affect compliance and/or persistence with therapy. In addition, extensive data are available to show a clear inverse relationship between increased compliance with treatment and healthcare costs.[38,39] Consequently, there appears to be no strong argument for rejecting the use of FDCs for managing hypertension on financial grounds. A further concern about the use of FDCs in hypertension is a fear of inducing postural hypotension. However, some of these concerns should have been dispelled by the results of the recently reported Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension Trial, which showed large reductions in BP levels in association with the use of both FDCs evaluated[5] without any important increase in postural hypotension.

In summary, our analysis is based on a limited database of studies, both in terms of quality and quantity. Nevertheless, it is to our knowledge the only evaluation of all of the currently available data regarding this important question in the context of hypertension. However, the results suggest that the use of FDCs of 2 antihypertensive agents is associated with significant improvement in compliance or persistence with therapy. Compatible with this finding, the data also suggested that FDC use may have beneficial effects on BP control and reported adverse effects compared with the use of corresponding free-drug regimens, although the latter findings did not reach statistical significance.

Perspectives

Compared with free-drug combinations, the use of FDCs of hypertensive agents is associated with a significant improvement in compliance and persistence with therapy and with possible beneficial trends on BP levels and reported adverse effects. More data from well-designed and conducted studies are badly needed to refute or corroborate these findings because, if true, the potential benefits for the prevention of cardiovascular outcomes are large. Meanwhile, assuming no major cost disadvantages, the use of FDCs should be encouraged in the management of hypertension.

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