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SCIENTIFIC LETTER

How many antihypertensives do patients need to achieve a target blood pressure?

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When treating blood pressure, guidelines recommend that clinicians aim to achieve a target level.[1] However, guidelines give only limited guidance on how many drugs patients may need to take to achieve these target levels. This paper models the effects of treatments in hypertensive patients to produce an estimate of the number of medications hypertensive patients aged 35–74 years might be expected to need to achieve a target systolic blood pressure of under 140 mmHg and a target diastolic blood pressure of under 90 mmHg.

Recent meta-analysis has produced robust estimates of the effects of treatment on blood pressure.[2] At standard dose an antihypertensive reduces blood pressure by 9.1/5.5 mmHg in a patient whose blood pressure is 154/97 mmHg; at twice standard dose the effect is 10.9/6.5 mmHg. (See www.smd.qmul.ac.uk/wolfson/bpchol for standard doses of all drugs, eg bendroflumethazide 2.5 mg, atenolol 50 mg.) The effect is proportionately larger in patients with higher blood pressures and proportionately smaller in those with lower. This provides an estimate of the likely effects of treatment on patients. Combined with data on the prevalence of hypertension and the pretreatment blood pressures of hypertensives, it can be used to obtain the best estimate of the number of drugs required to achieve target levels in a typical cohort of patients.

Data from the Health Survey for England of 1998, 1999 and 2000 were combined, providing a data set of 13 284 persons with complete cardiovascular risk factor information.[3] Of these, 8173 are aged 35–74 years. Individual 10-year coronary risks were calculated for each of these persons using the Framingham risk equation.[4] Patients are eligible for treatment if their true blood pressure and true coronary risk exceed treatment thresholds based on current British guidelines. These are either blood pressure over 160/100 mmHg (diastolic or systolic), or blood pressure over 140/90 mmHg with 10-year coronary risk exceeding 15%.[1] In addition, patients are eligible for further treatment if their blood pressure exceeds 140/90 mmHg and are already on antihypertensive treatment.

For each subject eligible, the effects on systolic and diastolic blood pressures of a single antihypertensive drug at standard dose were calculated using the following formulae, derived from Law *et al*'s meta-analysis:[2]

$$\mathrm{SystBP_{Post}} = \mathrm{SystBP_{Pre}} - \left(9.1 + \frac{\mathrm{SystBP_{Pre}} - 154}{10} \times 1.0\right)\mathrm{mmHg}$$

$$\mathrm{DiastBP_{Post}} = \mathrm{DiastBP_{Pre}} - \left(5.5 + \frac{\mathrm{DiastBP_{Pre}} - 97}{10} \times 1.1\right)\mathrm{mmHg}$$

The blood pressure effects of further drugs at standard dose are additive, whereas increasing the dose of the drug has only a small effect on blood pressure.[2] Addition of further drugs is therefore more likely to achieve target blood pressures than increasing the dose of existing drugs. From this was calculated the number of drugs required to achieve target blood pressure. Patients already on antihypertensive treatment were assumed to be already taking one drug. In a sensitivity analysis, the effect of assuming drugs are used at twice standard dose is also calculated.

Using the specified definition, there are a total of 1963 hypertensive patients in the age group 35–74 years. The prevalence of hypertension in men aged 35–74 years is 29.9% (1138 of 3804) and in women is 18.9% (825 of 4369). It is estimated that in 85.3% (1675) of hypertensives aged 35–74 years, more drugs are needed to achieve the systolic than the diastolic blood pressure target; in 5.7% (112) more drugs are needed to achieve the diastolic than the systolic blood pressure target; in 9.0% (176) both targets are achieved with the same number of drugs.

In this model, 53.9% of hypertensive men aged 35–74 years and 50.2% of women require two or three drugs to achieve target blood pressure. A significant minority of men (22.9%) and women (34.8%) will require four or more antihypertensive drugs. Some patients will require as many as seven. Hypertensive patients under 35 years require at least three drugs to achieve target levels. This is because their pretreatment blood pressure must exceed 160/100 mmHg to be eligible for treatment. Patients over 75 years of age also tend to require more drugs than younger patients (Table 1).

When the analysis is repeated with drugs given at twice standard dose 60.3% of hypertensive men aged 35–74 years and 61.9% of women require two or three drugs to achieve target blood pressure. At twice standard dose, 11.5% of men and 20.2% of women require four or more antihypertensive drugs.

Since patients on treatment are assumed to be already receiving only one drug, this analysis may underestimate the number of

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Table 1 Number of drugs needed to achieve target blood pressure in men and women[a]

Age band (years)	*Number of drugs needed to achieve blood pressure of 140/90 mmHg*				
	1	*2*	*3*	*4*	*5 or more*
Men					
16–24			5 (83.3%)	1 (16.7%)	
25–34			8 (88.9%)	1 (11.1%)	
35–44	5 (8.3%)	9 (15.0%)	36 (60.0%)	10 (16.7%)	
45–54	64 (30.3%)	60 (28.4%)	51 (24.2%)	27 (12.8%)	9 (4.3%)
55–64	105 (26.0%)	114 (28.2%)	94 (23.3%)	67 (16.6%)	24 (5.9%)
65–74	90 (19.4%)	128 (27.6%)	121 (26.1%)	82 (17.7%)	42 (9.1%)
75–84	50 (19.2%)	63 (24.2%)	75 (28.8%)	52 (20.0%)	20 (7.7%)
85+	19 (23.8%)	26 (32.5%)	18 (22.5%)	8 (10.0%)	9 (11.3%)
All ages	333 (22.3%)	400 (26.8%)	408 (27.3%)	248 (16.6%)	104 (7.0%)
Women					
16–24			1 (100.0%)		
25–34			3 (60.0%)	2 (40.0%)	
35–44	1 (3.6%)	5 (17.9%)	10 (35.7%)	10 (35.7%)	2 (7.1%)
45–54	11 (7.9%)	21 (15.1%)	58 (41.7%)	32 (23.0%)	17 (12.2%)
55–64	51 (19.5%)	68 (26.1%)	69 (26.4%)	45 (17.2%)	28 (10.7%)
65–74	61 (15.4%)	74 (18.6%)	109 (27.5%)	97 (24.4%)	56 (14.1%)
75–84	23 (6.3%)	78 (21.3%)	88 (24.0%)	89 (24.3%)	89 (24.3%)
85+	7 (4.9%)	17 (12.0%)	49 (34.5%)	42 (29.6%)	27 (19.0%)
All ages	154 (11.5%)	263 (19.6%)	387 (28.9%)	317 (23.7%)	219 (16.3%)

[a]Drugs given at standard dose, for example, bendroflumethazide 2.5 mg, atenolol 50 mg, enalapril 10 mg and amlodipine 5 mg.

Worked example of calculation of treatment effect

Patient with BP 164/102 mmHg

Effect of a standard dose on systolic BP

Standard effect = 9.1 mmHg
Plus an additional 1 mmHg for every 10 mmHg above 154 mmHg = (164–154) ÷ 10 × 1 mmHg
= 1 mmHg
Total effect on systolic BP = 10.1 mmHg
Post-treatment BP = 164 – 10.1 mmHg
= 153.9 mmHg

Effect of a standard dose on diastolic BP

Standard effect = 5.5 mmHg
Plus an additional 1.1 mmHg for every 10 mmHg above 154 mmHg = (102–97) ÷ 10 × 1.1 mmHg
= 0.6 mm Hg
Total effect on systolic BP = 6.1 mmHg
Post-treatment BP = 102–6.1 mmHg
= 95.9 mmHg

drugs patients will need. The model does not account for individual variation in patients' responses to treatment: younger, white patients respond better to drugs acting on the renin–angiotensin system and older (and black) patients respond better to drugs acting through other mechanisms. Combinations of drugs acting through different mechanisms have greater effects than combinations acting through the same mechanisms. However, since most patients require many drugs to achieve target blood pressures, most patients will require drugs acting through both mechanisms. It is not clear whether patients will always judge the incremental benefits of multiple drug treatment to be worthwhile. Young hypertensives are not at high risk of cardiovascular disease; therefore, the incremental benefits are very small. In old hypertensives, the disadvantages and adverse effects of polypharmacy may be greater; therefore, the incremental hazards may be significant. Nor is it clear that the incremental benefits are worth the costs to the health service. Attempts to persuade clinicians to achieve a blood pressure target may therefore conflict both with patients' preferences and rational use of health service resources. A more rational approach to cardiovascular disease prevention would explicitly consider the

incremental benefits of further treatment in relation to the incremental costs: both to the patient and to the wider health economy.

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* For original article with references please visit:
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Clinical Assessment of Early Morning Blood Pressure in Patients With Hypertension

William B. White, MD

In most individuals with hypertension, blood pressure (BP) shows a moderate to marked increase around the time of awakening, which has been linked to increases in cardiovascular complications occurring at this time of day. Many antihypertensive agents do not adequately control early morning BP, particularly when administered once daily in the morning. Points to consider in selecting an effective antihypertensive drug include pharmacokinetics and formulation of the agent and timing of administration. Agents with long pharmacologic half-lives, such as the angiotensin II receptor blocker telmisartan, the calcium antagonist amlodipine, and the β-blocker bisoprolol, are examples of antihypertensive drugs with demonstrated efficacy in controlling early morning BP. Bedtime administration of chronotherapeutic preparations is also effective for controlling early morning BP. Given the association between early morning BP and cardiovascular risk, future clinical trials should focus on the efficacy of antihypertensive drugs during this important period of risk. (Prev Cardiol. 2007;10:210–214)

Blood pressure (BP) shows a distinct circadian rhythm, characterized by a substantial reduction during sleep (the nocturnal dip) followed by a moderate to marked increase around the time of awakening (the morning surge) (Figure 1). The onset of acute cardiovascular (CV) events (eg, myocardial infarction, sudden cardiac death, stroke) also shows a circadian pattern, with peak occurrence during the morning (Figure 2).[1,2] Substantial circumstantial evidence shows that this increased occurrence of CV events is associated with the early morning increase in BP level. For example, the morning BP surge is positively related to degree of target organ damage, such as carotid intima-media thickness[3] and left ventricular hypertrophy.[4] The magnitude of the morning surge is also an independent predictor of cerebrovascular and cardiac events.[5,6] Although the impact of controlling early morning BP on CV risk has not been successfully studied in interventional trials, previously presented data suggest that targeting improved control of early morning BP will be valuable in treating hypertensive patients.

In this review, the factors that control circadian variation in BP are evaluated and the clinical relevance of BP measurements taken at different times of the day is also assessed using different measurement methods. These measurements include those taken in the office or clinic settings, measurements taken in the early morning by 24-hour ambulatory BP monitoring (ABPM), and patient self-monitoring measurements. The prognostic value of different measures of BP and the results of recent trials that have incorporated 24-hour and early morning assessment of BP are reviewed. Finally, antihypertensive agents that have shown particular efficacy in controlling early morning BP from controlled clinical trials are evaluated.

PHYSIOLOGIC AND PATHOLOGIC CIRCADIAN VARIATIONS IN BP

The morning surge in BP is influenced by a number of factors, including changes in activity of the autonomic and renin-angiotensin-aldosterone systems[7] and dietary sodium intake.[8] Other changes that occur during the early morning that may contribute to increased CV risk include increased heart rate, vascular tone, blood viscosity, and platelet aggregability.[9] ABPM has improved identification of patients with excessive morning surges[10] and has facilitated assessment of antihypertensive agents

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that may be particularly effective in this subgroup of the hypertensive population.

The normal 10% to 20% reduction in BP that occurs at night is largely mediated by changes in autonomic activity.[11] The renin-angiotensin-aldosterone system, a key regulator of BP, may also be involved and in salt-sensitive individuals, the nocturnal BP pattern is affected by sodium and potassium intake.[11] ABPM has allowed identification of patients who show alterations in this normal nocturnal BP pattern. These include *extreme dippers* (patients who show a ≥20% decrease in nocturnal BP compared with daytime BP), *nondippers* (patients in whom the nocturnal decrease in BP is <10% of daytime BP), and *inverted dippers/risers* (patients in whom BP does not decrease or actually increases at night) (Figure 1).[12] These variations in nocturnal BP pattern are associated with increased risk for CV disease and death.[12,13] Nondippers and risers typically do not show a surge in BP on awakening but usually have sustained early morning hypertension (HTN). An excessive morning surge is common in extreme dippers.[14]

Physiologic and pathologic variations in BP are far from static. A few determinations of BP in the doctor's office provide only isolated measurements of a continuously changing variable. Important clinical information related to BP behavior and "burden" can be derived from monitoring systems that allow determination of nocturnal, early morning, and 24-hour BP.

MEASUREMENT OF BP

BP can be measured in the clinic by physicians or nurses, using ABPM equipment, or by patients at home (self-monitoring or home monitoring).[15] Although the clinical relevance of office-measured BP has been established in multiple clinical outcomes studies, measurement of BP in this setting has clinical shortcomings. These include loss of calibration of equipment, failure of physicians to follow measurement guidelines, and the white coat effect.[15] Measurement of BP in the office setting typically does not determine BP values 12 to 24 hours after dosing of medications and cannot detect the presence and magnitude of BP during sleep or during the postawakening surge. For clinic BP measurements, 140/90 mm Hg is regarded as the upper limit of normal for most patients.[15,16] In patients with HTN and diabetes mellitus or kidney disease, however, a lower BP goal of <130/80 mm Hg has been established.[16]

Normalcy values for ambulatory BP (ABP) measurements have been reported by consensus from the literature. Measurements of BP recorded by ambulatory monitors include the daytime (awake), nighttime (asleep), and 24-hour averages. Based on a consensus group from the American Heart Association, patients are hypertensive if ABPM readings are ≥135/85 mm Hg for daytime, ≥120/70 mm Hg for

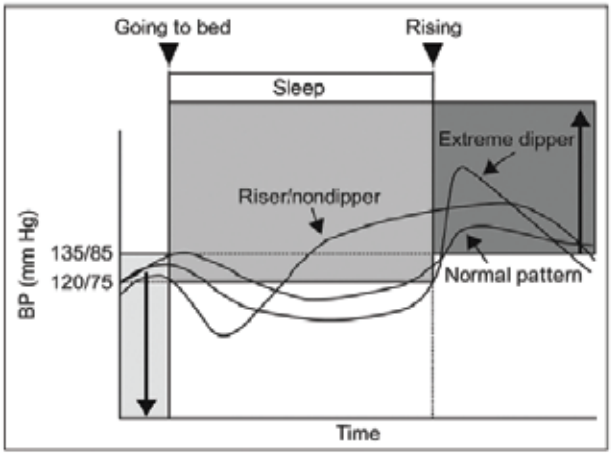

Figure 1. Normal circadian blood pressure (BP) rhythm is modified in some patients. The normal circadian BP rhythm features a nocturnal decrease in BP between 10% and 20% followed by a BP surge on awakening. Patients who exhibit this magnitude of nocturnal decrease in BP are known as dippers. Pathologic deviations from this normal pattern include extreme dipping (≥20% decline in nocturnal BP compared with daytime), nondipping (nocturnal BP decrease <10% of daytime BP), and inverted dipping/rising (no nocturnal decrease/nocturnal increase).[12] Patients who exhibit excess dipping typically show an excessive morning BP surge.[14] Adapted with permission from Giles.[7]

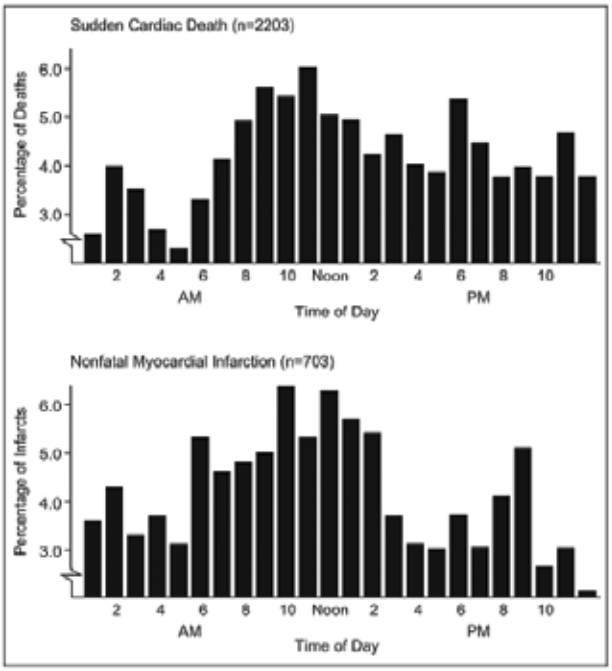

Figure 2. Occurrence of cardiovascular events peaks during the morning hours. Sudden cardiac death and nonfatal myocardial infarction both occur in a marked circadian rhythm, with a trough between midnight and 4 AM and a peak between 6 AM and noon. Reproduced with permission from Muller et al.[1]

nighttime, or ≥130/80 mm Hg for a 24-hour period.[15] ABPM measurements are typically lower than clinic BP measurements, and the cutoff for normal daytime BP correspondingly is lower (<135/85 vs

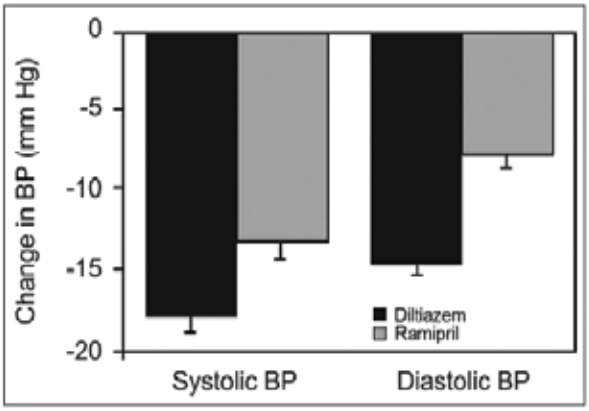

Figure 3. Bedtime administration of extended-release diltiazem (240–540 mg) is significantly more effective than bedtime administration of ramipril (5–20 mg) in reducing systolic and diastolic blood pressure (BP) in the first 4 hours after awakening (P≤.002). Adapted with permission from White et al.[27]

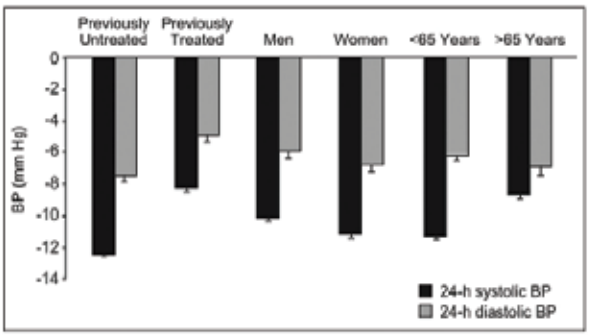

Figure 4. Reductions in 24-hour systolic and diastolic blood pressure (BP) after treatment with telmisartan alone or in combination with hydrochlorothiazide from the MICCAT-2 trial. In a 6- to 10-week community-based trial, a cohort of treated (n=675) and untreated (n=940) hypertensive patients were switched to/started with telmisartan-based antihypertensive therapy (telmisartan, 40–80 mg ± hydrochlorothiazide, 12.5 mg). Patient BP was monitored in the physician's office and using ambulatory BP monitoring. Telmisartan-based therapy was associated with significant reductions in systolic and diastolic BP in previously treated and previously untreated patients, in men and women, and in patients younger than 65 years and those aged 65 years or older (P<.0001 for all values). Adapted with permission from White et al.[33]

<140/90 mm Hg). BP is also typically lower when measured at home by patients than when measured in the clinic.[15] A recent comparison of home, office, and ABPM readings suggested that patients with home BP values <125/76 mm Hg should be classified as normotensive, those with home BP values ≥135/85 mm Hg should be classified as hypertensive, and those with intermediate home BP values should be evaluated further using ABPM.[17]

Self-monitoring of BP has some advantages over BP measurement in the clinic, particularly when new, validated electronic devices are used.[15] In a recent meta-analysis of 18 randomized controlled trials, self-monitoring was associated with significantly better BP control than was usual for office BP monitoring.[18] Home monitoring also gives patients a sense of empowerment. Although it does not allow identification of the nocturnal BP pattern, carefully performed self-monitoring can be used to detect early morning HTN.

PROGNOSTIC VALUE OF DIFFERENT BP MEASUREMENTS

Self-monitoring of BP has been reported in studies to be superior to clinic BP measurement in predicting CV events, CV death, and target organ damage.[19–21] Many of these studies were performed in general populations, however, and it has not been possible to derive normal self-monitoring values from these studies.

In 393 untreated elderly patients (mean age, 70 years) with isolated systolic HTN enrolled in the Systolic Hypertension in Europe (Syst-Eur) trial, ambulatory systolic BP was a significant predictor of CV risk, whereas systolic BP measured in the clinic was not.[22] Nighttime systolic BP was a better predictor of risk than daytime BP. Similar findings were reported by Clement and colleagues[23] in a 5-year prospective cohort study involving 1963 middle-aged patients receiving antihypertensive treatment (mean age at baseline, 56–57 years). In the prospective cohort study, ABPM values at baseline were significant independent predictors of CV events, even after adjustment for major CV risk factors and office-measured BP.[23] Using multivariate analyses that adjusted for serum cholesterol level, smoking, and the presence of diabetes, Björklund and associates[24] showed that ambulatory daytime systolic BP and isolated ambulatory HTN (normal office-measured BP and elevated ABP, also known as masked or hidden HTN) both were independent predictors of CV disease, whereas systolic BP measured in the clinic was not. Finally, a comparison of the effectiveness of ambulatory and clinic BP measurements in managing hypertensive patients showed that although clinic and ABPM readings were associated with similar levels of antihypertensive control and inhibition of left ventricular enlargement, patients monitored by ABPM required less intensive drug treatment.[25]

EFFICACY OF ANTIHYPERTENSIVE AGENTS IN CONTROLLING 24-HOUR AND EARLY MORNING BP

Effective control of early morning and 24-hour mean ABP has become a highly desirable characteristic of antihypertensive therapeutics. The degree of BP control achieved by antihypertensive agents at night and in the early morning depends on, among other things, pharmacokinetics, formulation, and timing of administration. For example, graded-release diltiazem is a chronotherapeutic preparation designed to combat the circadian BP rhythm. Evening administration of this preparation is more effective than morning administration in reducing

BP between 6 AM and noon.[26] Additionally, in a double-blind, titration-to-effect trial, White and colleagues[27] showed that bedtime administration of graded-release diltiazem was significantly more effective in reducing early morning BP than was bedtime administration of ramipril (Figure 3). Similarly, bedtime administration of a controlled-onset extended-release formulation of verapamil was more effective in reducing early morning BP than was morning administration of enalapril or losartan.[28]

The use of agents with a long half-life may also be an effective strategy for enhancing the control of BP in the early morning. For example, a single 10-mg dose of the β-blocker bisoprolol administered in the morning has been an effective means for reducing BP during an entire 24-hour period.[29] After 4 weeks of treatment in a population of 25 patients with essential HTN, bisoprolol reduced mean morning BP level from 145/97 mm Hg to 133/88 mm Hg.[29] Similarly, the calcium channel blocker amlodipine lowers morning systolic BP level and reduces the magnitude of the morning systolic BP surge. In 38 hypertensive patients allocated to a regimen of amlodipine (2.5–10 mg) administered immediately after breakfast for a period of 8 to 16 weeks, mean morning systolic BP level decreased from 156 mm Hg to 142 mm Hg, and the morning surge was reduced by 6.1 mm Hg.[30]

Recent recognition that activation of the renin-angiotensin-aldosterone system is substantial during sleep and in the early morning has led to the evaluation of using angiotensin II blockade as a strategy for controlling early morning HTN. Telmisartan, an angiotensin receptor blocker with a long half-life, has been effective in reducing early morning BP.[10,31] In 2 large-scale trials comparing telmisartan with valsartan, telmisartan 40–80 mg was more effective than valsartan 80–160 mg in reducing BP during the last 6 hours of the interdosing interval, which corresponded with the early morning BP.[31,32]

More recently, the effects of this therapeutic strategy on ABP were tested in a large, prospective, open-label trial conducted in a primary care setting (the Micardis Community Ambulatory Monitoring Trial [MICCAT-2]).[10,33] The hypothesis for the trial was that the use of ABPM would negate the potential drawbacks of the open-label design and that this study would provide objective BP data from hypertensive patients treated in a community rather than in a research environment.[33] MICCAT-2 involved 675 previously treated and 940 previously untreated patients.[33] The investigators also identified a subset of patients (n=95) who showed an excessive morning BP surge (mean systolic BP during the 2 hours after awakening >30 mm Hg higher than during the 2 hours before awakening).[10]

In the overall population, telmisartan (± hydrochlorothiazide) substantially reduced 24-hour (Figure 4), daytime, and nighttime mean BP as well as early morning (postawakening) BP.[10,33] Office-measured BP was also reduced (Figure 4).[33] Postawakening BP decreased by an average of 17.2/10.1 mm Hg in the morning surge group, and this was significantly greater than the effect on postawakening BP in the overall population (reduction of 11.5/7.0 mm Hg; $P \leq .001$).[10]

The Prospective Randomized Investigation of the Safety and Efficacy of Micardis vs Ramipril Using ABPM (PRISMA) studies recently evaluated the effectiveness of telmisartan 80 mg/d compared with ramipril 10 mg/d in controlling morning BP surge in patients with mild to moderate HTN. PRISMA I was conducted in Austria, France, Germany, the Netherlands, South Africa, Spain, Switzerland, and the United Kingdom,[34] and PRISMA II was conducted in Canada and the United States.[35] Pooled data from these studies (N=1287) show that telmisartan reduced the overall mean morning systolic BP surge by 1.5±0.47 mm Hg, whereas patients taking ramipril had an increase in morning BP surge of 0.3±0.47 mm Hg ($P=.0049$).[36] The magnitude of reduction was greatest in the quartile of patients with highest baseline morning systolic BP surge; in these patients, morning systolic BP surge was reduced by 12.7±0.91 mm Hg with telmisartan and 7.8±1.02 mm Hg with ramipril ($P=.0004$). Telmisartan also significantly reduced the magnitude of systolic morning BP surge in dippers compared with ramipril ($P=.0001$), but there was no significant difference between groups in nondippers.[36]

CONCLUSIONS

In healthy individuals, BP shows a highly reproducible circadian pattern. Characterization of this pattern has been facilitated by ABPM, a technique that is superior to clinic BP measurement as a predictor of adverse events. ABPM has also allowed clinicians to characterize a number of pathologic variations in this pattern, many of which are associated with increased risk of adverse events. These include nocturnal nondipping and excessive morning BP surges. The early morning surge in BP appears to be particularly problematic, because it coincides with the peak time of CV events. This has led physicians and drug developers to focus on antihypertensive agents that target the early morning period. Antihypertensive agents that show particular efficacy during the early morning hypertensive period include chronotherapeutic preparations of diltiazem and verapamil and agents with a long half-life (ie, 20–30 hours), such as the angiotensin II receptor blocker telmisartan and the β-blocker bisoprolol. Given the association between early morning BP and CV risk, it is important that future clinical trials focus on the efficacy of antihypertensive drugs during this important time period.

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CLINICAL RESEARCH STUDY

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Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

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ABSTRACT

OBJECTIVE: To quantify the incremental effect of combining blood pressure-lowering drugs from any 2 classes of thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers over 1 drug alone and to compare the effects of combining drugs with doubling dose.

METHODS: Meta-analysis of factorial trials in which participants were randomly allocated to 1 drug alone, another drug alone, both drugs together, or a placebo.

RESULTS: We identified 42 trials (10,968 participants). With a thiazide used alone, the mean placebo-subtracted reduction in systolic blood pressure was 7.3 mm Hg and 14.6 mm Hg combined with a drug from another class. The corresponding reductions were 9.3 mm Hg and 18.9 mm Hg with a beta-blocker, 6.8 mm Hg and 13.9 mm Hg with an angiotensin-converting enzyme, and 8.4 mm Hg and 14.3 mm Hg with a calcium channel blocker. The expected blood pressure reduction from 2 drugs together, assuming an additive effect, closely predicted the observed blood pressure reductions. The ratios of the observed to expected incremental blood pressure reductions from combining each class of drug with any other over that from 1 drug were, respectively, for thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers: 1.04 (95% confidence interval [CI], 0.88-1.20), 1.00 (95% CI, 0.76-1.24), 1.16 (95% CI, 0.93-1.39), and 0.89 (95% CI, 0.69-1.09); the overall average was 1.01 (95% CI, 0.90-1.12). Comparison of our results with those of a published meta-analysis of different doses of the same drug showed that doubling the dose of 1 drug had approximately one fifth of the equivalent incremental effect (0.22 [95% CI, 0.19-0.25]).

CONCLUSION: Blood pressure reduction from combining drugs from these 4 classes can be predicted on the basis of additive effects. The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug.

 • *The American Journal of Medicine (2009) 122, 290-300*

KEYWORDS: Angiotensin-converting enzyme inhibitor; Beta-blocker; Blood pressure; Calcium channel blocker; Combination blood pressure therapy; Randomized trial; Thiazide

Monotherapy is the standard initial treatment for reducing blood pressure in most patients with hypertension, moving to combination therapy (2 or more drugs from different classes) when stepwise increases in the dose of 1 drug fail to achieve the desired decrease in blood pressure.[1-4] A meta-analysis published in 2003 showed that halving the dose of most blood pressure-lowering drugs substantially reduced the prevalence of adverse effects but reduced the blood pressure-lowering effect by only approximately 20%,[5] supporting proposals for the use of low-dose drug combinations as the first-line treatment for the control of blood pressure.[5-8]

The effectiveness of this approach relies on there being additive effects between the different classes of drugs when used together, such that the combined blood pressure-lowering effect of 2 together is the sum of each alone. Ran-

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Conflict of Interest: Nicholas J. Wald and Malcolm Law hold patents (EU1272220 and GB2361186) for a combination pill for the prevention of cardiovascular disease (Polypill) and together with David Wald have interests in its development.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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domized trials of factorial design are required to quantify the effect of giving 2 drugs together, using 4 groups with 1 drug alone, the other drug alone, both drugs together, and placebo. Such trials have been published on each of the 4 most widely used classes of drugs (thiazides, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers).[9] We examine the evidence for additive effects of all pairwise combinations on a class-specific basis. For each of the 4 classes of drug we sought to quantify the incremental blood pressure-lowering effect of using any 1 class of drug in combination with another class and to assess the efficacy of combinations compared with using 1 drug in double dose.

CLINICAL SIGNIFICANCE

- Monotherapy is the standard initial treatment for reducing blood pressure, with stepwise increases in dose if the desired decrease in blood pressure is not achieved.
- Combining drugs from different classes is approximately 5 times more effective in lowering blood pressure than increasing the dose of 1 drug.
- Combination therapy is the preferred initial strategy in the treatment of high blood pressure.

MATERIALS AND METHODS

Randomized trials using a factorial design were identified using a search of Medline, Cochrane Collaboration, and EMBASE databases in English from 1966 to March 2008. We used generic and trade names of all drugs in the 4 classes, thiazide, beta-blocker, ACE inhibitor, and calcium channel blocker taken from reference pharmacopoeias as key or text words and combined them in pairs. The resulting citations were limited to those of Medline publication type "clinical trial" or "randomized-controlled trial." We excluded trials under 2 weeks duration, with no placebo group or with a nonrandomized order of treatment and placebo. These exclusions apart, we included all randomized placebo-controlled trials comparing any drugs of 2 of the 4 main classes specified above. The initial search identified 1697 articles, which was reduced to 778 after screening the title, to 92 after inspection of the abstracts, and to 42[10-51] after examining the full articles, including a hand search of citations in the reports of published trials and systematic reviews. We also undertook a search of Food and Drug Administration and Industry websites but identified no additional trials that met the inclusion criteria. Data were abstracted independently by 2 investigators, and any inconsistencies were resolved by discussion and referral back to the original articles.

Statistical Analysis

We calculated the mean blood pressure reductions in each trial as the reduction in the treated group minus that in the placebo group or, in crossover trials, end-treatment minus end-placebo blood pressure (with its standard error) for each drug taken separately and for both drugs taken together. For each of the 4 classes of drug in turn, we used a random effects model to estimate the average placebo-adjusted blood pressure reduction from the specified class of drug, the average reduction from the comparison drugs, and the 2 drugs together. For example, in all randomized trials that considered pairwise comparisons of thiazides and another class of drug, we calculated the mean placebo-adjusted reduction in blood pressure on thiazides alone, on the comparison drugs alone, and on both drugs together. We specified equivalent doses of different drugs by identifying the usual maintenance dose of each drug as recommended in reference pharmacopoeias.[5,52] We referred to this as the "standard dose" and expressed the dose of each drug in each trial as a multiple of the standard dose. Meta-regression analyses of blood pressure reduction on the standardized doses of the drugs were used to investigate possible sources of heterogeneity. STATA software was used (StataCorp, College Station, Tex).

For each class of drug the observed blood pressure reduction on the combination was compared with the expected blood pressure reduction based on the effect of both drugs together being additive. Because the blood pressure-lowering effect of a given dose of drug depends on pretreatment blood pressure, the expected blood pressure reduction from 2 drugs was the sum of each drug alone allowing for the smaller reduction from an added drug because of the decreased blood pressure from the initial drug.[52] For example, if 2 drugs, A and B, lower systolic blood pressure by a mm Hg and b mm Hg, respectively, from a given pretreatment blood pressure (z mm Hg) when used alone, the expected effect of both together is less than $(a + b)$ mm Hg because drug B effectively operates from a pretreatment blood pressure that is a mm Hg lower than z mm Hg, as a result of drug A. A previous meta-analysis[5] showed that the blood pressure-lowering effect of a drug is approximately 1 mm Hg less for each 10 mm Hg decrement in pretreatment blood pressure. So, the expected blood pressure reduction due to A plus B, is $(a + b - a \times 0.1)$ mm Hg, taking A as the initial drug and $(b + a - b \times 0.1)$ mm Hg, taking B as the initial drug; the average is $a + b - 0.1 \times (a + b)/2$ or $0.95\ (a + b)$ mm Hg. The expected effect of 2 classes of drug taken together is therefore 95% of the sum of the blood pressure reductions for each class of drug taken alone.

We also calculated the observed incremental blood pressure reduction from 2 classes of drug together relative to 1 drug alone and divided this by the expected incremental effect, to give a ratio of observed to expected incremental effects. For each trial, the observed incremental blood pressure reductions from 2 classes of drug together (A and B) compared with the reduction from 1 alone was calculated by subtracting the average blood pressure reduction for each

drug alone 0.5 ($a + b$) mm Hg from the reduction due to the combination of 2 drugs. The expected incremental blood pressure reduction from 2 classes of drug compared with 1 alone was the expected blood pressure reduction due to the combination (0.95 ($a + b$) mm Hg, as derived above) minus the average effect of each drug alone 0.5 ($a + b$) mm Hg. The ratios of observed to expected incremental effects had a log Gaussian distribution, so a weighted geometric mean was calculated for each class of drug by weighting the ratios for each trial by the number of participants allocated to each treatment in each study.

We compared the ratio of observed to expected incremental blood pressure reductions with the equivalent effects of doubling the dose of each class of drug by using the results of a previous meta-analysis that examined the blood pressure-lowering effects of different classes of drugs at fixed dose.[5] For each of the 4 classes of drug, the observed incremental effect of doubling dose was calculated by subtracting the blood pressure reduction at twice the standard dose from that at the standard dose.[5] The expected effect of doubling dose (eg, of drug A), assuming an additive effect, was double the blood pressure reduction from using the drug at standard dose (a mm Hg), allowing for the effect of the lower pretreatment blood pressure, as described above (ie, $0.95 \times 2a$ mm Hg). The expected incremental effect was therefore $0.95 \times 2a - a$, or $0.9a$ mm Hg. For each of the 4 classes of drug, the ratio of the observed to the expected incremental effect was calculated and compared with the incremental effects of combining each class of drug with any other class.

RESULTS

Table 1 shows details of the 42 randomized factorial trials included, involving 101 comparisons between pairs of drugs (some trials compared 2 drugs in different doses) and 10,698 participants (10,333 in parallel group design trials and 365 in crossover trials). All but 1 trial (conducted in general practice) recruited patients attending hospital outpatient hypertension clinics, generally without a history of coronary heart disease, stroke, diabetes, or renal disease. In the individual trials, the duration ranged between 4 and 12 weeks, mean age was between 46 and 71 years, and pretreatment blood pressure was between 136 and 173 mm Hg systolic and 84 and 110 mm Hg diastolic.

Figure 1 shows the mean (and 95% confidence intervals) placebo-subtracted systolic blood pressure reductions observed in the trials for each of the 4 drug classes alone, for the comparison drug alone (from any of the other 3 classes), and for 2 drugs together. The expected blood pressure reduction from both drugs together (assuming an additive interaction) is shown by the upper dotted line in Figure 1 for each of the 4 drug classes. The observed and expected effects of both drugs together are close, showing that the average effect of combining each class of drug with a drug from another class is approximately additive.

Figure 2 shows, for each of the 4 classes of drug combined with any other, the ratio of observed to expected incremental systolic blood pressure-lowering effects of 2 drugs compared with 1 drug alone. For each class of drug the effect of adding a second drug was close to that expected, that is, a ratio of 1.0. The estimates for each combination were thiazide plus any other class 1.04 (0.88-1.20), beta-blocker plus any other class 1.0 (0.76-1.24), ACE inhibitor plus any other class 1.16 (0.93-1.39), and calcium channel blocker plus any other class 0.89 (0.69-1.09). The average across all classes was 1.01 (0.90-1.12). Using 1 drug in double dose achieved ratios, respectively, of 0.19 (0.08-0.30), 0.23 (0.12-0.34), 0.20 (0.14-0.26), and 0.37 (0.29-0.45) for thiazides, beta-blockers, ACE inhibitors, and calcium channel blockers, respectively, an average of 0.22 (0.19-0.25). In every instance, combination therapy was more effective than increasing the dose of 1 drug, and this was statistically significant ($P < .05$) for all comparisons.

The mean doses of the drugs in the trials were close to the standard (or usual maintenance) dose,[52] ranging between 0.5 and 1.6 multiples of standard. There was evidence of heterogeneity of blood pressure-lowering effects across the individual trials of thiazides ($P < .01$), beta-blockers ($P = .06$), ACE inhibitors ($P = .08$), and calcium channel blockers ($P < .01$), which was largely explained by the different doses of drugs used in the trials. A meta-regression analysis of blood pressure reduction on dose (with all trials of a given class of drug stratified according to the dose used) showed that the heterogeneity was no longer present ($P > .05$ for all classes of drug).

Figure 3 shows, for each of the 4 classes of drug, a plot of the observed placebo-subtracted blood pressure reduction for that class of drug combined with any other drug compared with that expected, assuming an additive interaction and allowing for the blood pressure reduction due to the initial drug. Each circle represents a different 2-drug combination at the doses used. The area of the circle reflects the statistical precision of the points plotted. For each class of drug, the circles are on or close to the line of identity (where observed equals expected), revealing a consistent effect across all studies and across doses of drug within trials.

DISCUSSION

The results from this meta-analysis show that for each of the 4 classes of blood pressure-lowering drug considered, the blood pressure reduction from each class of drug combined with 1 from another class is approximately additive. The additional effect of combining given doses of 2 classes of drug is approximately 5 times more effective than doubling the dose of 1 drug.

The incremental effect of an additional drug was expressed as the ratio of the observed to expected extra blood pressure reduction. The latter is the sum of the reductions from each drug allowing for the reduced effect of the added drug due to the lower blood pressure achieved by the existing drug. This is needed to take account of a drug at a

Table 1 Details of the 42 Trials Included in the Meta-analysis

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Thiazide + beta-blocker									
Bateman[10]	1979	15	4	54	Cross-over	chlorthalidone atenolol	1 2	155	104
Chalmers[11]	1976	16	8	45	Cross-over	HCTZ pindolol	2	163	106
Chalmers[12]	1976	20	8	44	Cross-over	HCTZ timolol	2 3	159	99
Chalmers[13]	1982	16	8	53	Cross-over	indapamide pindolol	1 0.67	164	94
Chrysant[14]	1992	256	4	55	Parallel group	HCTZ atenolol atenolol	0.5 0.5 1	148	97
Durel[15]	1992	5	4	47	Cross-over	chlorthalidone atenolol	2	147	93
Erwteman[16]	1984	50	4	46	Cross-over	chlorthalidone metoprolol	1 2	143	94
Frishman[17]	1994	512	4	53	Parallel group	HCTZ HCTZ bisoprolol bisoprolol bisoprolol	0.25 1 0.25 1 4	148	97
La Courciere[18]	1994	240	12	52	Parallel group	HCTZ HCTZ nebivolol nebivolol	0.5 1 0.2 2	147	96
Zachariah[19]	1993	1059	4	47	Parallel group	HCTZ bisoprolol bisoprolol	0.25 1	149	95
Thiazide + ACE inhibitor									
Brown[20]	1990	40	4	58	Parallel group	HCTZ** perindopril	1 1	170	99

Table 1 Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Canter[21]	1994	460	8	53	Parallel group	HCTZ	0.25	159	102
						HCTZ	0.5		
						HCTZ	1		
						quinapril	0.125		
						quinapril	0.5		
						quinapril	2		
Chalmers[22]	1986	21	4	61	Cross-over	HCTZ	2	173	92
						enalapril	2		
Chrysant[23]	1994	505	8	53	Parallel group	HCTZ	0.5	148	98
						HCTZ	1		
						lisinopril			
Chrysant[24]	1996	334	6	53	Parallel group	HCTZ	1	159	98
						benazepril			
Fernandez[25]	1994	67	8	53	Parallel group	HCTZ	0.5	144	93
						fosinopril	2		
Kayanikis[26]	1987	211	8	54	Parallel group	HCTZ	1	161	93
						captopril	1		
Pool[27]	1997	550	8	52	Parallel group	HCTZ	0.2	147	96
						HCTZ	0.5		
						HCTZ	1.5		
						fosinopril	0.25		
						fosinopril	1		
						fosinopril	4		
Pordy[28]	1994	1162	4	54	Parallel group	HCTZ	0.5	144	95
						HCTZ	1		
						cilazapril	0.2		
						cilazapril	2		
						cilazapril	4		

Table 1 Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Scholze[29]	1993	534	6	48	Parallel group	HCTZ HCTZ ramipril ramipril ramipril	0.5 1 2 4	159	104
Thiazide + calcium-channel blocker									
Burris[30]	1990	297	6	52	Parallel group	HCTZ HCTZ HCTZ diltiazem diltiazem diltiazem diltiazem	0.5 1 2 0.5 0.75 1 1.5	152	99
Pool[31]	1993	298	6	53	Parallel group	HCTZ diltiazem	1	150	95
Salvetti[32]	1991	66	4	55	Cross-over	chlorthalidone nifedipine	1	158	97
Weir[33]	1992	298	4	54	Parallel group	HCTZ HCTZ diltiazem diltiazem diltiazem	0.5 1 0.5 0.75 1	149	95
Wing[34]	1997	19	4 4	71 71	Cross-over	HCTZ lacidipine	1	163	85
Beta-blocker + ACE inhibitor									
Wald[35]	2008	47	4	62	Cross-over	atenolol lisinopril	0.5	136	84
Wing[36]	1988	16	4	59	Cross-over	atenolol enalapril	1	171	97
Beta-blocker + calcium-channel blocker									
Clement[37]	1987	17	3	55	Cross-over	atenolol nifedipine	2 1	152	94
Dargie[38]	1986	14	4	52	Cross-over	propranolol verapamil	1.5	157	107
Lyons[39]	1994	12	2	52	Cross-over	atenolol lacidipine	2 1	154	102

Table 1 Continued

Combination of Drugs First Author	Year of Publication	Number of Participants	Treatment Duration (Weeks)	Mean Age	Trial Design	Drug	Dose (Multiple of Standard)	Mean Pretreatment Blood Pressure (mm Hg)	
								Systolic	Diastolic
Maclean[40]	1990	136	6	52	Parallel group	atenolol nitrendipi	1	173	110
McInnes[41]	1985	14	4	51	Cross-over	propranolol verapamil	1.5	158	107
Tonkin[42]	1990	17	4	61	Cross-over	atenolol diltiazem	1	181	102
Calcium-channel blocker + ACE inhibitor									
Chan[43]	1997	156	12	71	Parallel group	lisinopril diltiazem diltiazem	1 0.5 1	167	104
Cushman[44]	1998	891	12	56	Parallel group	enalapril diltiazem diltiazem	0.5 0.75	156	98
Frishman[45]	1995	401	8	54	Parallel group	benazepril amlodipine	0.5 0.5	157	101
Kuschnir[46]	1996	30	8	56	Parallel group	benazepril amlodipine	1	164	103
Levine[47]	1995	186	4	56	Parallel group	enalapril verapamil verapamil	1 0.5 1	153	100
Messerli[48]	1998	631	6	54	Parallel group	trandolopril verapamil	4 1	153	100
Scholze[49]	1998	456	6	55	Parallel group	trandolopril trandolopril trandolopril verapamil verapamil	0.5 1 2 0.5 0.75	163	104
Scholze[50]	1999	507	6	50	Parallel group	ramipril ramipril ramipril felodipine felodipine	1 2 4 1 2	155	99
Veratran[51]	1997	272	8	51	Parallel group	trandolopril verapamil	1 0.75	149	97

*ACE-I = ACE inhibitor; BB = beta blocker; CCB = calcium-channel blocker; **HCTZ = hydrochlorothiazid.

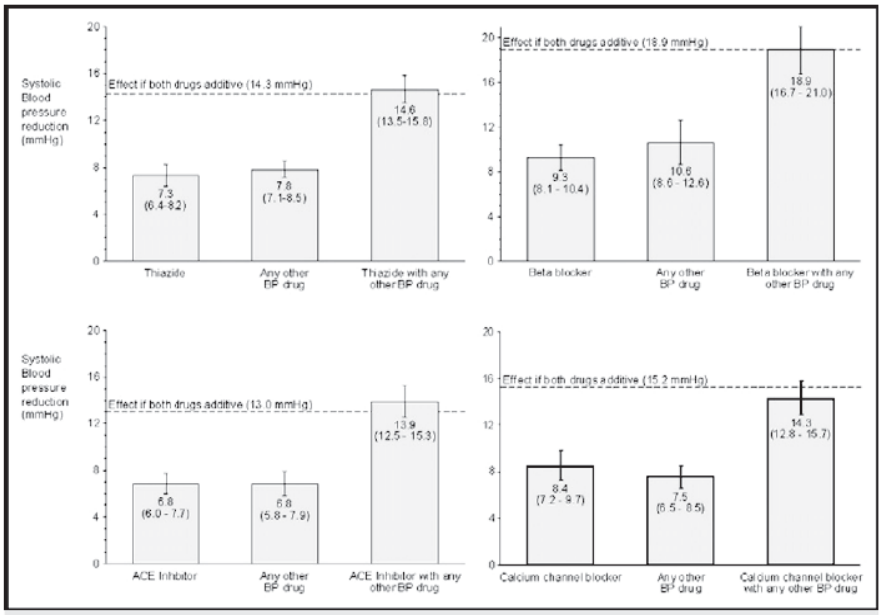

Figure 1 Mean placebo-subtracted systolic blood pressure reduction from a meta-analysis of 42 randomized factorial trials of thiazides, beta-blockers, ACE inhibitors, or calcium channel blockers using each class of drug separately, any 1 of the other 3 classes alone, and in combination with the specified drug class (95% confidence interval). The dashed line represents the expected blood pressure reduction from the combination assuming an additive effect, allowing for the smaller reduction from 1 drug given the lower pretreatment blood pressure because of the other. BP = blood pressure; ACE = angiotensin-converting enzyme.

given dose having a smaller blood pressure-lowering effect in a person with a lower blood pressure than in a person with a higher blood pressure.[52] An incremental effect of 1.0 thus indicates that the effect is exactly additive, 0.5 indicates a subadditive effect (equivalent to 50% of the extra additive effect), and 1.5 indicates a supra-additive (or synergistic) effect (equivalent to 50% greater than additive). Overall, our result of 1.01 (the average of the summary estimates from each class of drug) is close to the effect being exactly additive.

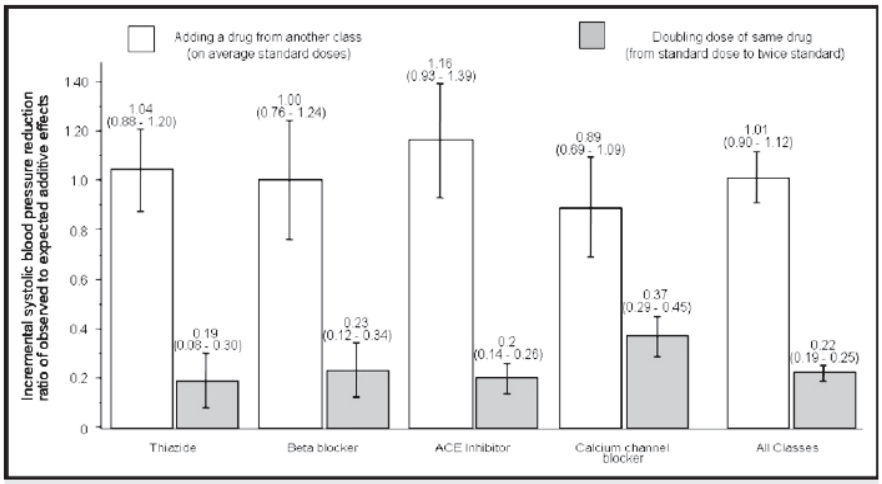

Figure 2 Ratio of observed to expected incremental blood pressure-lowering effects of adding a drug or doubling the dose according to the class of drug. The expected incremental effect is the incremental blood pressure reduction of the added (or doubled drug), assuming an additive effect and allowing for the smaller reduction from 1 drug (or dose of 1 drug) given the lower pretreatment blood pressure because of the other. ACE = angiotensin-converting enzyme.

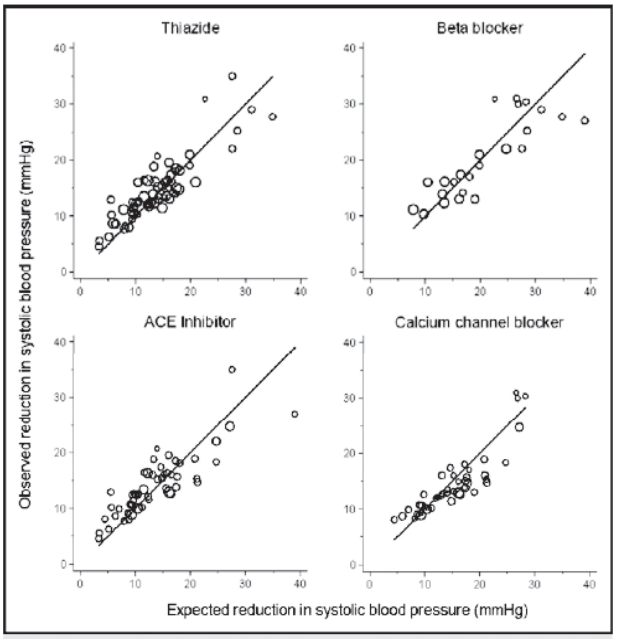

Figure 3 Comparison of observed placebo-subtracted reduction in systolic blood pressure of 2 drugs together against the expected effect of 2 drugs together according to the class of drug in factorial trials of 2 blood pressure-lowering drugs (the expected effect assumes a full additive effect and allows for the smaller reduction from 1 drug given the lower pretreatment blood pressure because of the other). Each circle represents a different drug and dose combination within a trial. There are more circles than trials because several trials examine different doses of different drugs. The area of the circle reflects the statistical precision of the points plotted. The diagonal lines are the lines of identity where observed equals expected. ACE = angiotensin-converting enzyme.

This analysis combined data from trials of all possible pairwise combinations of the 4 most widely used classes of blood pressure-lowering drugs, allowing the additive effects of each class of drug to be quantified on a class-specific basis. Angiotensin-II receptor blockers were not included in the meta-analysis because being a newer class of drug, there are few factorial trials and they do not encompass all the pairwise comparisons. Nonetheless, 3 published trials showed additive effects in combination with thiazides[53-55] and 1 published trial showed additive effects in combination with calcium channel blockers.[56]

"Monotherapy" and "stepped-care" is the usual initial approach to treating blood pressure in most patients with hypertension, in which a trial of treatment is started in each patient, increasing the dose of 1 drug before adding others if specified blood pressure "targets" are not reached. The British BHS 2004 and NICE/BHS 2006 clinical practice guidelines recommend this as the initial approach in all patients.[1,2] The American Joint National Committee VII[3] and the European Society of Cardiology/European Society of Hypertension 2007[4] guidelines also advocate this as the general approach, but recommend using 2 drugs initially if a person's blood pressure is particularly high (≥160 mm Hg systolic or ≥90 mm Hg diastolic) and in patients with specific indications (eg, diabetes or a myocardial infarction). Although the value of routinely starting treatment with combination therapy, particularly with low doses, has been proposed,[5-8] this has not been widely accepted. No guideline recommends combination rather than monotherapy as a matter of routine in all patients. The substantial advantage of this approach, over increasing dose, is clear from the results presented here, based on many studies, across different doses and pretreatment blood pressure levels. The results leave little doubt over the advantages of adopting low-dose combination blood pressure-lowering treatment as routine initial therapy for all, instead of a monotherapy and stepped-care approach.

A single blood pressure-lowering drug at standard dose reduces diastolic blood pressure by approximately 5 mm Hg,[5] equivalent to approximately a 25% reduction in risk of coronary heart disease events (relative risk 0.75) and approximately a 35% reduction in stroke (relative risk 0.65), at age 65 years, from a meta-analysis of 61 cohort studies supported by a meta-analysis of 147 randomized trials.[57,58] Our results indicate that doubling the dose of a single drug would increase the blood pressure reduction from approximately 5 to 6 mm Hg, which would reduce coronary heart disease events by 29% (because $0.75^{6/5} = 0.71$), an additional 4 percentage points, and reduce stroke by 40% ($0.65^{6/5} = 0.60$), an additional 5 percentage points. Combining 2 drugs from different classes would increase the blood pressure reduction from approximately 5 to 9 mm Hg, which would reduce coronary heart disease events by 40% ($0.75^{9/5} = 0.56$), an additional 15 percentage points, and reduce stroke by 54% ($0.65^{9/5} = 0.46$), an additional 19 percentage points. This means that for every 1 incremental coronary heart disease event or stroke prevented by doubling the dose of a single drug, 4 events would be prevented by using combination therapy.

Low-dose therapy has the advantage of reducing adverse effects that, with the exception of ACE inhibitors and angiotensin receptor blockers, are strongly dose related; for 2 classes (thiazides and calcium channel blockers), for example, adverse effects are 80% lower at half-standard than standard dose.[5] The prevalence of adverse effects from combining 2 drugs at half-standard dose would therefore, for most combinations, be lower than with 1 drug at standard dose. Using more than 2 drugs in combination also would increase efficacy; 3 drugs at half-standard dose (compared with 2 at standard dose) would, for example, reduce diastolic blood pressure by approximately another 2 mm Hg (from 9 to 11 mm Hg) with expected reductions in the risk of coronary heart disease and stroke of 46% and 63%, respectively. The use of combination low-dose therapy therefore has greater efficacy and less toxicity than using a higher dose of a single drug.

There may be concerns that such an approach may lower blood pressure below the so-called blood pressure "targets" often regarded as optimal.[1,2] The evidence, however, is against the view that there is some target blood pressure

level within the range of values in Western populations below which further blood pressure reduction has no further effect in preventing cardiovascular disease. Epidemiologic studies show a continuous proportionate reduction in risk of heart disease and stroke with decreasing blood pressure, without threshold.[57] Over time, patients entered into trials of blood pressure reduction have been selected with lower and lower blood pressures and the trials have shown no attenuation of the relative reduction in disease events,[59-63] as expected from the epidemiologic studies.[5] Setting blood pressure targets needlessly limits the potential for preventing heart attacks and strokes through blood pressure reduction.

CONCLUSIONS

Combining blood pressure-lowering drugs from different classes is approximately 5 times more effective than doubling the dose of 1 drug. It follows that to maximize efficacy combination therapy, preferably using low doses to minimize side effects, is substantially better than monotherapy and should be considered as routine initial therapy.

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* For original article with references please visit:
https://rb.gy/xs2fju

Original article

Benefits of a fixed-dose combination of bisoprolol and amlodipine in the treatment of hypertension in daily practice: results of more than 4000 patients

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Abstract

Objective:
The study objective was assessing patient adherence to a fixed-dose combination (FDC) of bisoprolol and amlodipine in daily practice in patients who had been switched from the free to the fixed-dose combination prior to recruitment.

Material and methods:
The non-investigational study was carried out in Poland. Patients over 18 years of age with essential hypertension were recruited if they had already been switched from a free combination to the FDC at least 4 weeks prior to recruitment. Exclusion criteria included pregnancy, lactation, any contraindication to the FDC, and other antihypertensive treatment. Adherence was measured by tablet count (tablets taken divided by tablets prescribed, times 100) and defined as follows: excellent >90%, good 76–90%, moderate 51–75%, bad ≤50%. Other patient data, clinical findings and laboratory values were recorded upon availability at study start, after 3 months (voluntary) and after 6 months.

Results:
Data of 4288 patients (mean age: 59 years; gender: 50% each) were documented. The average daily doses of the FDC were 5.8 mg bisoprolol and 6.4 mg amlodipine. These doses differ only slightly from those of the free combination. After 3 months' treatment with the FDC, a dose increase was carried out in 113 patients for bisoprolol and in 126 for amlodipine. After 6 months of FDC treatment, 82% of the participants of the study showed excellent adherence and for a further 15% the adherence could be considered good. This strong adherence may have led to the observed reduction in systolic and diastolic blood pressure of 11% (Cohen's D efficient size 1.23). In addition, pulse pressure decreased from 58.8 mm to 52.2 mm. Also in diabetic patients (21% of the cohort), further reduction of systolic blood pressure values could be achieved (mean before 150 mm, after 133), wherein the initial differences compared to patients without diabetes had disappeared. The pulse rate also changed from 75 b/min to 68 b/min under the FDC.

Conclusion:
These study results clearly show that the FDC leads to excellent patient adherence and therefore may result in better blood pressure control. Blood pressure control is crucial in the risk reduction of cardiovascular events. The key limitation of this study is that the study design does not allow a direct comparison of patient adherence under the free and the fixed-dose combination.

Introduction

Elevated blood pressure is related to an increased cardiovascular (CV) risk. In fact, arterial hypertension is one of the most prevalent cardiovascular diseases

in industrialized nations[1]. Thus, in hypertensive patients, the primary goal of treatment should be to achieve maximum reduction in the long-term total risk of CV disease[2].

The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend evaluating the total cardiovascular risk in each patient in order to decide on important aspects of treatment. These evaluations include the blood pressure threshold at which to commence drug administration, the target BP to be reached by treatment, the use of two-drug combinations as the initial treatment step, and the possible addition to the antihypertensive treatment regimen of lipid-lowering and antiplatelet agents.

Major guidelines on the management of hypertension recommend the initiation of antihypertensive drugs in all patients with a systolic blood pressure (SBP) of 140 mmHg or more and/or a diastolic blood pressure (DBP) of 90 mmHg or more, and adjusting the treatment strategy in order to achieve SBP/DBP values of <140/90 mmHg[3].

Large-scale meta-analyses of available data confirm that major antihypertensive drug classes – i.e. diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blocker (ARB), and beta-blockers – do not differ significantly in their overall ability to reduce BP in hypertension.

New data suggest that the majority of patients will require two or more antihypertensive agents in order to reach specified BP targets. Combining two drugs from different classes has the potential to target different aspects of hypertension, which may result in additional BP decreases compared with either agent used alone[4,5]. Low doses of two drugs are commonly prescribed instead of high doses of one agent, in the expectation that symptoms will be similarly controlled, but with fewer side effects[6,7]. Thus, combination therapy has an important place in the routine management of hypertension. However, it must be considered that for many, especially elderly, patients, the rules for taking multiple medications can be very distressing and lead to misconduct and to inadequate adherence.

As a consequence of the above-mentioned facts, a fixed combination tablet of the beta-blocker bisoprolol and the calcium channel blocker amlodipine in the strengths of 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg was developed as substitution therapy for patients whose blood pressure can be adequately controlled by the simultaneously administration of both substances of the same doses.

Bisoprolol is a highly beta1-adrenoceptor-selective antagonist devoid of any intrinsic sympathomimetic activity (ISA). Pharmacological features of bisoprolol are essentially related to its high beta1-selectivity and confer substantial clinical advantages to the drug compared with non-selective agents in terms of their respiratory, hemodynamic and metabolic effects[8,9,10]. Amlodipine is a long-acting calcium channel blocker of the dihydropyridine class. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells[11–13].

A first open, non-comparative study with the fixed combination of bisoprolol and amlodipine was carried out by Mehta *et al.*[14] in 106 patients suffering from mild to moderate essential hypertension. Patients were treated with a fixed-dose combination (FDC) of 2.5 mg bisoprolol and 5 mg amlodipine once daily for 8 weeks. In case of insufficient therapeutic effect after 7 or 15 days, this dose could be doubled. Treatment response was defined as a SBP below 140 mmHg and a DBP below 90 mmHg. Mean SBP and DBP were significantly lower after end of treatment compared to baseline ($p<0.0001$). Response rate was 89%.

Further experiences with a fixed-dose combination of the same substances were gained in an observational study in 801 patients with stage II essential hypertension[15]. Patients received a fixed-dose combination of 5 mg bisoprolol and 5 mg amlodipine once daily for 4 weeks. A total of 749 patients completed the study. Mean SBP decreased significantly from a baseline of 171.9 ± 17.9 mmHg to 152.9 ± 16.4 mmHg, 142.1 ± 13.1 mmHg and 134.3 ± 10.1 mmHg after 1, 2 and 4 weeks, respectively (all $p<0.001$). Mean DBP fell from 103.9 ± 9.6 mmHg at baseline to 93.5 ± 8.8 mmHg, 88 ± 7.3 mmHg and 83.4 ± 6.2 mmHg after 1, 2 and 4 weeks, respectively (all $p<0.001$). The authors concluded that the daily application of a fixed-dose combination of bisoprolol and amlodipine in stage II essential hypertension is effective, safe and well tolerated.

These data were confirmed by the results of a comparative, randomized study on sixty patients with stage II essential hypertension. Bisoprolol and amlodipine in a fixed-dose combination showed significant blood pressure control, and the antihypertensive effect was greater than individual monotherapy[16].

The most important advantage of a FDC compared to the free combination is the expected better patient adherence. Thus, the present study was conducted as a non-investigational study to evaluate the adherence of the FDC in daily practice in patients who had been switched from the free to the fixed-dose combination prior to recruitment.

Methods

This study was carried out as a non-investigational study in about 60 study centers in Poland. Patients over 18 years of age with essential hypertension were recruited after informed consent if they had already been switched from a free combination of bisoprolol 5–10 mg/d and amlodipine 5–10 mg/d to the FDC at least 4 weeks prior to recruitment. Reliable contraception was mandatory in women of

childbearing age. Exclusion criteria included pregnancy, lactation, any contraindication to the FDC according to the local label and any other antihypertensive medication.

The primary target parameter was patient adherence under the FDC. Adherence was measured by tablet count (tablets taken divided by tablets prescribed, times 100) and defined as follows: excellent >90%, good 76–90%, moderate 51–75%, bad ≤50%. All other patient data, clinical findings and laboratory values were recorded upon availability at study start, after 3 months (voluntary), and after 6 months. Blood pressure was measured in a supine position after at least 5 minutes rest. A unique subject number was assigned to each subject at inclusion. This number served as the subject's identifier in the study as well in the study database.

Only authorized persons had access to identifiable personal details, if required for data verification. Data protection and privacy regulations were guaranteed in capturing, forwarding, processing, and storing subject data. Subjects were informed accordingly, and were requested to give their consent on data handling procedures in accordance with national regulations. Any information relating to history and all clinical findings and laboratory values were recorded in the case record forms (CRFs) upon availability.

The study protocol included two consecutive examinations visits after 3 and 6 months. The visit after 3 months was not mandatory. In the follow-up, all the findings and laboratory values were recorded in the CRFs again. All patients were asked about the occurrence of adverse events.

All entries in the CRFs were transferred for evaluation into the BIAS file (Biometric analysis of samples, Hanns Ackerman, Univ. Frankfurt). Mean, standard deviation, median, quartiles, and confidence intervals (95%) were calculated, and the following tests were performed: test for Gaussian distribution, Spearman correlation, the Mantel–Haenszel test for contingency tables, the Welsh test for paired values (parametric), the Wilcoxon matched pairs test (non-parametric), and Cohen's *D* for effect size (M1 – M2/*s* pooled).

Results

This evaluation of the multicenter observational study refers to 4288 subjects who were treated in about 60 study centers. Basic data of the primary recording findings are summarized in Table 1.

The proportion of male and female study participants was equal. The mean age was 59.3 years, with no differences between female and male patients. The youngest patient was 19, the oldest 99 years old. There was a noticeably large proportion of patients with type 2 diabetes: 21%. The average dose in the fixed combination of 5.8 ± 2 mg

Table 1. Demographic data.

	N	%		
Participants	4288	100		
Male	2145	50.3		
Diabetes type 2	920	21		
Cardiovascular co-morbidities	1596	37.2		
Liver disease	41	1		
Kidney damage	117	2.7		
No smoker	2185	51		
Smoker	1093	25		
Ex-smoker	1010	24		
No alcohol	1617	38		
Parameters	Mean (SD)	Median	Q1–Q3	95% CI
Age (years)	59.3 (±15)	60	52–67	58.9–59.8
Size (cm)	170.1 (±24)	170	164–176	169.3–170.8
Weight (kg)	80.9 (±18)	80	71–89	80.4–81.5
BMI (kg/m^2)	27.86 (±4)	27.7	25.5–29.8	27.8–28
Systolic blood pressure (mmHg)	146.7 (±15)	146	135–160	146.3–147.2
Diastolic blood pressure (mmHg)	87.9 (±10)	90	80–95	87.6–88.2
Pulse beat/min	75.3 (±11)	75	68–82	75.0–75.7
Glucose (fasted) mg/dl)	99.1 (±22)	96	88–105	95.3–97.4
Duration of hypertension (years)	7.8 (±5)	7	3–10	8.5–8.9
Duration of free combination treatment prior to switch (months)	19.5 (±22)	12	7–24	16.5–17.7
Dosages (free combination)				
Bisoprolol (mg/daily)	5.5 (±2)	5	5–5	5.5–5.6
Amlodipine (mg/daily)	6.1 (±2)	5	5–5	5.9–6.9

Table 2. Comparison of dosing.

Free Combinations	Converted to Fixed-Dose Combination: Bisoprolol 5 mg plus Amlodipine 5 mg *N* (%)	Bisoprolol 10 mg plus Amlodipine 5 mg *N* (%)	Bisoprolol 5 mg plus Amlodipine 10 mg *N* (%)	Bisoprolol 10 mg plus Amlodipine 10 mg *N* (%)
Bisoprolol 5 mg plus Amlodipine 5 mg *N* = 2665 (63%)	**2532 (95)**	23 (0.9)	96 (3.6)	14 (0.5)
Bisoprolol 10 mg plus Amlodipine 5 mg *N* = 323 (8%)	112 (34.6)	**194 (60.1)**	6 (1.9)	11 (3.4)
Bisoprolol 5 mg plus Amlodipine 10 mg *N* = 847 (20%)	236 (27.8)	4 (0.5)	**585 (69.1)**	22 (2.6)
Bisoprolol 10 mg plus Amlodipine 10 mg *N* = 391 (9%)	122 (31.3)	23 (5.8)	61 (15.6)	**185 (47.3)**
Total: *N* = 4226	3002 (70.3)	244 (5.7)	748 (17.7)	232 (5.5)

Bold values are for those patients whose bisoprolol and amlodipine doses remained unchanged after the switch from the free combination to the FDC.

Table 3. Blood pressure at study start and after 6 months.

	SBP (mmHg) Mean (SD)	DBP (mmHg) Mean (SD)
Visit 1 (study start), all patients *N* = 4288	146.8 (±15)	87.9 (±10)
– Non-diabetic patients	145.8 (±15)	88.0 (±10)
– Diabetic patients	150.2 (±16)	87.5 (±10)
Visit 3 (after 6 months), all patients *N* = 3410	130.8 (±10)	78.6 (±7)
– Non-diabetic patients	130.1 (±10)	78.7 (±9)
– Diabetic patients	133.1 (±13)	78.5 (±7)
Difference before - after, all patients *N* = 3410	16.3 (±15)	8.8 (±10)
	N (%)	*N* (%)
Improvement	2845 (±84)	2529 (±75)
No change	319 (±9)	522 (±15)
Worsening	247 (±7)	358 (±10)

for bisoprolol and 6.4 ± 3 mg for amlodipine was not considerably different from the previous dose of both products in the free combinations. A contingency table (Table 2) shows that the initial dosage of the free combination was changed to the fixed combination in less than 20% of the cases.

During the visit at the official beginning of the study (4 weeks after switching to the FDC) the dosage regimen was somewhat corrected again in only 600 cases. These patients then received an average of 5.6 mg bisoprolol and 6.1 mg amlodipine per day. The most common changes in the dosages were thereby made to the patients who had been previously treated with bisoprolol 5 mg and amlodipine 5 mg.

At the end of the study, details of the main target, patient adherence, were available for 3411 participants. It was expected that more than 90% of the patients at Visit 3 would show an excellent to good adherence. In actual fact, the adherence of 97% of the patients was good to excellent. Thus, the expectation was exceeded. It turned out that the adherence was slightly improved even between the second and the third control. Approximately 97% of patients stated that they would prefer the fixed-dose combination.

The success of the good adherence under fixed-dose combination of bisoprolol and amlodipine may lie in an 11% reduction in systolic blood pressure and in diastolic blood pressure (Table 3). This level of blood pressure reduction was confirmed in the conversion of all dose regimes used. Blood pressure differences can also be registered regarding the proportions of patients per quartile between the values before and after the changeover when the first subdivision of quartiles is used after the conversion.

Assessing blood pressure values as a function of adherence shows a certain correlation of systolic, but not the diastolic, blood pressure to patient adherence. The potential benefits of good patient adherence are reinforced by the improvement of pulse pressure by an average of 58.8 mmHg ± 13 at study start versus 52.2 mmHg ± 11 6 months.

The division into quartiles is shown in Table 4. There were considerable differences between the systolic blood pressure values of diabetics and non-diabetics at study start

Table 4. Pulse pressure at study start and after 6 months divided by quartiles computed for the study start.

	Pulse pressure (mmHg)	Study start *N* (%)	After 6 months *N* (%)
Minimum	20	3	10
First Quartile	50	1496 (35)	1873 (55)
Median	60	1446 (34)	1113 (33)
Third Quartile	65	305 (7)	161 (5)
Maximum	120	1035 (24)	254 (7)
Total		4285	3411

(Table 3) – patients without diabetes: 145.8 mmHg ± 15 mmHg, patients with diabetes: 150.2 mmHg ± 16 mmHg. After the 6 month treatment with the fixed-dose combination, the values in patients without diabetes were 132.1 mmHg ± 10 mmHg, and in patients with diabetes 133.2 mmHg ± 10 mmHg. There were almost no differences in blood pressure values of patients with and without kidney disease or elevated creatinine values either at study start or after 6 months.

Further analyses revealed that there was no correlation between body mass indices and blood pressure values. Similarly, no correlations between diet (meatless/meaty) and blood pressure values could be detected (BP systolic 146:150 mmHg). There were no relevant differences in blood pressure values between smokers and non-smokers (149:146 mmHg), and therefore no correlation between these two parameters.

In contrast, a significant association between alcohol consumption and blood pressure values could be determined. In the case of subjects without any alcohol intake, the mean systolic blood pressure was 138 mmHg, while in patients with regular alcohol consumption the mean was 152 mmHg. The pulse rate per minute changed from an average of 75 ± 11 bpm to 69.1 ± 8 bpm after 3 months and to 68.7 ± 7 bpm after 6 months.

Adverse events

In total, 63 adverse events (AEs) were reported in 50 patients (1.2% of all patients). The majority of the adverse events were edema (29, 5% of AEs), followed by dizziness (6, 1% of AEs) and bradycardia (4, 7% of AEs). Only two adverse events (3% of AE) were considered serious, one case of atrial fibrillation and one case of chronic heart failure worsening. In total, seven patients discontinued the study due to adverse events. Overall, the FDC was well tolerated.

Discussion

In long-term treatment of chronic diseases, such as hypertension, patient adherence is a severe problem. Patients often fail to control their blood pressure because they do not comply with pharmacologic therapy[17]. This is particularly true in patients with a high pill burden, e.g. in patients that need a combination of drugs for the treatment of hypertension and for further disorders. On the other hand, strict blood pressure control is crucial in order to decrease the risk of cardiovascular events, particularly in hypertensive patients with additional risk factors such as type 2 diabetes. The general goal of antihypertensive therapy is to minimize the risks associated with blood pressure elevation without adversely affecting quality of life[18,19].

The importance of achieving goal BP in individual patients cannot be overemphasized. In major clinical trials, small differences in on-treatment BP frequently translate into major differences in clinical event rates. Recent data also suggest that inadequate BP control is itself an independent risk factor for the development of diabetes in hypertensive patients[20].

The biggest advantage of the FDC of bisoprolol and amlodipine is the reduction in the number of tablets to be taken. It could therefore be assumed that the FDC will improve patient adherence[21,22]. The effectiveness of the combination of bisoprolol and amlodipine has been duly established in studies. However, the specific issue of such studies with a strict selection of well defined patients is that it more or less limits the validity of the results to this selected group. In daily practice, however, the physician has to encounter individuals of different ages with different initial findings, comorbidities, concomitant medications and lifestyle habits. In order to meet the possibilities and limitations of antihypertensive treatment under these circumstances, studies with a large number of cases are required and there must be recruited patients with virtually no limitations on daily practice. It is understood that such studies can only be performed multi-centrically.

With a sample size of more than 4000 patients, the present multicenter study met these requirements. The cohort recruited in this study can be considered as representative. Thus, the study covers a wide range of ages; 22% of patients were aged below 50 years and 16% were older than 70 years so that, as expected, most patients suffering from high blood pressure were between 50 and 70 years of age.

The limitations of this study are mainly due to the non-investigational study design. As clinical findings and laboratory parameters were only documented upon availability, a lot of values are missing. A direct comparison of patient adherence under the free and the fixed-dose combination was not possible.

A certain correlation between the age of the patients and the level of blood pressure could also be seen. When compared to this – contrary to expectations – no correlation between body mass index and blood pressure values could be found. On average the difference amounts to only

3 mmHg. However, it must be noted that the patients had been treated for hypertension for quite some time. Other examples of the importance of additional factors are blood sugar levels and intake of alcohol.

The analysis of the study after 6 months based on the data of 3411 patients, compared to the initially recruited patients, this represents a dropout rate of 20%. Experiences in implementing such observational studies show that such a loss of data is quite common and inevitable. Thus, it can be assumed that this loss rate will hardly influence the overall results of the study.

The improved adherence to the FDC of bisoprolol and amlodipine was impressively demonstrated by this observational study. Shortly prior to recruitment, patients had been switched from the free to the fixed-dose combination of bisoprolol and amlodipine. The majority of patients (>80%) maintained the doses of both components over the whole duration of the 6 month study, with a good to excellent adherence in 97% of the patients. In most of the patients, the dose of the two components was not changed during the switch from the free to the fixed-dose combination. Thus, the improvements in blood pressure control could mainly be due to this outstanding adherence. Not only blood pressure, but also pulse pressure and heart rate as independent risk factors for cardiovascular disease could be considerably improved.

The high acceptance of the FDC by the patient was also shown by the fact that 97% of the patients preferred the FDC to the free combination at study end. Although the benefits of a fixed combination for the treatment of patients with high blood pressure are well recognized, some experts criticize the restriction of flexibility in dosing. The results of this study have shown that the combinations used with four fixed doses are quite sufficient to meet the requirements for effective blood pressure therapy.

Both substances in the FDC are proven effective antihypertensive substances, which have long been used to treat patients with high blood pressure and they are proven even in combined application. Both substances have a known spectrum of adverse effects that can be well controlled. Prior to the study start, the recruited patients of this study were pretreated with the same two substances, so that the occurrence of adverse effects could hardly be expected from this combination. Based on the very low incidence of adverse reactions it can be stated that the switch from the free to the fixed combination did not affect tolerability or safety of this therapy[23,24,25,26].

Conclusion

The study results clearly show high adherence under the FDC of bisoprolol and amlodipine that may lead to better blood pressure control and, thus, to risk reduction for cardiovascular events. Apart from the effect on blood pressure control itself, participation in this study may also result in educational value for the patients – and the doctors – who might have learned that simplified handling when taking the FDC reduces the risk for excessive blood pressure values and thus for other cardiovascular risks.

Transparency

Declaration of funding
This study was carried out as a company-sponsored trial by Merck KGaA.

Author contributions: D.C. and U.H. contributed to the conception and design of the study. E.M.W.K. and U.H. were involved in the data analysis and interpretation. E.M.W.K. drafted this article. D.C. was the principal investigator of the study. No assistance in the preparation of this article is to be declared.

Declaration of financial/other relationships
U.H. has disclosed that she is an employee of Merck KGaA. E.M.W.K. has disclosed that he is a consultant to the company. D.C. has disclosed that she has given lectures for Merck KgaA.

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Medication Utilization Patterns and Hypertension-Related Expenditures among Patients Who Were Switched from Fixed-Dose To Free-Combination Antihypertensive Therapy

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ABSTRACT

Using a retrospective cohort study of medical and pharmacy claims data, we evaluated medication compliance, persistence, and hypertension-related expenditures among patients who were switched from fixed-dose combination (FDC) to free-combination (FC) antihypertensive therapy. An example of a fixed-dose combination product for hypertension would be a valsartan/HCT tablet, and a free-combination product would be a valsartan tablet plus a diuretic tablet.

The 7,224 patients identified from January 2003 to December 2005 were matched, in a 1:1 ratio, by propensity scores to controls who remained on their FC antihypertensive medications. Compliance, defined as a medication–possession ratio, was measured over 12 months. Persistence was measured as the percentage of patients who did not experience a lapse in therapy of more than 30 days since their last prescription refill.

The patients continuing with FDC therapy had better persistence (42.5% higher; $P < 0.002$) and compliance (22.1% higher; $P < 0.001$), compared with patients who were switched to FC therapy. The 22.1% higher compliance rate for patients continuing the FDC regimen was associated with significantly lower expenditures for hypertension-related health care ($P < 0.001$) and an estimated 5% reduction in hypertension-related expenditures.

Key words: fixed-dose combinations, antihypertensive therapies, health care costs, compliance, persistence

INTRODUCTION

More than 72 million adults in the U.S. have hypertension, making it the most common cardiovascular disease.[1] If hypertension is not properly managed, it can lead to serious adverse cardiovascular and cerebrovascular events, including myocardial infarction (MI), angina pectoris, stroke, and renal disease.[2] Although lifestyle and diet modifications have the potential to decrease the incidence of hypertension in the general population and improve patients' blood pressure (BP) control rates, many patients require pharmacological intervention to maintain control of BP.[3–5]

Medications commonly prescribed for hypertension include thiazide-type diuretics such as hydrochlorothiazide (HCTZ), angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme (ACE)–inhibitors, and calcium-channel blockers. These medications are either prescribed as monotherapy (one agent taken as a single tablet or capsule) or as combination therapy (multiple agents taken as a daily regimen of multiple tablets or as a single tablet in a fixed-dose combination (FDC) agent. The evidence suggests that most patients with hypertension require combination therapy to reach target BP.[2,6–10] For example, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that most patients need two or more drugs to achieve BP control.[2]

Although free-combination (FC) medications are chemically equivalent to FDC products, FC regimens increase the complexity of using and acquiring medications. Simpler regimens can improve medication persistence and compliance for different diseases and age groups.[11–15] Studies specifically comparing single-tablet FDC and FC antihypertensive regimens have demonstrated better persistence and compliance with FDC therapies.[16–19] One study that compared FDC lisinopril/hydrochlorothiazide (HCTZ) with FC lisinopril plus a diuretic, and FDC enalapril/HCTZ versus FC enalapril plus a diuretic, showed a 21.7% and an 18.8% improvement, respectively, in persistence in the FDC arm after 12 months.[20]

Another study examined medication compliance, use of health care resources, and costs in FDC amlodipine besylate/benazepril HCl therapy and a comparable FC component-based therapy.[17] The study demonstrated a 7% absolute increase in the compliance rate in the FDC group. The total

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average annual costs of cardiovascular-related care were $726 for the FDC patients and $1,600 for the two-tablet FC group.

In a study by Gerbino et al.,[18] better compliance was noted with amlodipine/benazepril than with an ACE-inhibitor plus a dihydropyridine calcium-channel blocker, independent of the number of concomitant medications used.

Therapeutic regimens that improve medication persistence and compliance are more likely to produce better health outcomes and lower health care costs. Several studies have demonstrated the positive correlation between persistence and compliance rates and control of hypertension.[21–24]

In addition to the link between compliance and BP control, studies have shown an inverse relationship between compliance with medication regimens and health care costs in the treatment of hypertension.[25–34] Inadequate control of BP has been associated with a significant cost burden[35,36] in treating avoidable complications[37] such as congestive heart failure,[38] coronary heart disease,[37,38] stroke,[39] and renal disease.[40,41] Because hypertension is highly prevalent, with estimated direct and indirect costs of $66.4 billion in the U.S. in 2007,[1] improved management of hypertension through better medication compliance has the potential to reduce costs of a disease that generates a significant cost burden in the U.S.

STUDY OBJECTIVE

Evidence is limited on the impact of persistence and compliance when patients are switched from FDC to FC antihypertensive regimens. We sought to compare patients who were switched from a FDC to the corresponding free combination of the same medications with patients who continued taking FDC antihypertensive regimens.

We hypothesized that patients continuing with FDC hypertension drugs would be more persistent and compliant than patients who were switched to FC medications. Our second hypothesis was that increased compliance would reduce the use of resources and expenditures for total hypertension-related health care as a result of improved management of hypertension.

METHODS

A retrospective cohort study was conducted to compare:

- persistence and compliance with an antihypertensive regimen for patients switching from FDC therapy to FC therapy, consisting of the same compounds, versus patients continuing to take FDC medications.
- hypertension-related utilization of health care resources and expenditures for both cohorts.

All study data were obtained from the Thomson Medstat MarketScan database, which was compliant with HIPAA regulations and contained medical and pharmacy insurance claims obtained from more than 100 health insurance payers.

Sample Selection

We evaluated patients who switched from three FDCs: an ARB/HCTZ, an ACE-inhibitor/HCTZ, and an ACE-inhibitor/calcium-channel blocker. To be eligible for enrollment, members of the sample:

- had to have filled prescriptions for an FDC medication for three or more months before the date on which they switched to the FC regimen (the study index date).
- were required to have an index date on or after January 1, 2004.
- had to have had medical and pharmacy coverage for 12 months before the index date and for 12 or more months after the index date.
- had to have a diagnosis of hypertension within 12 months before the index date, according to the International Classification of Diseases-9 (ICD-9-CM 401.XX–404.XX).
- had to have initial prescriptions for each compound of the FC regimen with fill dates within 15 days of each other to identify the switch to the FC regimen.
- had to have two or more prescriptions for each compound after the index date.

Comparable cohorts of patients not switching from FDC medications were identified separately for each of the three combinations according to a propensity-matching algorithm.[42,43] The nearest-neighbor method was used to match FDC patients to FC patients, in a 1:1 ratio, according to:

- age (younger than 45, 45 to 64, and 65 years and older).
- sex.
- payer type (Medicare or commercial insurance).
- medical comorbidities and risk factors identified from claims diagnoses in the six months prior to the index (i.e., diabetes, tobacco use, time from a prior acute MI, prior heart failure, chronic obstructive pulmonary disease, and lipid disorder).

For each FC patient, the FDC patient with the closest match in propensity score was selected and was assigned an index date so that the duration of FDC therapy prior to the assigned index date matched the length of FDC therapy prior to the index date of the FC match. Like the FC cohort, the selected FDC patients had to have medical and pharmacy coverage 12 months before the index date and 12 months after the index date.

Measurement of Outcomes

Using pharmacy claims data, we measured medication persistence by the percentage of patients continuing therapy without a lapse in therapy of more than 30 days from the date of end of supply of the prior prescription during the 12-month follow-up period after the study index date. Thus, FDC patients were classified as "not persistent" after a lapse of more than 30 days without a supply of their FDC medication available.

For example, a patient in the FDC cohort with prescriptions for 30-day supplies of the medication, with each one to be filled on the dates of January 1, 2004, February 15, 2004, March 31, 2004, and none thereafter, would no longer be "persistent" as of April 30, 2004. FC patients were classified as "not persistent" if they had a lapse of more than 30 days without a supply of both medications available each day. Days on which only one drug was available were considered to represent a lapse in therapy.

As an example of persistence within the FC cohort, a patient was taking an ARB plus HCTZ. The patient had prescriptions

for 30-day supplies for each prescription fill and then filled the ARB prescriptions on January 1, 2004, February 15, 2004, and March 31, 2004. The patient then filled the HCTZ prescriptions on January 1, 2004, February 15, 2004, March 31, 2004, and April 30, 2004 with no further refills. Such a patient was defined as being "no longer persistent" as of April 30, 2004—the day on which both drugs were not available to the patient.

Medication compliance was measured by the *medication–possession ratio* (MPR) for the one-year follow-up period:

MPR = (days supply of the medication filled during one year) divided by 365 × 100.

For patients in the FC cohort, both medications had to be available to the patient on the same day for that day to be included in the numerator of the medication–possession ratio. A drug was considered to be available to the patient on all calendar days from the fill date to end of day's supply for the prescription fill (e.g., from January 1 through January 30 for a prescription filled on January 1 with a 30-day supply). Thus, for the FC cohort, all calendar days on which both drugs were available to patients were identified and included in the numerator of the medication–possession ratio.

During the 12-month follow-up period, we identified hypertension-related health care services received in a hospital, an emergency department, and physician office settings from medical claims with a primary diagnosis code for hypertension (ICD-9-CM 401.XX–404.XX). For each of the three service settings, we measured hypertension-related utilization of resources as the percentage of patients receiving hypertension-related health care in that setting.

Using total reimbursements from claims data, we created two hypertension-related health care expenditure variables: (1) total health care expenditures over the 12-month follow-up period for services with a primary diagnosis of hypertension, and (2) total expenditures for hypertension-related services and medications (i.e., study drugs and all other hypertension-related agents).

Statistical Methods

We used *chi*-square tests for proportions and *t*-tests for means to compare descriptive statistics of outcomes for the FDC and FC cohorts. We estimated the FDC–FC differences in compliance using generalized linear models with the log–link function and gamma distribution,[44,45] and we estimated differences in persistence for FDC and FC using logistic regression. All models included patient demographics, medical comorbidities, and risk factors as control variables.

We used multivariate logistic regression models to estimate the effect of improved compliance on the risk of hospitalization, emergency admissions, and physician office use for hypertension-related services, and we used generalized linear models to estimate the effect of improved compliance on expenditures for hypertension-related services and medications.

The log–link function and gamma distribution were used for the generalized linear models to address the skewed distribution of the expenditure data.[44,45] The utilization and expenditure models controlled for the patient's study cohort, demographics, health care expenditures (measured six months prior to the index date), and medical comorbidities and risk factors (measured six months prior to the index date).

To estimate the difference between the FDC and FC cohorts in annual hypertension-related costs associated with the difference in compliance for the cohorts, we computed the product of (1) the percentage point difference in compliance for FDC and FC cohorts estimated in the generalized linear model of compliance, and (2) the change in hypertension-related costs for each percentage point change in compliance estimated in the generalized linear model of hypertension-related expenditures. We also computed similar estimates for the annual risks of hypertension-related hospitalization, emergency admissions, or physician-office visits.

Outcomes were analyzed separately for Medicare beneficiaries, commercially insured patients ("commercial"), and the two groups combined ("total"). Statistical software (Stata and SAS) was used to conduct all analyses.

RESULTS

A total of 14,449 patients taking either antihypertensive FDC or FC agents within the same drug classes were enrolled (Table 1, page 660). The sample included 1,216 patients switching from an FDC of an ARB/HCTZ; 1,331 patients switching from an FDC of an ACE-inhibitor/HCTZ; and 4,678 patients switching from an FDC of an ACE-inhibitor/calcium-channel blocker and their respective matched controls (N = 7,224), who continued with their corresponding FDC medications.

Overall, the treatment groups were closely matched between FC and FDC cohorts for all demographic variables and risk factors. This method verified that the propensity score-matching algorithm was successful in selecting cohorts that were balanced on these characteristics.

Of the two cohorts, 8,217 patients were commercially insured and 6,232 patients had Medicare coverage. Mean patient age was 62.06 years (standard deviation [SD] ± 12.67) for the FDC cohort and 62.86 years (SD ± 13.10) for the FC cohort. Women were similarly represented in 56.9% of both cohorts. Prevalence rates for comorbid conditions and risk factors were well matched across the two groups but were relatively low in the overall study population based on the six-month time frame assessed.

Persistence

Persistence with therapy declined more rapidly over time for patients who switched from the FDC to the FC regimen. The FDC–FC difference in persistence was greater for Medicare patients than for commercially patients (Table 2, page 661).

At the end of the 12 months of follow-up, persistence rates for FDC and FC were 58.3% and 14.9%, respectively ($P < 0.001$) for the total sample; 56.2% and 15.2%; for commercial coverage; and 61.2% and 14.4% for Medicare coverage ($P < 0.001$ for all contrasts) (see Table 2 for unadjusted rates).

Multivariate regression-adjusted differences in persistence for FDC, compared with FC regimens, were 42.5% for the total sample, 40.4% for commercial patients, and 45.2% for Medicare patients ($P < 0.001$ for all contrasts) (see Table 2 for regression-adjusted differences).

Compliance

Patients who continued taking the FDC regimen also had significantly higher rates of compliance, compared with those

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Table I **Demographics and Comorbidities for Patients Receiving Fixed-Dose Combination (FDC) and Free-Combination (FC) Antihypertensive Medications**

	FC: Commercial (n = 4,109)		FDC: Commercial (n = 4,108)		FC: Medicare (n = 3,116)		FDC: Medicare (n = 3,116)		FC: Total (n = 7,225)		FDC: Total (n = 7,224)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	53.32	(7.39)	52.88	(7.35)	75.44	(6.88)	74.16	(6.60)	62.86	(13.10)	62.06	(12.67)
Months on FDC prior to index date	8.45	(5.73)	8.59	(5.81)	8.47	(5.74)	8.67	(5.62)	8.46	(5.73)	8.63	(5.79)
Sex	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Female	2,117	51.52%	2,117	51.53%	1,997	64.09%	1,993	63.96%	4,114	56.94%	4,110	56.89%
Male	1,992	48.48%	1,991	48.47%	1,119	35.91%	1,123	36.04%	3,111	43.06%	3,114	43.11%
Presence of risk factors (measured six months prior to index date)*												
Congestive heart failure	9	0.22%	13	0.32%	39	1.25%	49	1.57%	48	0.66%	62	0.86%
COPD	11	0.27%	11	0.27%	31	0.99%	32	1.03%	42	0.58%	43	0.60%
Diabetes	171	4.16%	170	4.14%	108	3.47%	105	3.37%	279	3.86%	275	3.81%
Lipid disorder	101	2.46%	101	2.46%	42	1.35%	43	1.38%	143	1.98%	144	1.99%
Myocardial infarction	18	0.44%	14	0.34%	20	0.64%	9	0.29%	38	0.53%	23	0.32%
Tobacco use	1	0.02%	1	0.02%	1	0.03%	2	0.06%	2	0.03%	3	0.04%

* Risk factors were measured in the six-month interval prior to index date using ICD-9-CM diagnoses codes from claims data.
COPD = chronic obstructive pulmonary disease; SD = standard deviation.

patients who were switched to FC therapy. The FDC–FC difference was slightly greater for the Medicare patients than for the commercial group (see Table 2). For the total sample, compliance rates were 76.9% for FDC and 54.4% for FC; for commercial coverage, 74.9% for FDC and 55.4% for FC; and for Medicare coverage, 79.4% for FDC and 52.9% for FC ($P < 0.001$ for all contrasts) (see Table 2 for unadjusted rates).

Regression-adjusted differences in compliance for FDC, compared with FC, were 22.1% for the total sample, 19.3% for commercial patients, and 25% for Medicare patients ($P < 0.001$ for all contrasts) (see Table 2 for regression-adjusted differences).

Health Care Utilization and Costs

Unadjusted utilization and expenditures for hypertension-related health care were higher for the FC cohorts, although some differences between Medicare cohorts were not significant (Table 3). The percentages of patients receiving health care services for a primary diagnosis of hypertension in the total sample were as follows: for inpatient services, 3.11% with FC and 2.45% with FDC ($P = 0.016$); for emergency department visits, 1.72% with FC and 0.82% with FDC ($P = 0.001$); and for office visits, 65.81% with FC and 59.39% with FDC ($P = 0.001$).

The percentage of patients using hypertension-related services was also higher for FC in the commercial and Medicare samples; however, the difference in rates for inpatient services was not significant in the Medicare sample (see Table 3).

Unadjusted hypertension-related expenditures in the total sample were $657 for FC and $469 for FDC ($P = 0.012$) for hypertension-related services and $1,424 for FC and $1,139 for FDC ($P = 0.001$) for total hypertension-related health care (services and medications).

Unadjusted hypertension-related expenditures were also significantly higher for FC patients than for FDC patients in the commercial sample, but they were not significantly higher in the Medicare sample (see Table 3).

Impact of Compliance on Health Care Costs

Regression-adjusted estimates of the relationship between medication compliance and utilization and expenditures for hypertension-related health care show decreased usage as compliance increased (Table 4). All differences between FDC and FC regimens were statistically significant except for the percentage of Medicare patients making a hypertension-related office visit.

The results imply that the higher compliance rates for FDC were associated with lower utilization of and expenditures for hypertension-related services for FDC patients. For instance, in the total sample, each 10-percentage point increase in the compliance rate was associated with a 0.3% reduction in the number of commercially insured patients hospitalized for hypertension (see Table 4) or a 0.03% reduction for each percentage point increase in compliance. Because compliance for

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Table 2 Persistence and Compliance over the 12-Month Study Period with Fixed-Dose Combination (FDC) and Free-Combination (FC) Regimens

	Unadjusted Rates									Regression-Adjusted Differences: FDC vs. FC§†		
	Total Sample			Commercial			Medicare					
	FDC	FC	FDC–FC†	FDC	FC	FDC–FC†	FDC	FC	FDC–FC†	Total	Commercial	Medicare
Persistence at month 12*	58.3%	14.9%	43.4%	56.2%	15.2%	41.0%	61.2%	14.4%	46.8%	42.5% (40.6%–44.5%)¶	40.4% (37.8%–43.0%)	45.2% (42.2%–48.2%)
Compliance at month 12‡	76.9%	54.4%	22.5%	74.9%	55.4%	19.5%	79.4%	52.9%	26.5%	22.1% (19.9%–24.1)	19.3% (16.5%–22.0%)	25.0% (21.5%–28.1%)

* Patient must remain on therapy through the month to be considered persistent at that month. Patients are classified as non-persistent if they have a lapse in therapy more than 30 days from the date of the last available day of medication supply from one prescription to the refill date for the next prescription.

† *P* values less than 0.001 for the FDC–FC difference in rates.

‡ Compliance is measured by the medication–possession ratio (MPR), the percent of the study follow-up period (365 days) for which the patient has a supply of the medication (MPR = [days supply] divided by 365 x100). Days supply is obtained from prescription drug claims data.

§ Regression-adjusted differences were derived from marginal effects of generalized linear models, controlling for cohort, age, sex, comorbidities, and health care expenditures six months prior to index date.

¶ Numbers in parentheses are 95% confidence intervals.

Table 3 Unadjusted Hypertension-Related Health Care Utilization and Costs for Patients Receiving Fixed-Dose Combination (FDC) and Free-Combination (FC) Antihypertensive Medications

	Total			Commercial			Medicare		
	FC n =7,225	FDC n = 7,224	P Value	FC n = 4,109	FDC n = 4,108	P Value*	FC n = 3,116	FDC n = 3,116	P Value
Percent with hypertension-related inpatient service	3.11%	2.45%	0.016	2.14%	1.36%	0.007	4.40%	3.88%	0.303
Percent with hypertension-related emergency department visit	1.72%	0.82%	0.001	1.48%	0.80%	0.004	2.02%	0.83%	0.001
Percent with hypertension-related office visit	65.81%	59.39%	0.001	65.54%	58.01%	0.001	66.17%	61.20%	0.001
Hypertension-related expenditures for services	$657.18 ($4,976.36)†	$468.94 ($4,013.98)	0.012	$625.44 ($5,202.00)	$331.80 ($3,229.74)	0.002	$699.03 ($4,662.63)	$649.74 ($4,852.80)	0.683
Hypertension-related expenditures for services and prescriptions	$1,423.99 ($5,040.68)	$1,138.91 ($4,062.68)	0.001	$1,343.64 ($5,268.22)	$949.62 ($3,282.15)	0.001	$1,529.95 ($4,722.64)	$1,388.47 ($4,894.86)	0.246

* *P* values are for *chi*-square tests on FC–FDC differences in percent using a service and for *t*-tests on FC–FDC differences in mean expenditures.

† Standard deviations for expenditures are in parentheses.

the total number of FDC patients was 22.1 percentage points higher than the total number of FC patients (see Table 2 for regression-adjusted differences), the estimated percentage of total FDC patients hospitalized for hypertension was 0.44% less than the percentage for the total number of FC patients (i.e., –0.03% × 22.1% = –0.66%). This figure represents a 21.3% reduction in the number of FDC patients hospitalized for hypertension, compared with FC patients (based on the 3.11% of the total number of FC patients hospitalized).

When we used the same methodology, the higher compliance for total FDC patients was associated with a 25.7% annual reduction in the number of patients needing emergency visits for hypertension and a 1.3% annual reduction in the number of patients making physician visits for hypertension, compared with the total for FC. Similarly, higher compliance for total FDC patients was associated with a $133 reduction (20%) in annual expenditures for hypertension-related services, and a $73 reduction (5%) in total hypertension-related health care (services and medications). Commercial and Medicare patients experienced similar patterns of lower utilization and expenditures, as reported previously, for the total patient sample except for Medicare office visits.

Table 4 **Effect of Higher Increase in Compliance on Hypertension-Related Utilization and Costs***

	Effect of a 10-Percentage Point Increase in Compliance (Medication–Possession Ratio)					
	Total		*Commercial*		*Medicare*	
Utilization and Expenditures	*Effect*	*P Value*	*Effect*	*P Value*	*Effect*	*P Value*
Percent with hypertension-related inpatient service	–0.3% (–0.4%, –0.2%)†	0.001	–0.2% (–0.4%, –0.2%)	0.001	–0.3% (–0.5%, –0.2%)	0.001
Percent with hypertension-related emergency department visit	–0.2% (–0.2%, –0.1%)	0.001	–0.2% (–0.3%, –0.1%)	0.001	–0.1% (–0.2%, 0.0%)	0.004
Percent with hypertension-related office visit	–0.4 (–0.7%, –0.1%)%	0.003	–0.6% (–1%, –0.2%)	0.001	–0.2% (–0.6%, 0.2%)	0.337
Total hypertension-related expenditures (services only)	–$60 (–$64, –$58)	0.001	–$53 (–$56, –$50)	0.001	–$70 (–$75, –$65)	0.001
Total hypertension-related expenditures (services and prescriptions)	–$33 (–$40, –$26)	0.001	–$25 (–$33, –$17)	0.001	–$48 (–$61, –$36)	0.001

* Effect size derived from marginal effects of generalized linear models, controlling for cohort, age, sex, comorbidities, and health care expenditures six months prior to the index date.

† Numbers in parentheses are 95% confidence intervals.

DISCUSSION

Persistence and compliance were significantly higher for patients continuing with fixed-dose combination (FDC) therapy, compared with patients who switched from FDC therapy to free-combination (FC) therapy. This finding supports the hypothesis that simplifying antihypertensive drug regimens may improve persistence and compliance. The results are consistent with a meta-analysis by Bangalore et al., which showed a reduction of 24% in noncompliance when FDC regimens were prescribed instead of FC for treating hypertension.[19] Simplifying medication regimens is particularly important, because most patients need more than one antihypertensive agent to reach their BP goal.[2,6–10]

Patients' use of and expenses for hypertension-related services decreased as medication compliance increased. Total expenditures for hypertension-related services and medications also decreased as compliance increased, suggesting that the reductions in expenditures for hypertension-related services were greater than the increased medication expenditures associated with higher compliance.

Uncontrolled BP significantly increases the risk of adverse cardiovascular outcomes such as MI, stroke, and mortality.[37] Previous studies have demonstrated that improved compliance with antihypertensive medications is associated with improved BP control[21–24] and lower health care costs.[25,27,28,34,37] Our results showed higher compliance with FDC medications and reduced utilization and costs, attributed to improved compliance; these findings suggest that FDC regimens, when compared with FC regimens, are likely to produce positive health benefits through better control of hypertension and positive economic benefits through lower utilization and expenditures for hypertension-related health care.

Notable are the estimated reductions for FDC, compared with FC, of 21.3% in hypertension-related hospitalizations, 20.2% in expenditures for hypertension-related services, and 5.1% in expenditures for hypertension-related services and medications combined. The relative economic benefits of FDC regimens are likely to extend beyond hypertension-related health care, because improved BP control reduces the incidence and severity of other costly diagnoses such as congestive heart failure, stroke, and renal disease.[1,46,47] Thus, estimated reductions in the use of health care resources and costs derived from this study may be conservative estimates of potential impact of FDC regimens on total health care utilization and costs over time.

Our findings and the growing volume of published literature suggest that clinical and formulary design decisions should focus on the complexity of drug regimens and their potential impact on persistence and compliance behaviors of patients, in addition to the costs of medications. Changes based solely on medication costs can have deleterious effects on compliance and patient outcomes.

STUDY LIMITATIONS

The study was limited in several ways. The severity of hypertension could not be assessed and treatment cohorts were nonrandomized groups, thus limiting the internal validity of the study. Persistence and compliance were also measured from medication refill patterns observed within pharmacy claims data and were not based on observations of patients taking their medications. Because most patients incur an out-of-pocket cost for refilling a medication with a copayment and with a time-cost for filling the prescription, purchases are more likely to correspond with actual use, making medication fill rates an accepted measure of persistence and compliance.[48–52]

Our study did not measure the overall complexity of patients' drug regimens, the presumed reason for lower compliance and persistence in the FC cohort. Thus, we did not

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estimate the direct effect of regimen complexity on compliance and persistence in this study.

At least one study[53] has shown that switching from one statin to another can result in lower compliance and persistence without added complexity in the regimen. However, persistence for patients who switch at 12 months was only 5.9% less than that for non-switchers, a figure that is far less than the 43.4% lower persistence for switchers found in our study. Furthermore, the Thibaud study offered no reasons for the observed differences between switchers and non-switchers.

Although propensity-score matching was used to select FDC and FC samples of patients who were similar on observed factors, patients who switched from FDC to FC may differ from patients who stayed with the FDC regimen in characteristics that were unobserved and that may correlate with compliance. For example, if a change in health insurance coverage prompted the switch from FDC to FC therapy, then changes in plan benefit design, such as prescription copayment rates, could also influence the observed rate of prescription refills and, therefore, persistence and compliance.

Finally, reasons for a patient's switch from FDC to FC regimens were not available for further stratification.

CONCLUSION

Patients who continued with fixed-dose combination (FDC) antihypertensive therapies showed higher rates of compliance and persistence and had lower utilization and expenditures for hypertension-related health care, compared with patients who switched from FDC to free-combination (FC) therapy. Higher compliance and persistence are likely to produce positive health benefits through better control of hypertension and positive economic benefits through lower expenditures for hypertension-related health care. The possible benefits of FDC therapy should be considered in clinical and formulary decisions on antihypertensive medications.

* For original article with references please visit:
https://rb.gy/yg8mox

ORIGINAL RESEARCH

Treatment of Hypertensive Patients with a Fixed-Dose Combination of Bisoprolol and Amlodipine: Results of a Cohort study with More Than 10,000 Patients

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ABSTRACT

Introduction: Many patients need more than one antihypertensive agent for effective blood pressure (BP) control. Prescription of a fixed-dose combination (FDC) of bisoprolol and amlodipine in one tablet has been shown to significantly improve patient adherence. This non-interventional study investigated the effects on adherence and BP control of switching from a free-dose combination of the two antihypertensive substances to a FDC in a larger patient population.

Methods: Patients aged ≥18 years with essential hypertension were switched at least 4 weeks prior to study initiation from a free-dose combination of bisoprolol and amlodipine to the FDC. Dosage adjustment was implemented only if medically indicated. Adherence was assessed on the basis of the ratio of pills used to pills dispensed (%) at each visit (pill count). BP and key laboratory values were determined at baseline, 3 and 6 months.

Results: 10,532 patients (average age 59 years; 48% female) were recruited between 2013 and 2014; 22% of patients had type 2 diabetes and 38% had cardiovascular disease. The mean doses of the freely combined drugs prior to switching were 5.5 mg bisoprolol and 6.1 mg amlodipine once daily. The mean daily doses prescribed in the FDC were 5.8 and 6.4 mg, respectively. Pill counts at 6 months revealed a good to excellent adherence in >95% of the patients. Comparison of BP at baseline and at 6 months showed substantial changes (mean systolic BP: 147.3 vs. 130.9 mmHg; mean diastolic BP: 87.9 vs. 79.1 mmHg). Clinically relevant improvement in systolic BP was established for 82% of patients. In patients with comorbidities, switching to FDC produced a substantial improvement in BP. A total of 89 (0.7%) adverse events (AEs) were reported, including edema, headache, dizziness,

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bradycardia, nausea, and skin reactions. Only three AEs were classified as serious.

Conclusion: These data from a non-interventional study in a large patient population demonstrate the benefits of prescribing a FDC of bisoprolol–amlodipine in terms of an excellent adherence and an associated improvement in control of previously elevated BP, which may be relevant in real-life practice.

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Keywords: Adherence; Amlodipine; Bisoprolol; Blood pressure control; Fixed-dose combination

INTRODUCTION

For a number of medical research questions, the results produced by the "gold standard" of clinical research—randomized, double-blind, controlled trials (RCTs) of drugs or medical applications—are limited in the evidence they provide regarding potential applications and effects, risks, and patient adherence in a routine medical setting [1, 2]. Without diminishing the importance and necessity of RCTs in documenting the efficacy and safety of medicinal products, there is a consensus that additional data are required from studies in patients whose diagnosis, treatment, and monitoring exclusively follow normal medical practice [3], while the patients involved benefit from the increased therapeutic freedom versus participation in a RCT.

Carefully planned, conducted, and evaluated non-interventional studies may be particularly useful in drawing conclusions regarding the effects, safety, and—in some cases—acceptance of therapeutic procedures, medicinal products, or medical devices, based on immediate observation of a wide range of individual circumstances and not on findings in a specific selection of clinical trial patients chosen to meet strictly defined criteria. In a non-interventional study, the medical procedures carried out have the sole purpose of providing the best possible care for the individual patient. Non-interventional studies include a varied range of patients with and without comorbidities and do not dictate additional interventions or instructions beyond the treatment concept based on the needs of the patients concerned. Regulatory authorities in many countries now require non-interventional studies—in most cases following the approval of a new drug—and study design guidelines are now available [4].

Systematic analysis of data from RCTs versus non-interventional studies has shown virtually no evidence of superiority of RCTs in terms of assessing the effects of medicinal products [5]. This conclusion applies regardless of the specific design, study population criteria, and data acquisition periods.

Non-interventional studies are conducted in various designs. One such format is a cohort study, in which participants undergo specific medical care and their outcome is monitored and evaluated at certain times [1, 6, 7]. A prerequisite is that the expected effects in real-life conditions are largely similar to those investigated in RCTs and that the investigating sites are qualified to use the investigational material. This helps to minimize the dropout rate. Non-interventional studies of this kind generally involve large sample sizes and may therefore help to identify rare adverse events (AEs).

Event rates in non-interventional studies may also indicate effects and/or risks attributable to certain factors that do not feature in RCTs because of the strict exclusion

criteria. Non-interventional studies, for instance, enable adherence to a new medication or formulation to be analyzed in real life and correlated with treatment response or other parameters. These data may be important if the success of a prescribed long-term therapy very much depends on adherence with the regimen, e.g., in the treatment of patients with hypertension. Hypertension is one of the most common conditions seen in primary care. Untreated, it is associated with a high risk of myocardial infarction, stroke, renal failure, and premature death [8, 9]. There is an abundance of evidence showing that blood pressure (BP) should be below 150/90 mmHg in patients aged ≥60 years. The corresponding level for younger patients and people with diabetes or renal failure is 140/90 mmHg [10].

Clinical trial results show that a very large proportion of patients receiving antihypertensive treatment from primary care physicians do not achieve these recommended BP levels [11, 12]. Many patients require more than one antihypertensive drug for successful BP control [13, 14] in a regimen encompassing different pharmacologic mechanisms of action. A combination of a beta-blocker such as bisoprolol with a calcium channel blocker such as amlodipine is an established option for successful drug treatment of patients with high BP [15]. It is also cited repeatedly in international guidelines [10]. However, prescribing this free-drug treatment regimen presents an adherence challenge for patients, which may considerably jeopardize the desired treatment response [16]. Hence, it seemed justified to develop and investigate a fixed-dose combination (FDC) of the two active substances in all potentially administered dosage regimens (bisoprolol plus amlodipine: 5 + 5 mg, 10 + 5 mg, 5 + 10 mg, 10 + 10 mg). These FDCs were tested in various clinical trials [17–19] and produced a significant reduction in previously elevated BP at the respective dose levels employed. The FDCs also achieved better results than regimens based on a free-dose combination of the two agents.

To produce additional evidence for these FDCs, an extensive non-interventional study was conducted involving two chronologically separate periods. The first part of the study was evaluated after 4288 patients had been enrolled and treated for 6 months [20]. Monitoring of the percentage of tablets taken at 6 months revealed a very high rate of good to excellent adherence (>95%). At the same time, a clinically relevant decline in previously elevated BP was noted (systolic 15%, diastolic 11%), although most patients had been receiving the same doses of bisoprolol and amlodipine in a free combination.

To further verify the accuracy of these results, the study was continued at the same sites, and a number of new sites were added to include results for around 10,000 patients. This enabled data from the first study period to be checked against the data for the whole of this non-interventional study.

METHODS

The plan for this non-interventional study proposed individualized antihypertensive treatment in terms of procedures, dosages, follow-up, and final assessment with four different regimens of the active substances bisoprolol and amlodipine in a FDC: 5 mg bisoprolol plus 5 mg amlodipine, 5 mg bisoprolol plus 10 mg amlodipine, 10 mg bisoprolol plus 5 mg amlodipine, and 10 mg bisoprolol plus 10 mg amlodipine. No

additional measures departing from routine care in this patient population were proposed. Investigating sites were at liberty to choose any necessary medical interventions or additional drugs as they saw fit.

Patients aged ≥18 years with essential hypertension were recruited if they had already been switched from a free combination of bisoprolol 5–10 mg/day and amlodipine 5–10 mg/day to the FDC at least 4 weeks prior to recruitment. Reliable contraception was mandatory in women of childbearing age. Exclusion criteria included pregnancy, lactation, any contraindication to the FDC according to the local label, and any other antihypertensive medication.

The primary endpoint was patient adherence under the FDC measured by tablet count (tablets taken/tablets prescribed × 100) and defined as follows: excellent >90%, good 76–90%, moderate 51–75%, and bad ≤50%. BP was measured in a supine position after at least 5 min rest. All other patient data, clinical findings, and laboratory values were recorded upon availability at study start, after 3 months (voluntary), and after 6 months into case record forms (CRFs). Upon completion of the study, all the entries from the CRFs were transferred to an assessment table (BIAS: Biometric Analysis of Samples, Hanns Ackermann, Frankfurt, Germany).

Access to patient data was restricted exclusively to the investigators. All patients were assigned an ID number before the study to enable anonymous documentation for evaluation purposes. Patients were informed about these data protection measures at the start of the study and asked to sign a consent form to participate in accordance with the conditions described. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

For data analysis, calculation of means with standard deviations, medians with quartiles and Spearman's correlation analyses, Mantel–Haenszel test for contingency tables, and Cohen's D for effect size were used.

RESULTS

This multicenter non-interventional study included 10,532 patients who were treated in 68 Polish centers. The demographic data of the patients are summarized in Table 1. The mean age was 59 years, with a broad range from 19 to 99 years. There was almost no correlation between BP values and patient age. As shown by the median body mass index (BMI), most of the patients were overweight. Dependence of BP values on BMI could not be determined. A large proportion of patients had concomitant cardiovascular diseases ($N = 4011$, 38.1%) or type 2 diabetes ($N = 2313$, 22%). Angina pectoris (12.3%) and arrhythmia (11.1%) were the most frequent concomitant cardiovascular diseases.

Prior to the switch to the FDC, all patients had been pretreated with a free combination of bisoprolol (mean 5.5 mg once daily) and amlodipine (mean 6.1 mg once daily). The lowest possible dose (5 mg bisoprolol and 5 mg amlodipine once daily) was prescribed for the majority of patients (75%); data in Table 1 show that most patients did not reach the target value for systolic BP below 140 mmHg. The average dose in the FDC after switching from the free dose was 5.8 ± 2 mg bisoprolol and 6.4 ± 3 mg amlodipine once daily. In this respect, the switch to the FDC was only associated with

Table 1 Demographic data

Parameter	*N* (%)
Participants	10,532
Female	5050 (47.9)
Male	5435 (52.1)
Diabetes type 2	2313 (22)
Cardiovascular comorbidities	4011 (38.1)
Liver disease	157 (1.5)
Kidney damage	347 (3.3)
Smoking status	
Non-smoker	4962 (47.1)
Smoker	2.690 (25.5)
Ex-smoker	2799 (26.6)
No data	81 (0.8)
Alcohol consumption	
None	3779 (35.9)
Not regularly (0–1× weekly)	5374 (51.1)
Regularly (2–7× weekly)	1295 (12.2)
No data	84 (0.8)

Parameter	Mean (±SD)	Median	Q1–Q3
Age (years)	59 (11)	59	52–67
Height (cm)	170.1 (17)	170	164–177
Weight (kg)	81.3 (15)	80	72–90
BMI (kg/m^2)	28.1 (4)	28	25.5–30
Systolic BP (mmHg)	147.3 (15)	148	139–160
Diastolic BP (mmHg)	88.6 (10)	90	80–95
Pulse (beats/minute)	76 (10)	76	68–82
Fasting glucose (mg/dL) ($N = 2429$)	99.1 (21)	96	88–105
Duration of hypertension (years	9.2 (5)	7	2.5–12
Duration of free combination treatment prior to switch (months)	19.5 (22)	14	7–24
Dosages (free combination) (mg/day)			
Bisoprolol	5.5 (2)	5	5–5
Amlodipine	6.1 (2)	5	5–5

BMI body mass index, *BP* blood pressure, *SD* standard deviation

minimal dose modification. Thus, when switching from the free to the FDC, no changes in bisoprolol or amlodipine doses were performed in 84% of patients. A correlation between the amount of the respective doses of bisoprolol and amlodipine on BP values before study entry could not be detected.

At the end of the study (Visit 3 after 6 months), data on patient adherence were available for 8830 (82.2%) patients (Table 2). Overall, 3710 patients attended Visit 2 after 3 months, as well as Visit 3 after 6 months. Adherence was stable between the second and the third visits; 80.3% of patients showed an equal share of tablet consumption in both controls. A comparison of the adherence ratings did not show any difference between male and female patients.

The analysis of data for BP control showed a clinically relevant regression of systolic and diastolic values, although no considerable dose changes were made during the study period (Table 3). BP was measured in a supine position after at least 5 min of rest. Figure 1 shows the proportion of patients with systolic BP changes after 6 months of FDC treatment. It is noteworthy that BP reductions were confirmed for all drug doses tested (Table 4).

Accordingly, remarkable differences can be registered regarding the proportions of patients per quartile between the values at study start and after 6 month if the subdivision of quartiles at study start is maintained (Fig. 2). The reductions in diastolic BP were very similar to the reductions in systolic BP shown in Fig. 2. There was a noticeable correlation between BP values prior to the study and the extent of their decline (r 0.8).

The importance of adherence for good BP control becomes particularly evident when comparing BP values as a function of patient's behavior. Although only 2% of patients showed moderate or poor adherence, their BP measurements were remarkably higher than those of patients with good to excellent adherence (Table 5). The benefits of adherence on BP control are confirmed by the improvement in pulse pressure by an average of 58.7 mmHG ± 13 (median 60) at study start versus 51.7 mmHg ± 11 (median 50) after 6 months of treatment. All patients were asked whether they would choose the free combination or the FDC; approximately 97% of patients preferred the FDC.

Although all patients had been treated with a free-dose combination of bisoprolol and amlodipine and switched to the FDC at least

Table 2 Patient adherence at Visit 3 (after 6 months)

Adherence (% of prescribed tablets taken)	*N* (%)
Excellent (>90%)	7562 (85.6)
Good (76–90%)	1098 (12.4)
Good to excellent (≥76%)	8660 (98.1)
Moderate (51–75%)	145 (1.7)
Bad (<50%)	25 (0.3)
Total	8830 (100.0)

Table 3 BP at study start and after 6 months

	Systolic BP (mmHg) *N* = 9435 Mean (±SD)	**Diastolic BP (mmHg)** *N* = 9585 Mean (±SD)
Visit 1 (Study start)	147.3 (15)	87.9 (10)
Visit 3 (after 6 months)	130.9 (10)	79.1 (7)
Difference before–after	16.6 (16)	9.5 (11)
	Systolic BP (mmHg) *N* = 9435 *N* (%)	**Diastolic BP (mmHg)** *N* = 9585 *N* (%)
Improvement	7754 (82.2)	7010 (73.2)
No change	884 (9.4)	1478 (15.4)
Worsening	797 (8.4)	1097 (11.4)

BP blood pressure, *SD* standard deviation

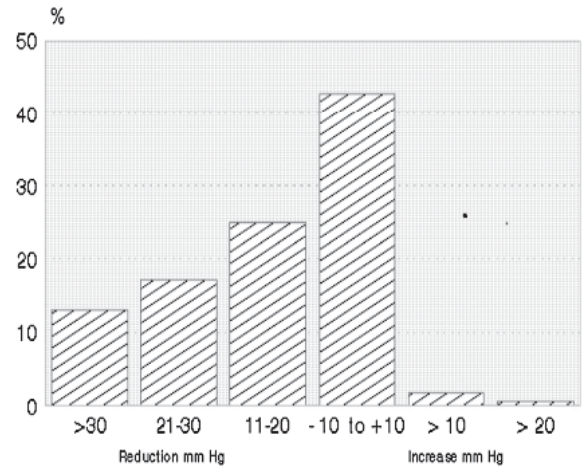

Fig. 1 Changes in systolic blood pressure as 6 months fixed-dose combination treatment. Proportion of patients (%) showing gradual changes

4 weeks before starting the study, BP measurement at study start showed differences in systolic readings, which were attributable to the respective comorbidities (Table 6). In contrast, patients who reported none of the listed comorbidities had a lower systolic BP (average 145 ± 10 mmHg).

After 6 months of treatment with the FDC of bisoprolol and amlodipine with no major dose changes, differences in systolic BP in relation to comorbidities were no longer evident (with diabetes 130.5 ± 10 mmHg, without diabetes 131.9 ± 10 mmHg; with cardiovascular diseases 130.4 ± 10 mmHg, without cardiovascular diseases 131.5 ± 10 mmHg; with renal diseases 130.9 ± 10 mmHg, without renal diseases 131.2 ± 11 mmHg).

Another improvement observed during the study was a considerable reduction in heart rate from an average of 75 ± 10 to 68.6 ± 10 bpm, which can also help to reduce the health risk for these patients.

Safety Evaluation

In total, 89 AEs were reported in 70 patients (0.7%). The majority of these were edema (41, 46.1%), headache (7, 7.8%), dizziness (6, 6.7%), and bradycardia, nausea, and skin burning/redness (4, 4.5% each). Only three AEs (3.4%) were considered serious, one case of atrial fibrillation (not related), one case of chronic heart failure worsening, and one head injury leading to death (not related). Just nine patients (0.09%) discontinued the study due to AEs, including lower limb or ankle swelling or other edema, nausea/malaise, skin burning/redness/

Table 4 Changes in systolic and diastolic BP after 6 months based on drug dose

	Reduction of systolic BP mmHg		Reduction of diastolic BP mmHg	
	Median	1–3 quartiles	Median	1–3 quartiles
Bisoprolol 5 mg–amlodipine 5 mg	15	5–25	10	0–15
Bisoprolol 10 mg–amlodipine 5 mg	15	6–25	10	0–20
Bisoprolol 5 mg–amlodipine 10 mg	15	7–28	10	0–20
Bisoprolol 10 mg–amlodipine 10 mg	20	6–30	10	0–20

BP blood pressure

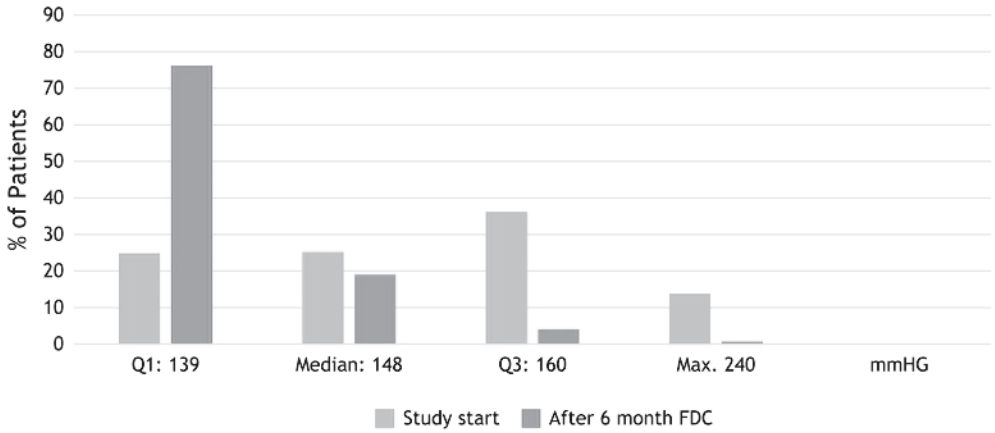

Fig. 2 Comparison of proportion of patients quartiles for systolic blood pressure values. *FDC* fixed-dose combination

flushing, congestive heart failure worsening/decompensation, dyspnea, or arrhythmia.

There were only a few laboratory values documented: fasting plasma glucose, HbA1C, serum creatinine, aspartate aminotransferase, and alanine aminotransferase. There were no noticeable changes in these parameters during the study.

DISCUSSION

Many patients with hypertension have other concomitant conditions, including lipid abnormalities, renal disease, diabetes, cardiovascular events, obesity, and/or smoking. The success of treating hypertension has been limited, and despite well-established approaches to diagnosis and treatment, fewer than half of all hypertensive patients have adequately controlled BP [21].

The most important goal of treatment is to manage hypertension and to deal with the other identified risk factors for cardiovascular disease. For hypertension, the treatment goal for systolic BP is usually <140 mmHg and for diastolic BP <90 mmHg. Most patients will require more than one drug to efficiently control their BP. The choice of drugs will be influenced by many different aspects and conditions (e.g., diabetes and coronary disease). Generally, there are many clinically proven recommendations for drug selection either for patients whose primary problem is hypertension, or for patients who have a major comorbidity associated with their hypertension.

Table 5 Correlation of BP after 6 months and adherence

Adherence *N* = 8830	Systolic BP (mmHg) Mean (± SD) Median Q1–Q3	Diastolic BP (mmHg) Mean (SD) Median Q1–Q3
Excellent (>90%)	130.5 (9)	79.1 (7)
	130	80
N = 7562	125–136	75–83
Good (76–90%)	132.2 (11)	79.4 (8)
N = 1098	130	80
	125–140	75–85
Moderate (51–75%)	137.1 (17)	76.7 (10)
	140	80
N = 145	120–150	70–85
Bad (<50%)	144.1 (17)	79.8 (9)
N = 25	140	80
	127–160	70–88

BP blood pressure

As regards calcium channel blockers, most experience with these agents has been gained with the dihydropyridines, such as amlodipine and nifedipine, which have shown beneficial effects on cardiovascular and stroke outcomes in hypertension trials [22]. Beta-blockers reduce cardiac output and decrease the release of renin from the kidney. They have strong clinical outcome benefits in patients with histories of myocardial infarction and heart failure and are effective in the management of angina pectoris [23, 24].

However, patients find having to take a large number of tablets burdensome [24]. This manifests itself in non-compliance with treatment as directed, or discontinuation of treatment [25]. Failure of hypertensive treatment is demonstrably attributable mainly to poor adherence to treatment on the part of patients [26]. European guidelines for the management of hypertension accordingly recommend treatment with a combination tablet [10] and the results of various studies indicate the clinical relevance of this recommendation [25, 27, 28].

The study results available to date demonstrate the relationship between successful BP management and patient adherence, in particular since the results from the first study period in more than 4000 patients corresponded fully to those generated in the total population of more than 10,000 patients [20].

The cohort recruited in this study can be considered as representative of real-life hypertension treatment. The study covered a wide range of ages: 23% of patients were aged <50 years and 15% were aged >70 years, thus, most patients were aged between 50 and 70 years. Good to excellent adherence was

Table 6 Dependence on systolic BP values and comorbidities prior to study entry

Comorbidity	Disease present		Disease absent	
	Systolic BP (mmHg)		Systolic BP (mmHg)	
	Mean (±SD)	Q1–median–Q3	Mean (±SD)	Q1–median–Q3
Diabetes	150.7 (16)	140–150–160	146.4 (±15)	135–145–158
Cardiovascular diseases	149.5 (16)	140–150–160	145.9 (±15)	135–145–160
Renal diseases	149.1 (17)	140–150–160	147.2 (15)	139–147–160

BP blood pressure

observed in more than 95% of patients, and approximately 86% of prescribed tablets were taken. It can be assumed that the investigators helped to convince patients through intensive discourse and that the consent of patients to take part in this study likewise contributed to this outcome. The consequence is a clinically important decline in previously elevated systolic BP in 82% of patients, and diastolic BP in 73% of patients; BP declined overall by 11 percentage points. A therapeutic goal has hence been met that is in line with international guidelines. Regardless of the doses prescribed in each case, similar reductions in BP were achieved. Patients with very high BP benefitted most from the use of the FDC.

Comparison of results of the preceding study with those of the overall group identified no differences in the changes in BP, which is an indication of rigorous and meticulous project conduct. The results do not contradict those obtained in investigational controlled trials [18, 19]. To that extent, the results of this non-interventional study tend to contradict the commonly postulated study design hierarchy and confirm the insights of other authors on this subject [29, 30].

Beyond that, this non-interventional study provides insights into additional factors in the lives of hypertension patients, in particular with regard to their comorbidities and treatment outcomes in these circumstances while receiving routine medical care. The absence of strict inclusion criteria, such as apply in RCTS, enables data to be collected from patients with a variety of comorbidities that may have a meaningful impact on their condition and may constitute additional risks.

The results of this study demonstrate that systematic adherence with treatment instructions contributes to a clinically relevant improvement in BP control in these patients too. The high acceptance of the FDC by the patient was also shown by the fact that 97% of patients preferred the FDC over the free combination at study end.

Not only BP, but also the pulse pressure and the heart rate as independent risk factors for cardiovascular disease were improved in the study. As far as the safety of treatment is concerned, no AEs or reactions outside the known profile for these active pharmaceutical ingredients occurred during the 6-month period.

The analysis of the study after 6 months was based on the data of 8830 patients, which represented a dropout rate of 17%. Experiences in implementing observational studies show that such a loss of data is quite common and inevitable, and is unlikely to influence the overall result of the study.

When evaluating the data from this study, we paid more attention to clinically relevant results than statistically calculated differences or correlations, because the high number of cases could lead to incorrect conclusions by assessing statistical results only. To that extent, the assessment of the results was more orientated to differences in the confidence intervals and the *C* values of the effect size taken.

CONCLUSION

These study results suggest that high adherence rates under a FDC of bisoprolol and amlodipine may lead to better BP control and, thus, to risk reduction for cardiovascular events. The implementation of an observational study with such a high number of patients provides a wide range of information for daily practice and enables us to draw conclusions about the

relationships between the drug's effect and additional factors.

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Compliance with Ethical Standards

Conflict of interest D. Czarnecka was the Principal Investigator and has given lectures for Merck KGaA. U. Hostalek is an employee of Merck KGaA, and E. M. W. Koch is a consultant to the company. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Compliance with ethics guidelines All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

* For original article with references please visit: https://rb.gy/ntitx2

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

A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter

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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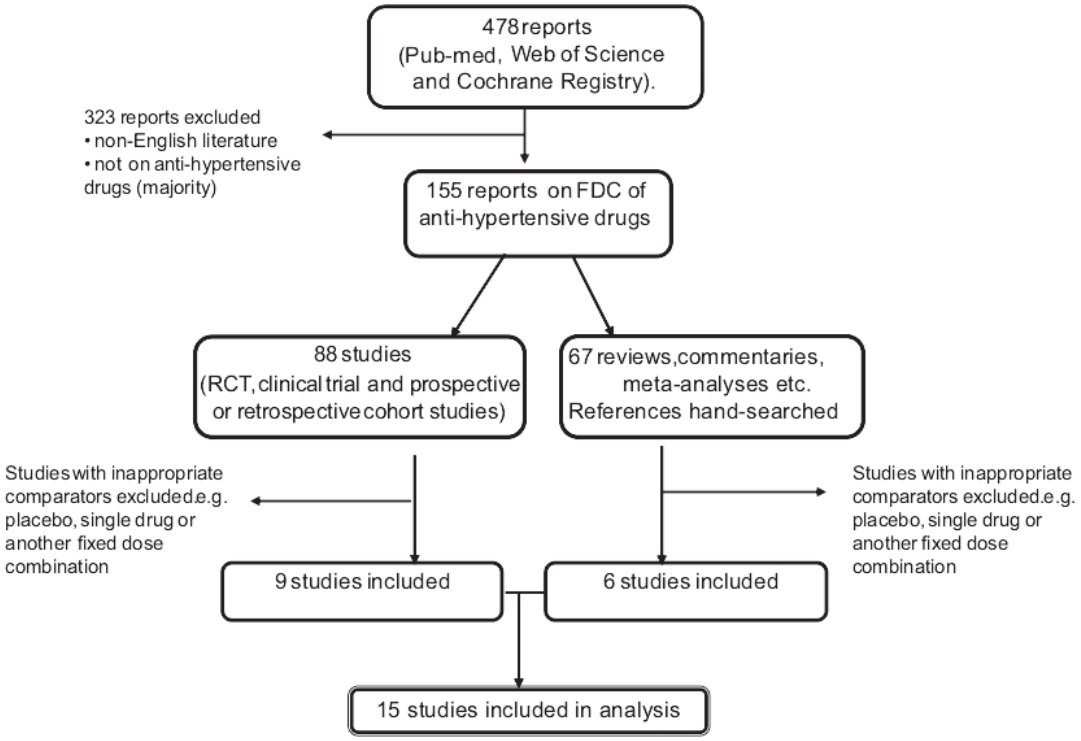

Figure 1. Selection of included studies. AHT indicates antihypertensive; RCT, randomized controlled trials.

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.

**The article from this abstract has been published subsequently in *Curr Med Res Opin*. 2008;24:2597–2607.

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.

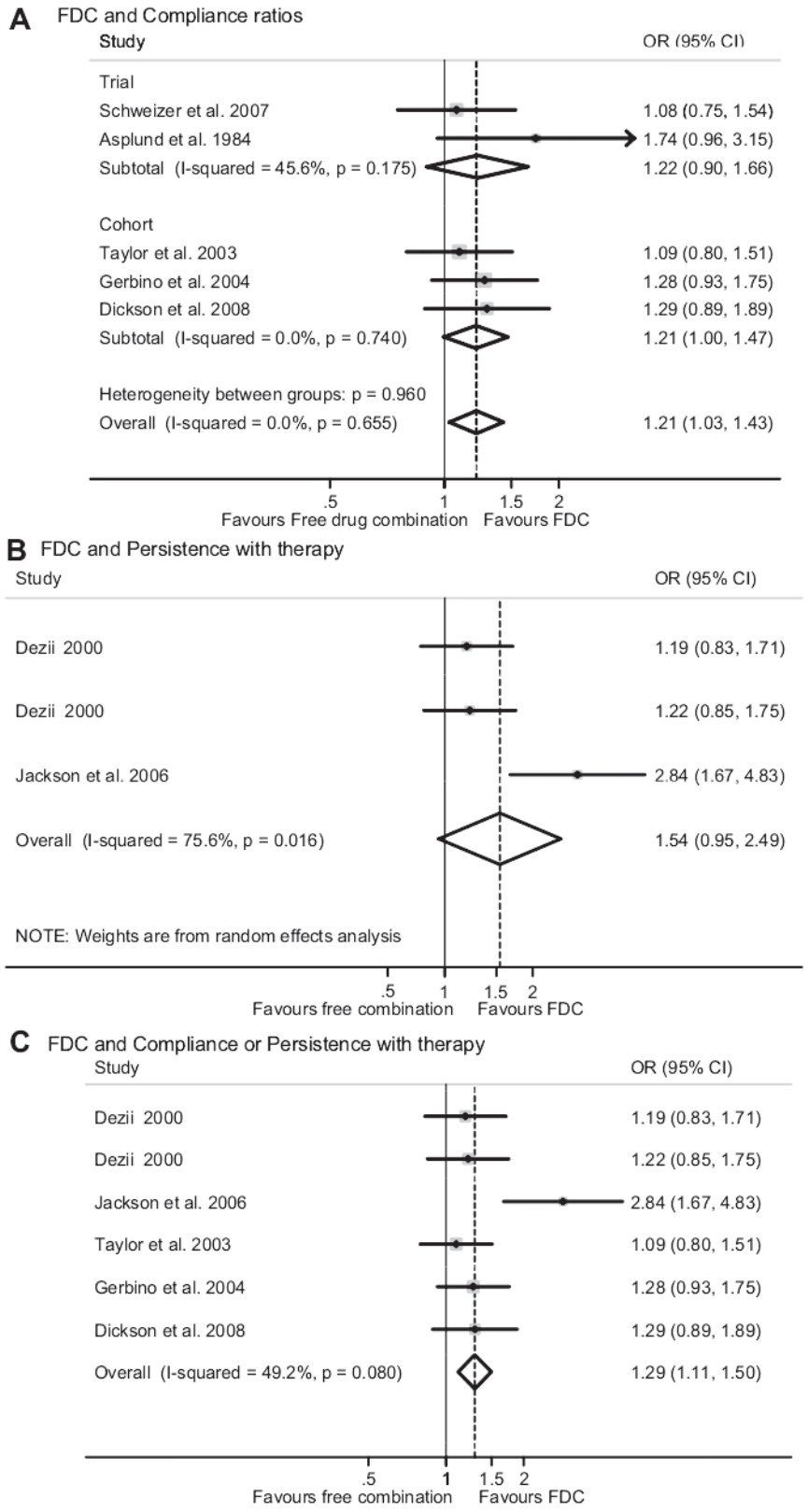

Figure 2. Compliance and persistence with therapy associated with the use of an FDC of 2 antihypertensive agents as compared with its corresponding free-drug combination. Fixed-effect model used where there is no evidence of heterogeneity (A and C).

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.

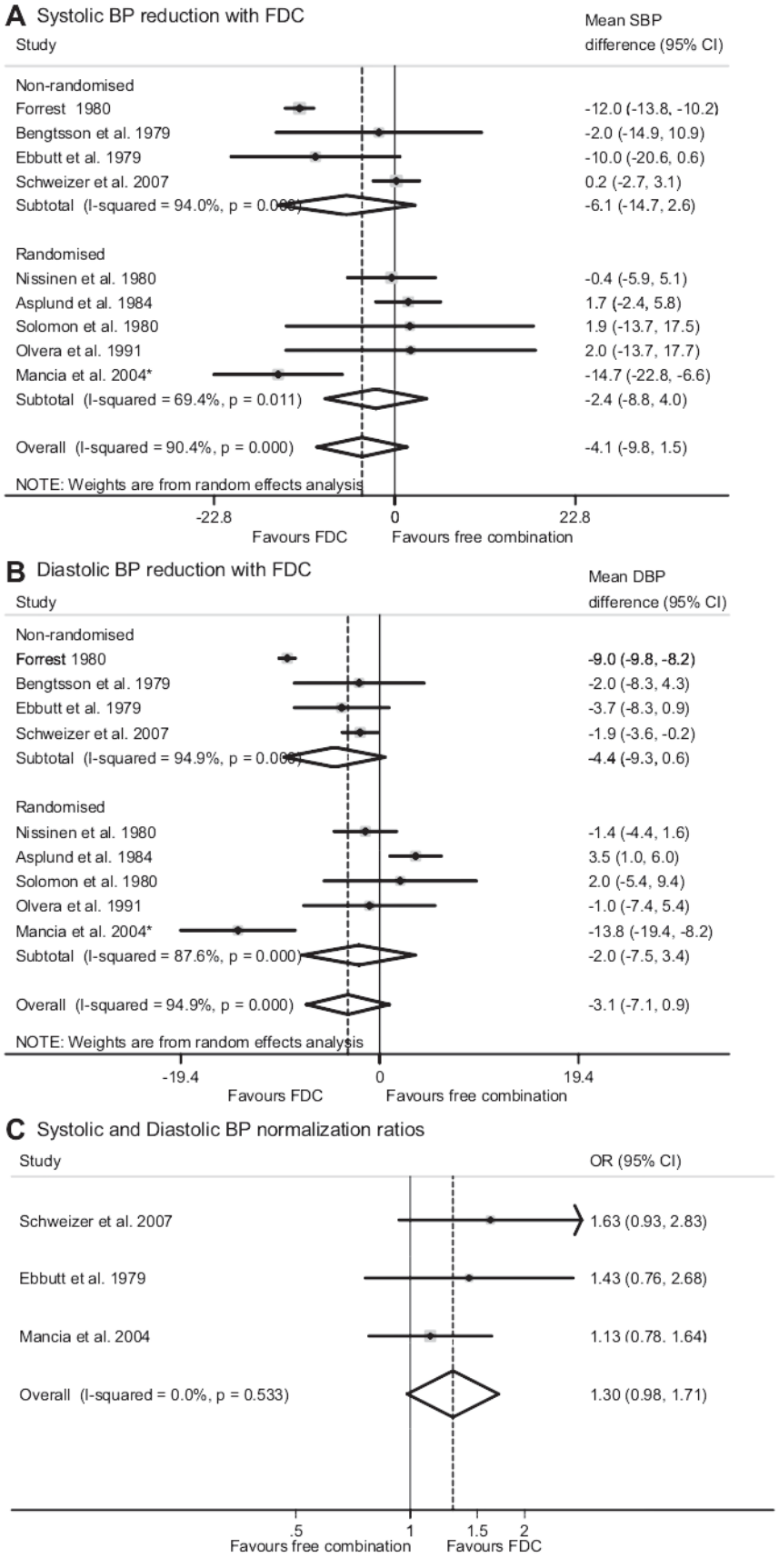

Figure 3. Systolic (A) and diastolic BP (B) reduction and BP normalization ratios (C) with use of an FDC as compared with its free-drug combination. Results were reported according to use of randomization in the included trials, because of the presence of heterogeneity. Random-effect model as used for 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.

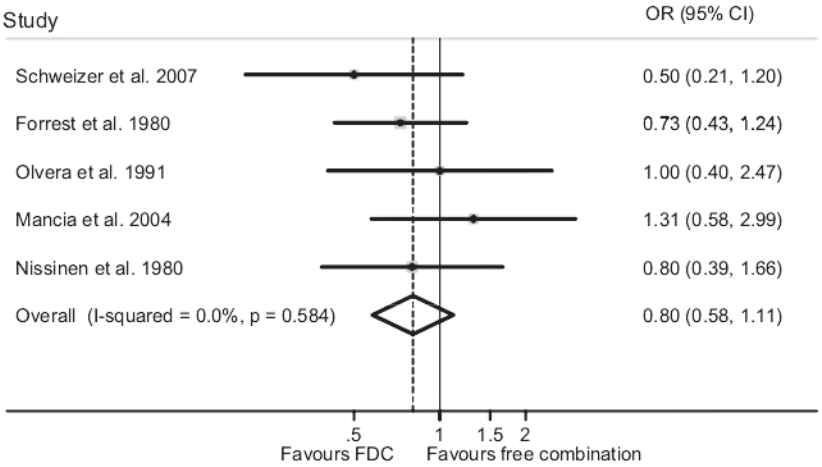

Figure 4. Adverse effects associated with the use of an FDC as compared with its free-drug combination. Fixed-effect model was used for the analysis, because there is no evidence of heterogeneity.

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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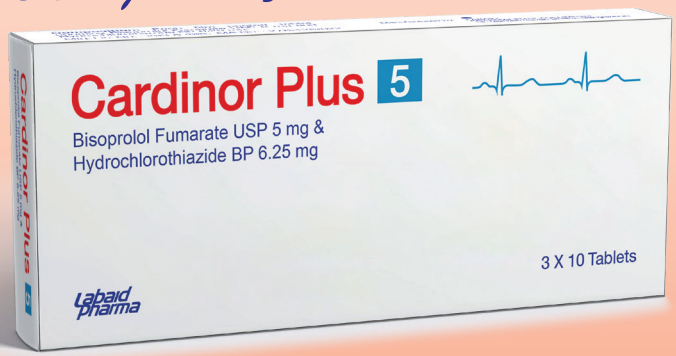

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