

Cardiovascular Protection by Initial and Subsequent Combination of Antihypertensive Drugs in Daily Life Practice

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See Editorial Commentary, pp 550–551

Abstract—Guidelines recommend a combination of 2 drugs to be used as first-step treatment strategy in high-risk hypertensive individuals to achieve timely blood pressure control and avoid early events. The evidence that this is associated with cardiovascular (CV) benefits compared with initial monotherapy is limited, however. The objective of this study was to assess whether, compared with antihypertensive monotherapy, a combination of antihypertensive drugs provides a greater CV protection in daily clinical practice. A population-based, nested case-control study was carried out by including the cohort of 209 650 patients from Lombardy (Italy) aged 40 to 79 years who were newly treated with antihypertensive drugs between 2000 and 2001. Cases were the 10 688 patients who experienced a hospitalization for CV disease from initial prescription until 2007. Three controls were randomly selected for each case. Logistic regression was used to model the CV risk associated with starting on and/or continuing with combination therapy. A Monte-Carlo sensitivity analysis was performed to account for unmeasured confounders. Patients starting on combination therapy had an 11% CV risk reduction with respect to those starting on monotherapy (95% CI: 5% to 16%). Compared with patients who maintained monotherapy also during follow-up, those who started on combination therapy and kept it along the entire period of observation had 26% reduction of CV risk (95% CI: 15% to 35%). In daily life practice, a combination of antihypertensive drugs is associated with a great reduction of CV risk. The indication for using combination of blood pressure drugs should be broadened. (*Hypertension*. 2011;58:566-572.)

Key Words: blood pressure-lowering agents ■ cardiovascular outcomes ■ combination therapy ■ monotherapy ■ record linkage

Guidelines on hypertension recommend the combination of 2 antihypertensive drugs as the initial treatment step in patients with severe hypertension or an otherwise high cardiovascular (CV) profile to control blood pressure (BP) more promptly than by initiating treatment with a single antihypertensive drug.^{1,2} However, this recommendation is largely based on the consideration that, because high-risk individuals may experience an event soon after treatment initiation, timely BP control is desirable. This is because evidence is substantially limited to the post hoc analysis of the Valsartan Antihypertensive Long-Term Use Evaluation Trial, which showed that, in hypertensive patients with a high CV risk, achieving BP control within 1 month of treatment was associated with less CV events than achieving BP control later.³ However, because they do not involve randomized

groups, post hoc comparisons are open to alternative explanations, particularly if, as in the Valsartan Antihypertensive Long-Term Use Evaluation Trial, data are not adjusted for differences in baseline clinical and demographic characteristics.

The present study reports data from a large, population-based, nested case-control study aimed at comparing the risk of CV events in patients starting BP-lowering therapy with a drug combination and those starting treatment with 1 drug and moving to combination treatment later. Strengths of the study are as follows: (1) information was derived from a large number of unselected patients who were prescribed BP-lowering drugs in the context of daily life practice; (2) data collection spread over several years, which guaranteed a large number of CV events; and (3) an approach based on sensi-

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tivity analysis was used to account for the effect of unmeasured confounders on the results.

Methods

Setting

The data used for the present study were retrieved from the health service databases of Lombardy, a region of Italy that accounts for ≈16% (9 million) of its population. In Italy, the population is covered by the National Health Service, and in Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information, including the following: (1) an archive of residents who receive National Health Service assistance (practically the whole resident population), reporting demographic and administrative data; (2) a database on diagnosis at discharge from public or private hospitals; and (3) a database on outpatient drug prescriptions reimbursable by the National Health Service. For each patient, we linked the above databases via a single identification code. To preserve privacy, each identification code was automatically converted to an anonymous code. The inverse process was prevented by deletion of the conversion table. Full details of the procedure have been reported elsewhere.⁴

Cohort Selection and Classification

The Lombardy residents aged between 40 and 79 years who were beneficiaries of the National Health Service represented the target population. According to the 2001 Italian Census, this population was composed of 4 341 438 individuals. Of these, those who were prescribed BP-lowering drugs from January 1, 2000, until December 31, 2001, were identified, and the first prescription was defined as the index prescription. The drugs considered belonged to all of the available BP-lowering drug classes, that is, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, calcium channel blockers, diuretics, antisympathetic agents (central agents and α -blockers), and β -blockers, dispensed either as monotherapy or as a fixed-dose or extemporaneous combination of ≥ 2 drugs.

To make the data as relevant as possible to the study aim, 4 categories of patients were excluded from data analysis. The first category includes patients who had received BP-lowering drug prescriptions within the 3 years before the index prescription to favor the inclusion of only newly treated individuals. The second category includes patients who had been hospitalized for CV disease or at whom drugs used for coronary heart disease or heart failure (eg, digitalis and nitrates) had been prescribed within the 3 years before the index prescription to focus results on primary CV prevention. The third category includes patients who did not reach ≥ 1 year of follow-up, to ensure ≥ 1 year of potential exposure at the treatments of interest. The final category includes patients who had received only 1 BP-lowering drug prescription during the first year after the date of index prescription, based on the assumption that, for these patients, continuous drug treatment might not be indicated.

Cohort members were classified according to initial BP-lowering treatment strategy, that is, whether 1 (monotherapy) or ≥ 2 BP-lowering agents (combination therapy) were dispensed at the index prescription. Follow-up information included persistence or change (switch from monotherapy to combination therapy or vice versa) in the BP-lowering treatment strategy, as well as prescription of lipid lowering, antidiabetic, or other CV drugs (including digitalis and nitrates). In addition, for each cohort member, the Charlson comorbidity index score was calculated⁵ using the diagnostic information available from inpatient charts in the 3 years before and 1 year after the index date. Each member of the cohort accumulated person-years of follow-up from the date of index prescription until the earliest among the dates of hospital admission for CV disease, death, emigration, or December 31, 2007.

Case Patients and Controls

Case patients were members of the cohort who, during follow-up, experienced ≥ 1 coronary or cerebrovascular event as diagnosed at discharge from hospital. The World Health Organization Multina-

tional Monitoring of Trends and Determinants in Cardiovascular Disease criteria were adopted to define coronary and cerebrovascular events.^{6,7} Based on the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease codes, coronary events included acute myocardial infarction, acute or subacute types of ischemic heart disease, and interventions of coronary revascularization. Cerebrovascular events included subarachnoid hemorrhage, intracerebral hemorrhage, unspecified intracranial hemorrhage, occlusion of cerebral arteries, acute cerebrovascular disease, and surgical interventions on intracranial or extracranial head or neck vessels. The earliest date of hospital admission for one of these events was considered as the event date.

For each case patient, 3 controls were randomly selected from the cohort to be matched for sex, age at cohort entry, and date of index prescription and were at risk for the outcome at the time when the matched case had the event.

Conventional Data Analysis

χ^2 test, or its version for the trend, was used where appropriate to test for differences, or trends, in the measured variables between cases and controls. Conditional logistic regression models⁸ were fitted to the case-control data with the aim to estimate the odds ratio, as well as its 95% CI, of CV outcome associated with treatment initiation with a single drug or the combination of ≥ 2 drugs. In either group, the risk of CV outcome was further related to the subsequent treatment strategy, that is, persistence on monotherapy or switch to combination treatment in patients on initial single drug therapy and persistence on combination treatment or switch to monotherapy in patients on initial treatment with ≥ 2 drugs. Adjustments were made for the type and number of BP-lowering drug classes prescribed initially or during follow-up and the concomitant use of drugs for the treatment of heart failure, coronary heart disease, diabetes mellitus, and other CV diseases.

Sensitivity Analysis

The robustness of our findings with regard to potential bias generated by unmeasured confounders was evaluated by the Monte-Carlo sensitivity analysis,⁹ also known as the external adjustment method. The Monte-Carlo sensitivity analysis quantifies the change in the association between 2 variables when adjustment is made for an unmeasured potential confounder, selected among those to which patients are exposed with an independent predicting ability for the study outcome. This requires information on the differences between the groups undergoing different treatment regimens, as well as on the strength of the association between potential confounders and outcome. The clinical characteristics of patients undergoing different treatment regimens were obtained from the Health Search/Cambridge Structural Database (HSD), which provided patient records from >700 general practitioners, as reported in detail previously.¹⁰ The cohort of HSD patients who started BP-lowering drug therapy from 2004 until 2007 was identified and selected as was done for the Lombardy cohort. In addition, patients were classified according to 3 pieces of clinical information that were not available from the Lombardy database, that is, severity of hypertension (mild, moderate, or severe), chronic disease score (0, 1, or 2 according to the coexistence of comorbidities, such as heart failure, peripheral artery disease, diabetes mellitus, dyslipidemia, and chronic kidney disease), and body mass index (<25, 25 to 30, or >30 kg/m²).

Concerning the strength of the confounder-outcome association, it was assumed that, on a logarithmic scale [$\ln(\text{RR})$], the relative risk (RR) increased linearly with the severity of hypertension, the chronic disease score, and body mass index, and, for each confounder, the $\ln(\text{RR})$ linear increase was 0.2, 0.4, or 0.8. In other words, we assumed that patients on the maximal level of any confounder (ie, those with severe hypertension, with 2 comorbidities, or with body mass index >30 kg/m²) had an increase of CV risk of [$\exp(0.2 \times 2)$]=1.5 (scenario 1), [$\exp(0.4 \times 2)$]=2.2 (scenario 2), or [$\exp(0.8 \times 2)$]=5.0 (scenario 3), with respect to patients on level 0 (ie, those with mild hypertension, without comorbidities, or with body mass index <25 kg/m²).

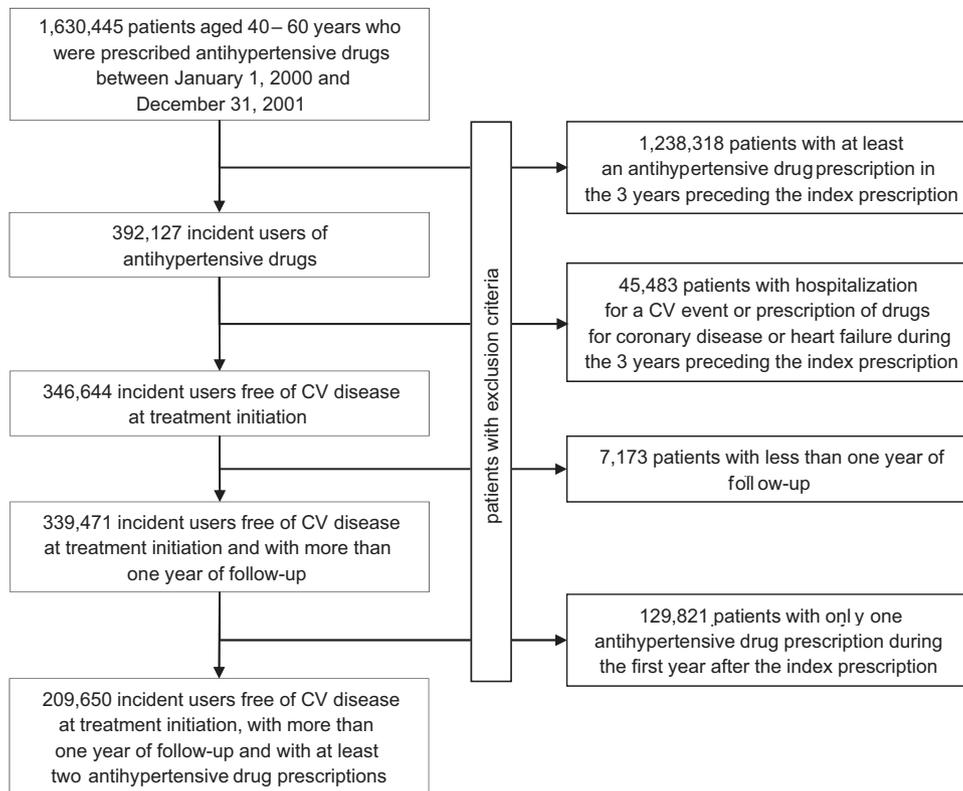


Figure 1. Flowchart of inclusion and exclusion criteria.

The Monte-Carlo sensitivity analysis consisted of correcting the observed odds ratio for the bias factor calculated from the above data, taking into account the random uncertainty of adjusted estimates through a specific sampling procedure. For this purpose, we generated 5000 sets of exposure, CV relative risks from a normal distribution with the mean equal to the $\ln(\text{RR})$ imposed from the above described scenarios, and variance of 0.04. Full details on the Monte-Carlo sampling procedure are reported elsewhere.¹¹

All of the analyses were performed using the SAS software (version 9.0, SAS Institute, Cary, NC). Statistical significance was set at the 0.05 level. All of the *P* values were 2 sided.

Results

Patients

The distribution of the exclusion criteria is shown in Figure 1. At entry, the 209 650 patients included into the cohort had a mean age of 59.9 years (SD: 10.2 years), 55.6% of them were women, and most by far of them started BP-lowering drug therapy with 1 agent only (82.1%). During follow-up, the cohort accumulated 1 244 870 person-years of observation (on average, ≈ 6 years per patient) and generated 10 688 hospital admissions either for coronary ($n=6077$) or cerebrovascular ($n=4611$) events, with a rate of 49 and 37 cases per 10 000 person-years, respectively.

The 10 688 patients who experienced hospitalization for CV outcomes (case patients) were matched to 32 064 controls. At the date of the index prescription, mean age of cases and controls was ≈ 64 years, and $\approx 36\%$ of them were women (matching variables). As shown in Table 1, monotherapy was by far the most common initial treatment ($>80\%$). During follow-up, most patients experienced both monotherapy and combination therapy and were exposed to >1 antihyperten-

sive drug class, whereas only a small number ($\approx 5\%$) kept combination therapy throughout the entire observation period. Cases and controls did not show a statistically significant difference in the initial BP-lowering treatment strategy. Compared with controls, case patients more frequently switched from monotherapy to combined therapy and vice versa, used more often antihypertensive drugs of different classes, and had a worse profile of cotreatments and comorbidities.

BP-Lowering Drug Therapies and CV Risk

As shown in Figure 2, compared with initial monotherapy, initial combination therapy was associated with a lower incidence of CV outcomes (-11%), this being the case also for coronary (-8%) and cerebrovascular (-12%) events considered separately. There was no evidence that coronary or cerebrovascular risk was differently affected by the initial BP-lowering treatment strategy ($P=0.12288$).

The combined effect of initial and subsequent BP-lowering drug therapy on CV risk is shown in Table 2. Patients who kept monotherapy throughout the entire period of observation and those who switched from monotherapy to combination therapy, or vice versa, did not show any appreciable difference in CV risk. In contrast, CV risk was significantly lower in patients starting on combination therapy and keeping it throughout the entire period of observation (-26%).

Sensitivity Analysis

At index date, the 41 199 patients included into the HSD cohort and the 209 650 patients included in the Lombardy cohort had similar characteristics, including their mean age,

Table 1. Therapeutic BP-Lowering Treatment Strategies and Cotreatments and Clinical (Charlson Comorbidity Index Score) Features in the 10 688 Case Patients Hospitalized for a Coronary or Cerebrovascular Event and the Corresponding 32 064 Controls Considered for the Nested, Case-Control Analysis

Therapeutic and Clinical Features	Case Patients, n (%)	Controls, n (%)	P*
Initial BP-lowering therapy			0.6272
Monotherapy	8693 (81.3)	26 011 (81.1)	
Combined therapy	1995 (18.7)	6053 (18.9)	
BP-lowering therapy during follow-up			<0.0001
Monotherapy only	3149 (29.5)	11 549 (36.0)	
Switching from monotherapy to combined therapy	5544 (51.9)	14 462 (45.1)	
Combined therapy only	486 (4.5)	2071 (6.5)	
Switching from combined to monotherapy	1509 (14.1)	3982 (12.4)	
No. of BP-lowering drug classes used during follow-up			<0.0001
1	2384 (22.3)	9255 (28.9)	
2	3233 (30.3)	10 371 (32.3)	
3	2730 (25.5)	7411 (23.1)	
≥4	2341 (21.9)	5027 (15.7)	
Concomitant use of other drugs			
Digitalis or nitrates	2184 (20.4)	2730 (8.5)	<0.0001
Lipid-lowering agents	3432 (32.1)	7445 (23.2)	<0.0001
Other cardiovascular drugs	2193 (20.5)	3889 (12.1)	<0.0001
Antidiabetic drugs	2389 (22.4)	4364 (13.6)	<0.0001
Charlson comorbidity index score			<0.0001
0	8650 (80.9)	27 838 (86.8)	
1	739 (6.9)	1857 (5.8)	
2	496 (4.6)	1058 (3.3)	
≥3	803 (7.5)	1311 (4.1)	

BP indicates blood pressure.

*Data are shown according to χ^2 test (antihypertensive therapy at entry and during follow-up; concomitant use of other drugs) or its version for the trend (No. of BP-lowering drug classes employed during follow-up, Charlson comorbidity index score).

respectively, at 60.8 years and 59.9 years; the proportion of women, at 55.2% and 55.6%; the prevalence of patients starting on combined therapy, at 18.3% and 17.9%; and concomitant use of antidiabetic agents, at 11.9% and 12.5% of patients.

Table 2. Combined Effect of the Initial and the Following BP-Lowering Treatment Strategies on the Risk of CV (Cerebrovascular and Coronary) Outcomes

Initial BP-Lowering Therapy	BP-Lowering Therapy During Follow-Up	OR*	95% CI*
Monotherapy	Monotherapy	1.00	Reference
	Combined therapy	1.00	0.91 to 1.10
Combined therapy	Monotherapy	0.96	0.86 to 1.07
	Combined therapy	0.74	0.65 to 0.85

CV indicates cardiovascular; BP, blood pressure; OR, odds ratio.

*Data were adjusted for age, No. of BP-lowering drug classes used during follow-up, and concomitant use of drugs for the treatment of heart failure, coronary heart disease, diabetes mellitus, and other CV diseases.

Table 3 shows the clinical characteristics of the HSD cohort according to the initial BP-lowering drug treatment strategy. Compared with patients starting on monotherapy, patients on combination therapy had a higher prevalence of severe hypertension, chronic disease score, and higher body mass index.

Figure 3 shows the CV relative risks of the Lombardy cohort associated with the initial treatment strategy after adjustment for hypertension severity, chronic disease score, and body mass index, as derived from the HSD cohort data. For each confounder, adjustment made the beneficial effect of combination therapy with respect to monotherapy more evident, the difference from the unadjusted benefit becoming progressively greater as the association confounder-outcome became steeper.

Discussion

Our study on a large cohort of patients followed for several years shows that initiating and maintaining treatment with a combination of >1 BP-lowering drug is accompanied by a lower incidence of CV events as compared with initiating treatment with a single drug or failing to maintain combination treatment after its initial adoption. It further shows that initial combination treatment is accompanied by a greater CV protective effect compared with that of starting treatment with 1 drug and moving to a drug combination later. It finally shows that the beneficial effects of combination treatment include prevention of both cerebrovascular and coronary events. This allows us to conclude that, compared with monotherapy, an antihypertensive treatment based on drug combination is associated with a more effective CV protection, which is also more effective if a drug combination is

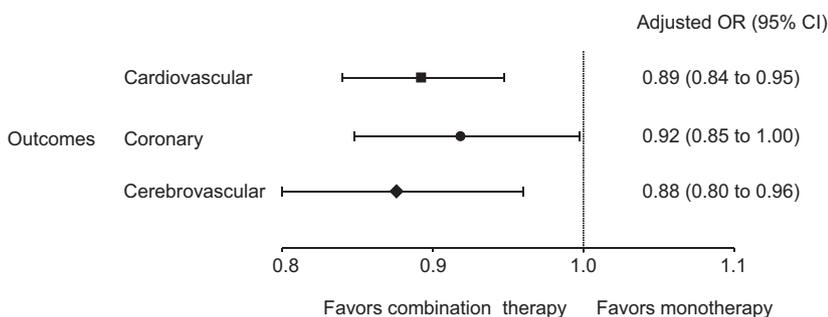


Figure 2. Forest plot comparing odds ratios (and corresponding 95% CIs) of nonfatal cardiovascular (CV) outcomes as a whole, coronary heart disease, or cerebrovascular events associated with an initial combination of blood pressure-lowering agents, with respect to initial monotherapy. Data show the estimates obtained by fitting a conditional logistic model and adjusted for the number of blood pressure-lowering drug classes used during follow-up and the concomitant use of drugs for the treatment of heart failure, coronary heart disease, diabetes mellitus, and other CV disease.

Table 3. Baseline Clinical Characteristics of the 41 199 Hypertensive Patients Classified According to Categories of Initial BP-Lowering Drug Therapy in the HSD Cohort

Clinical Characteristics	Initial BP-Lowering Drug Therapy, %	
	Monotherapy	Combined Therapy
Severity of hypertension*		
Mild	49.0	46.9
Moderate	39.1	36.7
Severe	11.9	17.3
Chronic disease score†		
0	62.5	56.1
1	30.9	36.5
≥2	6.6	7.5
Body mass index, kg/m ²		
<25	23.7	18.2
25 to 30	42.3	40.6
>30	34.0	41.2

BP indicates blood pressure.

*Mild hypertension includes systolic BP 140 to 159 and/or diastolic BP 90 to 99 mm Hg; moderate hypertension, 160 to 179/100 to 109 mm Hg; and severe hypertension, ≥180/≥110 mm Hg.

†Data show the No. of patients with 0, 1, or ≥2 concurrent diseases among the following: heart failure, peripheral artery disease, diabetes mellitus, dyslipidemia, and chronic kidney disease.

used initially rather than after ≥1 prescription of a single antihypertensive agent. Although the former result extends to a real-life context, the conclusions drawn by meta-analyses of clinical trials,¹² the latter represents new large-scale evidence in favor of using drug combinations as a first-step antihypertensive treatment strategy.^{1,2}

The database used in our study does not provide the information necessary to identify the factors responsible for the greater CV protective effect of combination treatment versus monotherapy. It seems reasonable to suggest, however, that ≥2 drugs may more effectively reduce CV events by summation of their individual direct (or BP-independent) protective properties¹³ and/or multidrug treatment may more markedly lower BP,^{1,2,14} because of its more extensive interference with the multifold mechanisms involved in BP control. The latter possibility is strongly supported by the results of a meta-analysis of a large number of trials showing that the incidence of CV events is linearly associated with the magnitude of the treatment-induced BP reduction, irrespective of the type of treatment used.¹⁵ It should be emphasized that the above 2 possibilities may also explain the superior CV protective effect of initial versus later combination treatment, if one considers that, in real life, it may take months to change from monotherapy to combination therapy. During this interval, the advantages of combination treatment (earlier BP control and possibly multidrug BP-independent protective properties^{16–22}) may result in a measurable reduction of CV events.

Several other results of our study deserve to be mentioned. First, in line with previous studies,^{10,23} our findings show that monotherapy is a far more commonly used strategy than

combination treatment. Considering its superiority, a more extensive use of the latter strategy seems an important goal to pursue in the future. Second, in addition to those mentioned in the introduction, another point of strength of our study is that drug prescription databases are characterized by a high degree of accuracy, because filing of prescriptions is necessary for the pharmacies to obtain reimbursement from the Public Health Care System, with, thus, frequent cross-checking and other control procedures.²⁴

Our study is not completely devoid of inaccuracies because of use of only nonfatal CV events, misclassification of patients by errors in coding, and prescriptions of BP-lowering drugs for conditions other than hypertension. However, none of these limitations appears to endanger the interpretation of our findings, because antihypertensive drug trials have shown that the benefit of antihypertensive treatment is directionally similar for nonfatal and fatal CV events,¹⁵ Lombardy hospital discharge and drug prescription databases show a close concordance either with population-based local registry of coronary and cerebrovascular events²⁵ and with data provided by a network of Italian general practitioners,¹⁰ and, in Italy, hypertension represents by far the most common reason for prescribing BP-lowering drugs.²⁶

Finally, because in our study allocation of antihypertensive therapy was not randomized, the results may be affected by confounding factors. That is, the reduction in CV risk associated with combination of BP-lowering drugs might rather reflect the patients' characteristics, such as severity of hypertension, comorbidities, other CV risk factors, and difference in income and educational level. At first sight, our study did not show any evidence that cases and controls differed in the initial BP-lowering treatment strategy (please see Table 1), that is, that the type of initial drug regimen was associated with the CV risk. However, because, as expected, cases showed a worse clinical profile than controls, assuming that combinations of BP-lowering drugs would be preferentially prescribed to patients with poor prognosis, under the null hypothesis (ie, absence of association between therapy at starting and CV risk) one would expect that case patients show a higher prevalence of combination therapy. This explains why the greater CV protection associated with combination treatment was seen when data were adjusted for the concomitant use of drugs for conditions characterized by a high risk, such as heart failure, coronary disease, hyperlipidemia, and diabetes mellitus. Furthermore, to take into account the difficulty in achieving BP control, we considered, as a proxy variable, the number of different classes of antihypertensive medications dispensed during follow-up.²⁷ It should be emphasized, however, that studies performed by record linkage of healthcare use databases such as ours, have a limited amount of clinical data so that, despite our in-depth effort to adjust for differences between the groups that were compared, we cannot completely exclude that sources of selective prescribing generated residual confounding by indication. For this reason, we also accounted for external data informative of the prescribing behavior of primary care physicians to address the possible extent of such indication confounding. In this way, we have shown that further adjustment for severity of hypertension, score for chronic

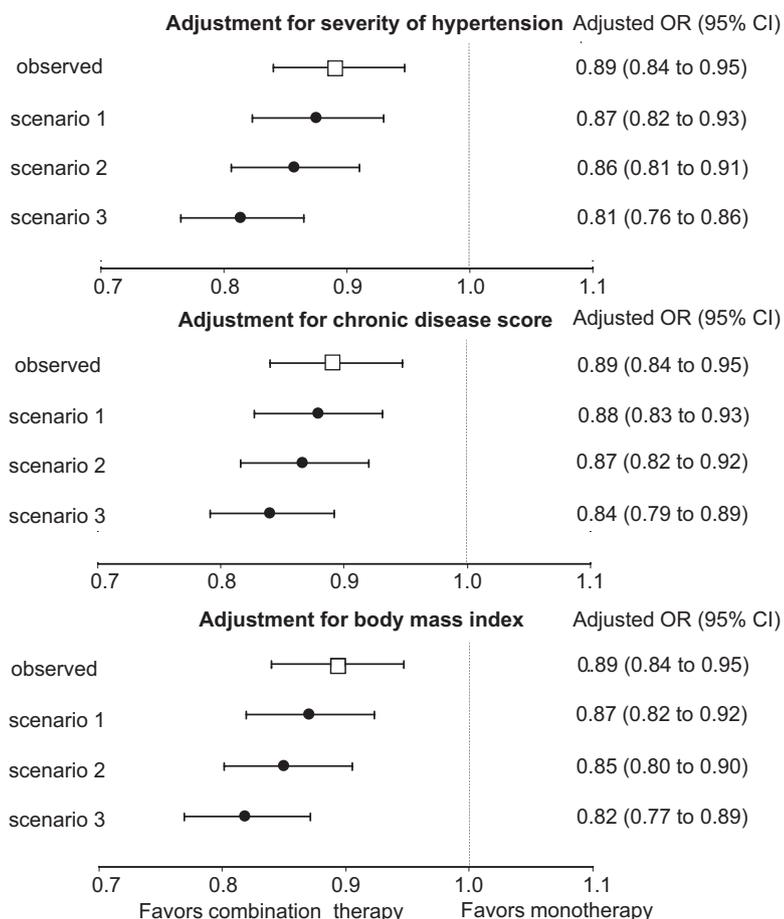


Figure 3. Forest plot comparing odds ratios (and corresponding 95% CIs) of nonfatal cardiovascular outcomes associated with initial combination of blood pressure-lowering agents, with respect to initial monotherapy, after adjustment for severity of hypertension (**top**), chronic disease score (**middle**), and body mass index (**bottom**) measured from the Health Search/Cambridge Structural Database (HSD). Adjustments were performed by means of Monte-Carlo sensitivity analysis taking into account differences in the severity of hypertension, chronic disease score, and body mass index between patients classified according to initial regimens of antihypertensive therapy (ie, monotherapy or combination therapy; see Table 3) and 3 scenarios imposing that $\ln(\text{RR})$ linearly increases with a increasing slopes across the categories of the confounder (see text).

disease, and body mass index enhanced the difference between monotherapy and combination therapy treatment, suggesting that our finding cannot be explained by the unlikely better clinical profile of patients who were treated with a combination of ≥ 2 drugs. It should, nevertheless, be emphasized that our analysis cannot remove the possibility that other undetected confounders played a role. For example, the greater reduction in CV risk among patients using drug combinations might be an artifact because of their preferential prescription to those patients at better socioeconomic status. However, we have reported recently from the Lombardy database that the chance of starting with a combination of 2 drugs, rather than with monotherapy, is substantially independent by patient income.²⁸

In summary, our data on real-world drug use offer evidence that antihypertensive therapy with a combination of drugs reduces the risk of CV outcomes with respect to treatment with 1 drug only. They also offer evidence that this is the case when combination treatment is used as first-step therapy compared with patients in whom it is used after initial monotherapy. Increasing use of initial and subsequent combination of antihypertensive drug may, thus, help in reducing the rate of CV events in the hypertensive population.

Perspectives

The current study offers evidence that a combination of antihypertensive drugs is associated with a greater reduction of CV risk than monotherapy. The indication for using

combination of blood pressure drugs should be broadened. Future studies should concern even open clinical questions, such as the generalizability of the observed benefits according to a patient's clinical features and physician's therapeutic choices, as well as public health implications, such as cost-effectiveness balance of increasing the use of antihypertensive drug combinations in daily life practice.

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Disclosures

None.

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