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CLINICAL RESEARCH
Prevention and epidemiology

Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension

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Aims Guidelines support use of drug combinations in most hypertensive patients, and recently treatment initiation with two drugs has been also recommended. However, limited evidence is available on whether this leads to greater cardiovascular (CV) protection compared to initial monotherapy.

Methods and results Using the healthcare utilization database of the Lombardy Region (Italy), the 44 534 residents of the region (age 40–80 years) who in 2010 started treatment with one antihypertensive drug ($n = 37\,078$) or a two-drug fixed-dose combination (FDC, $n = 7456$) were followed for 1 year after treatment initiation to compare the risk of hospitalization for CV disease associated with the two treatment strategies. To limit the confounding associated with non-randomized between-group comparisons, data were also analysed by: (i) matching the two groups by the high-dimensional propensity score (HDPS) and (ii) comparing, in patients experiencing one or more CV events ($n = 2212$), the CV event incidence during subperiods in which patients were prescribed mono- or FDC therapy (self-controlled case series design). Compared to initial monotherapy, patients on initial FDC therapy showed a reduced 1 year risk of hospitalization for any CV event (-21%, $P < 0.01$). This was the case also when groups were compared according to the HDPS analysis (-15%, $P < 0.05$). Finally, in patients experiencing CV events, the event incidence was much less when, during the 1 year follow-up, they were under FDC therapy than under monotherapy (-56%, $P < 0.01$). The reduced risk of hospitalization was always significant for ischaemic heart disease and new onset atrial fibrillation, and included hospitalization for cerebrovascular disease and heart failure when monotherapy and FDC therapy were compared within patients.

Conclusion In a real-life setting, a comparison of the incidence of early CV events during antihypertensive monotherapy and FDC shows that the latter strategy leads to a more effective CV protection. This scores in favour of a two-drug FDC strategy as first step in the hypertensive population.

Keywords Hypertension • Fixed-dose combinations • Healthcare utilization databases • Population-based cohort studies • Cardiovascular risk

Introduction

Uncontrolled hypertension is extremely common worldwide[1] and, based on epidemiological data, accounts for a huge number of yearly deaths and disability (18% or 9.4 million of premature deaths and 173 million disability-adjusted years) globally.[2] Several studies suggest that initiating treatment with two antihypertensive drugs may represent a more effective treatment strategy compared to the time-honoured conventional initial monotherapy.[3] For example, initial two-drug combinations lower blood pressure (BP) more promptly,[4–8] possibly with a more timely protective effect in patients at high or very high cardiovascular (CV) risk, in whom a CV event may occur within a

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short period.[9] Furthermore, treatment discontinuation is lower when treatment starts with two rather than one drug,[10] no matter which drug is used,[11] possibly because a more effective initial BP reduction increases patient's motivation to comply with the prescribed drug regimen.[12] Finally, and most importantly, initial combination treatment has been shown to be associated with a more frequent BP control up to 1 year or more after treatment initiation,[13] probably because, in addition to improving adherence, starting treatment with two drugs neutralizes therapeutic inertia, i.e. reluctance to move from monotherapy to more complex treatments even when BP is not controlled.[14,15]

Limited evidence exists on whether and to what extent the above advantages translate into a difference in CV outcomes,[16,17] i.e. a fundamental aspect for validation of two-drug combinations as a better 1st step treatment approach. This may not be ideally addressed by clinical trials because, although remaining the gold standard for obtaining medical evidence, trials minimize some of the reported advantages of initial combination treatment, e.g. higher adherence, lower therapeutic inertia, and lesser therapeutic errors etc., which are an important component of real-life medicine. We carried out an observational study to explore whether, compared to initial use of antihypertensive monotherapy, initial use of two antihypertensive drugs was associated with a reduced risk of CV outcomes during an early (1 year) treatment period. The study was conducted in a large real-life cohort of Italian patients who were not prescribed antihypertensive treatment in the previous years. To minimize the confounding effect of comparing two non-randomized groups, data were also analysed according to a high-dimensional propensity score (HDPS) and a self-controlled case series (SCCS) design,[18] the latter allowing comparison to be made within patients who during the year of follow-up experienced an event and were prescribed monotherapy in some subperiods and a two-drug combination therapy in others. Data analysis focused on two-drug fixed-dose combinations (FDCs) because in Italy FDCs are used much more frequently than free drug combinations to treat hypertension.[3]

Methods

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, a Region of Italy that accounts for about 16% (almost 10 million) of its population. The Italian population is covered by the National Health Service (NHS) and, in Lombardy, an automated system of databases has been created to collect a variety of information, including: (i) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data; (ii) a database on hospital discharge records, including information about primary diagnosis and up to five co-existing conditions and performed procedures, coded according to the 9th International Code of Diseases (ICD-9-CM); and (iii) a database providing information on all prescriptions reimbursed by the NHS, with drugs coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The use of a unique identification code allows linkage of all databases. In order to preserve privacy, each identification code is automatically converted into an anonymous code. Details on utilization of the Lombardy databases for pharmacoepidemiology in general,[19] and more specifically for the therapeutic area related to the present study, are reported elsewhere.[11,20,21] According to the rules from the Italian Medicines Agency (available at: http://www.agenziafarmaco.gov.it/sites/default/files/det_20marzo2008.pdf), retrospective studies using administrative databases do not require Ethics Committee protocol approval.

The ICD-9-CM and ATC codes used for hospital and antihypertensive drug information provided by the databases are reported in the Supplementary material online, *Table S1*.

Cohort selection

The target population consisted of all beneficiaries of the NHS resident in Lombardy aged 40–80 years. According to the 2011 Italian Census, this population amounted to 5 097 075 individuals. From these, we identified patients for whom at least one prescription of an antihypertensive agent was dispensed during 2010, and the first dispensation was defined as the index prescription. We excluded patients who (i) had received antihypertensive drug prescriptions within 10 years before the index prescription, to focus the study on newly treated patients[22]; (ii) started antihypertensive therapy with a free drug combination, because in Italy two-drug FDC combination is by far the most common type of initial combination treatment specifically used for hypertension[3]; (iii) did not reach at least 1 year of follow-up (the period of interest); and (iv) during the year of follow-up experienced one or more episodes of treatment discontinuation, i.e. spent 90 days or more without antihypertensive drug coverage, to avoid between-group discrepancy in a factor that majorly affects outcome[23]. The remaining patients were included into the final cohort (*Figure 1*).

Drug exposure

Cohort members were classified according to initial antihypertensive treatment strategy, i.e. whether monotherapy or two-drug FDC therapy was dispensed at the index prescription date. All the antihypertensive agents dispensed during the year after the index prescription date were identified and classified as belonging to the category of mono or FDC combination therapy. Fixed-dose combinations did not include ACE inhibitors or angiotensin receptor antagonists with calcium channel blockers because in 2010–2011 fixed-dose renin angiotensin system-calcium channel blocker combinations were not reimbursable by the NHS, and thus were not part of the database. The period covered by an individual prescription was calculated by dividing the total amount of the drug prescribed for the defined daily dose. For overlapping prescriptions, the patient was assumed to have used all the drugs contained in the first prescription before starting those contained in the second one. Because during hospitalizations information on drug therapies was not available, the exposure to antihypertensive drugs before hospital admission was assumed to continue for the entire duration of the hospital stay.[24] In this way, the entire sequence of subperiods of the follow-up during which each cohort member was under mono or FDC therapy was obtained. As described in detail in previous studies,[20,21] adherence to antihypertensive therapy was assessed as the cumulative days in which the drug was made available by prescription divided by the number of days of follow-up (i.e. 365 days or 1 year).

Additional information included cotreatments with CV drugs, cotreatments with non-CV drugs, comorbidities, and hospital admission for CV disease during the 10-year period before the index prescription. The Multisource Comorbidity Score,[25] was also calculated from the information based on the large set of data available in the healthcare utilization databases of Lombardy and other Italian regions. This score has been recently found to be more sensitive predictor of mortality than the Charlson comorbidity[26] and other scores.

Outcome identification

We identified cohort members who during the year after the index prescription date experienced one or more hospital admissions for which a CV event was a primary diagnosis. Hospitalization for ischaemic heart disease, cerebrovascular disease, heart failure and atrial fibrillation were

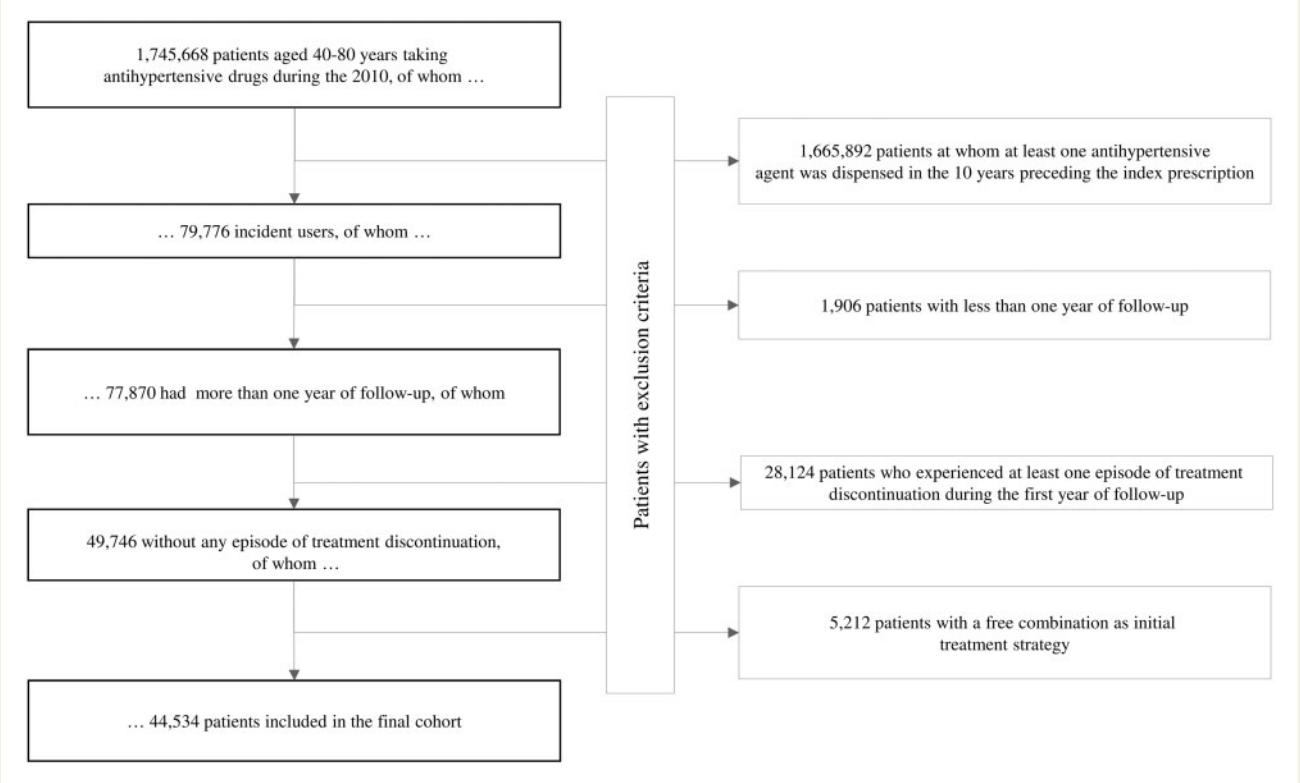

Figure 1 Flow-chart of inclusion and exclusion criteria that were used to select the final cohort.

separately analysed because of the close relationship of all three events with BP levels.[27–29] The WHO-MONICA criteria were adopted for defining ischaemic heart and cerebrovascular disease.[30,31]

Data analysis

Several statistical tests (χ^2, its version for the trend and *t*-test) were used, when appropriate, to test differences in demographic and clinical characteristics between patients starting on mono or combined antihypertensive drug therapy. Intention-to-treat principle and time-to-event techniques were used for comparing patients on mono- or combination therapy. The Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR), and its 95% confidence interval (CI), for patients with initially dispensed FDC therapy with respect to monotherapy. Calculations addressed individual and all CV events combined.

Comparing patients starting treatment with one or two antihypertensive drugs is open to the criticism that effects on outcome may depend on differences in initial demographic and clinical characteristics rather than on therapeutic differences. For this reason, adjustments were made for the aforementioned baseline covariates, including cotreatments with CV and non-CV drugs, comorbidities and CV diseases, type of treatment (e.g. use or no use of renin angiotensin system blockers), and the Multisource Comorbidity Score. Furthermore, because adjustments are an imperfect approach to elimination of baseline confounders, data were analysed according to the (i) matching of the two groups by the HDPS and (ii) the self-controlled series design, as described below.

High-dimensional propensity score

The HDPS[32] was calculated using the above-mentioned baseline covariates plus the covariates automatically selected from the archives of prescriptions and hospitalizations in the 2-year period before the date of the index prescription. The aim of HDPS algorithm is to empirically identify the variables strongly associated with the exposure and outcome. We decided to select the 200 most prevalent covariates, and for each patient in the initial combination treatment group, randomly selected one patient under initial monotherapy who was matched with that patient for the HDPS (±0.01). In this way, two groups similar for the pre-treatment risk of outcomes, based on a large number of variables, were formed.

Self-controlled case series design

The HDPS matching overcomes some limitations of the covariates adjustment approach, but it cannot remove the possible role played by unmeasured variables. In our setting, this was a relevant limitation because administrative databases suffer from lack of some crucial clinical information, such as BP values.[19] We address this confounding by using a special case-only (within-person) approach known as the self-controlled or SCCS design,[33] which, unlike the conventional between-person designs, offers the advantage of removing time-invariant confounders.[34,35] We selected cohort members who during the first year after the index prescription (i) experienced at least one CV outcome and (ii) used monotherapy in some subperiods and FDC therapy in others, in the SCCS subperiods. The incidence of CV outcomes during person-times on mono- or on combination therapy was calculated, and a conditional Poisson regression model was fitted for estimating the between subperiods incidence rate ratio (IRR), and the corresponding 95% CI.[36]

We further consider the possibility that, in the SCCS analysis, treatment exposure (monotherapy or FDC) and outcome occurred without a causal link. This would happen, for example, if patients experienced an outcome during the first months after treatment initiation, as a result of

Table 1 Demographic, clinical and therapeutic characteristics of subjects starting antihypertensive treatment with a single drug or with a fixed-dose two-drug combination

	Monotherapy ($n = 37\,078$)	Combination therapy ($n = 7456$)	*P*-value[a]
Age: mean (standard deviation)	59.1 (10.4)	59.2 (10.3)	0.34
Men	20 876 (56.3%)	3663 (49.1%)	<0.01
Cotreatments			
Digitalis or nitrates	446 (1.2%)	43 (0.6%)	<0.01
Antiarrhythmic agents	701 (1.9%)	73 (1.0%)	<0.01
Antiplatelet drugs	6127 (16.5%)	739 (9.9%)	<0.01
Oral anticoagulant agents	839 (2.3%)	66 (0.9%)	<0.01
Statins	4940 (13.3%)	747 (10.0%)	<0.01
Antidiabetic drugs	2880 (7.8%)	337 (4.5%)	<0.01
Drugs for respiratory disease	8382 (22.6%)	1623 (21.8%)	0.11
Antidepressant agents	4276 (11.5%)	802 (10.8%)	0.05
Multisource Comorbidity Score			
0	33 482 (90.3%)	7063 (94.7%)	<0.01
1	2111 (5.7%)	206 (2.8%)	
2	983 (2.7%)	131 (1.8%)	
3	225 (0.6%)	20 (0.3%)	
4	277 (0.7%)	36 (0.5%)	

[a]According to *t*-test (age), χ^2 (gender and cotreatments) or its version for the trend (categories of the Multisource Comorbidity Score).

Table 2 Hazard ratios (HR), and 95% confidence intervals (CI), estimating the effect of starting antihypertensive treatment with fixed-dose two-drug combinations with respect to monotherapy on the 1 year risk of CV outcomes

Outcome	Unadjusted event rate (*1000 PY)		HR[a] (95% CI)	*P*-value
	Monotherapy ($n = 37\,078$)	Combination therapy ($n = 7456$)		
Any CV event	87	52	0.79 (0.71–0.88)	<0.01
Ischaemic heart disease	32	13	0.61 (0.50–0.75)	<0.01
Cerebrovascular disease	12	9	0.95 (0.73–1.22)	0.67
Heart failure	6	4	0.82 (0.55–1.23)	0.34
Atrial fibrillation	12	5	0.63 (0.45–0.88)	<0.01

CV, cardiovascular; PY, person-year.
[a]Hazard ratios estimated according to Cox proportional hazard model. Estimates were adjusted for covariates listed in *Table 1*; the HR reduction in patients with initial combination treatment was significant for any CV event, ischaemic heart disease, and atrial fibrillation ($P < 0.01$).

which doctors changed treatment, either from monotherapy to FDC therapy or vice-versa. It would also happen if, in patients at high CV risk, an event occurred just after the index prescription. We tried to account for this source of bias by two types of analysis. First, the SCCS design was applied to early (first 6 months) and late (next 6 months) subperiods of the year of follow-up, the Mantel–Haenszel estimator being used as a common, subperiod adjusted, IRR. Second, we compared the IRR estimate obtained with the above-described SCC design with the IRR estimate obtained from a referent group. This was drawn by randomly selecting, for each patient included into the SCCS design, one patient from the cohort members who, during the year of follow-up, used both monotherapy and FDC therapy and did not experience a CV outcome. Case and referent patients were matched for gender, age at cohort entry, and date of index prescription. Referent patients were assumed to experience the outcome when the matched case suffered from it. In this way, a self-controlled referent series design was performed, to which the conditional Poisson regression model was again fitted for estimating the between periods reference rate ratio (IRR^r). Because referent subjects did not experience an event, IRR^r does not estimate the association between exposure and outcome but only the portion of IRR due to change in therapeutic strategy. By dividing IRR by IRR^r, an IRR adjusted for time-trend was obtained.

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA) was used for the analyses. For all hypotheses tested, two-tailed *P*-values less than 0.05 or, in an equivalent manner, 95% CI of HR or IRR which does not contain the value expected under the null hypothesis (i.e. the value 1), was considered to be significant.

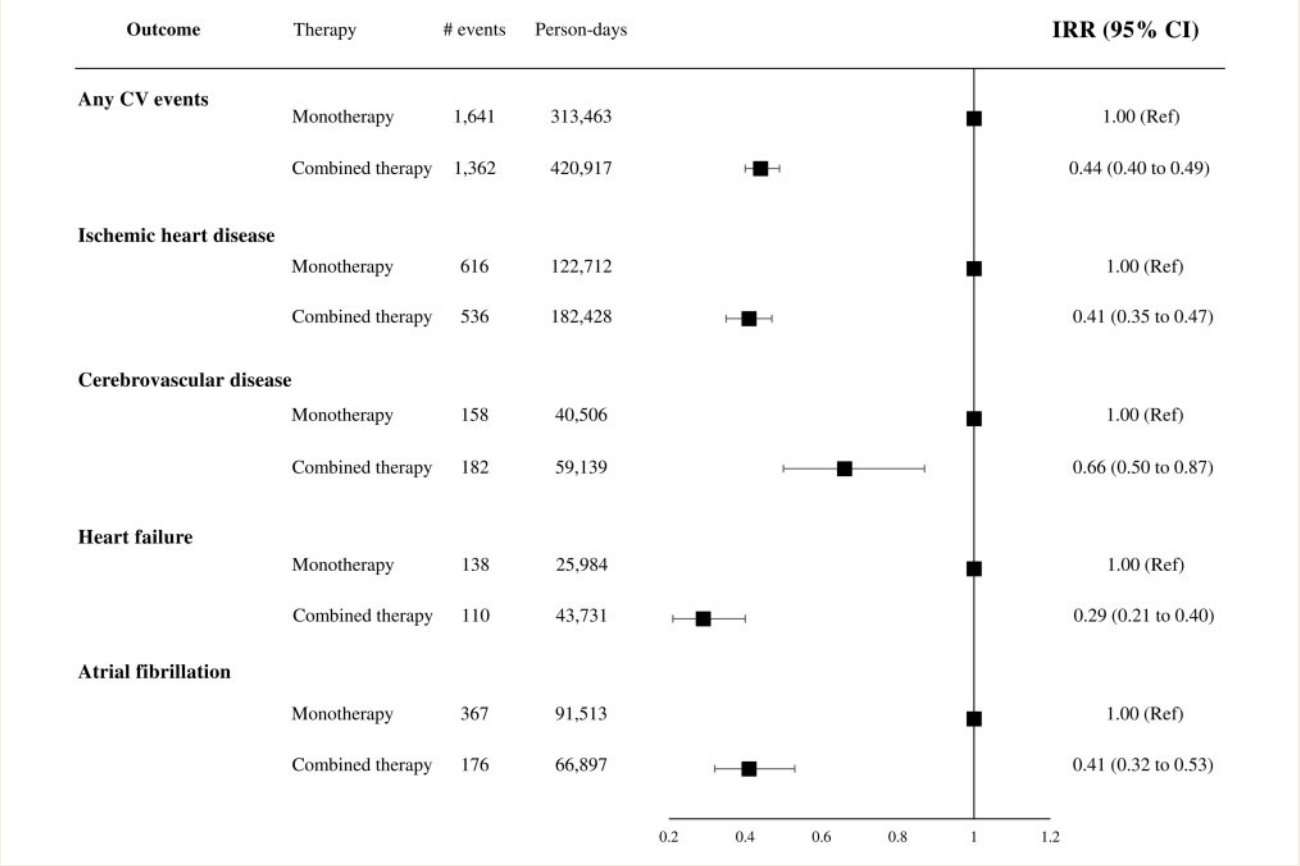

Figure 2 Incidence rate ratio (IRR), and 95% CI, of CV outcomes in patients ($n = 2212$) who during the year of follow-up experienced CV events and were under a two-drug FDC in some subperiods and monotherapy in others. IRR under monotherapy is taken as reference. IRR was obtained by fitting a conditional Poisson regression model to data arranged according to the self-controlled case series design (see Methods section). CV, cardiovascular.

Results

Main analyses

Among the large number of treated hypertensive patients available in the Lombardy database, 44 534 patients met the inclusion criteria and represented the study cohort (*Figure 1*). In all, 37 078 (83%) started treatment with one drug, those on initial two-drug FDC therapy being 7 456 (17%). Prescription of FDCs was largely limited to an ACE inhibitor or an angiotensin receptor blocker with a diuretic (77%), whereas the most common monotherapy prescription was a blocker of the renin angiotensin system (68%) followed by a beta-blocker (16%) and a calcium channel blocker (12%). Based on prescription coverage (see Methods section), adherence to therapy was similar in the two groups, i.e. on average 74% and 73% of patients in the groups starting with one drug and FDC, respectively.

Table 1 shows that patients starting on mono- and FDC therapy did not substantially differ for age and use of drugs for respiratory disease and depression. Compared to initial monotherapy, however, patients prescribed an initial two-drug FDC were more frequently females and less frequently co-treated with either non-CV or CV drugs. They also reported a less frequent history of hospitalization for a variety of CV diseases (Supplementary material online, *Table S2*). As shown in *Table 2*, when estimates were adjusted for the available covariates (see Methods section), there was evidence that, with respect to patients prescribed an initial monotherapy, patients on initial FDC therapy had a significant reduction in the 1 year risk of

Table 3 Hazard ratios (HR), and 95% confidence intervals (CI), estimating the effect of starting antihypertensive treatment with fixed-dose two-drug combinations with respect to monotherapy on the 1 year risk of CV outcomes after HDPS matching

Outcome	HR[a] (95% CI)	*P*-value
Any CV event	0.85 (0.74–0.97)	0.02
Ischaemic heart disease	0.73 (0.56–0.95)	0.02
Cerebrovascular disease	0.83 (0.61–1.14)	0.26
Heart failure	0.90 (0.54–1.51)	0.69
Atrial fibrillation	0.63 (0.42–0.94)	0.02

CV, cardiovascular; HDPS, high-dimensional propensity score.
[a]Hazard ratios estimated according to Cox proportional hazard model. Estimates were obtained after HDPS matching; the HR reduction in patients with initial combination treatment was significant for any CV event, ischaemic heart disease, and atrial fibrillation ($P < 0.05$).

Table 4 Incidence rate ratios (IRR), and 95% CI, of CV outcomes in patients on antihypertensive treatment during 1 year of follow-up

	Any CV event	Ischaemic heart disease	Cerebrovascular disease	Heart failure	Atrial fibrillation
Subperiods stratification					
First 6 months	0.34 (0.30–0.39)	0.26 (0.21–0.32)	0.59 (0.29–1.17)	0.22 (0.15–0.34)	0.35 (0.25–0.50)
Later 6 months	0.67 (0.52–0.88)	0.68 (0.46–1.02)	0.83 (0.56–1.23)	0.28 (0.11–0.68)	0.45 (0.25–0.84)
Mantel–Haenszel estimate	0.39 (0.35–0.45)	0.31 (0.26–0.38)	0.77 (0.54–1.07)	0.23 (0.16–0.34)	0.37 (0.27–0.51)
Time-trend adjustment					
Self-controlled case series (main analysis)	0.44 (0.40–0.49)	0.41 (0.35–0.47)	0.66 (0.50–0.87)	0.29 (0.21–0.40)	0.41 (0.32–0.53)
Self-controlled referent series	0.64 (0.50–0.82)	0.62 (0.43–0.90)	0.65 (0.33–1.28)	0.63 (0.29–1.36)	0.77 (0.49–1.20)
Time-trend adjusted estimate	0.67 (0.51–0.87)	0.66 (0.44–0.99)	1.01 (0.48–2.14)	0.46 (0.22–0.98)	0.53 (0.32–0.89)

In the upper part, data are shown for subperiods during which patients were on a fixed-dose two-drug combination with respect to the subperiods in which they were on monotherapy, separately for the first and later 6 months of the year. In the lower part, IRR are shown after the time-trend adjustment provided by the inclusion of the self-controlled referent series. IRR and 95% CI were obtained by fitting a conditional Poisson regression model to data arranged according to the self-controlled case series design. See text for explanation about methods for taking into account time-trend bias.

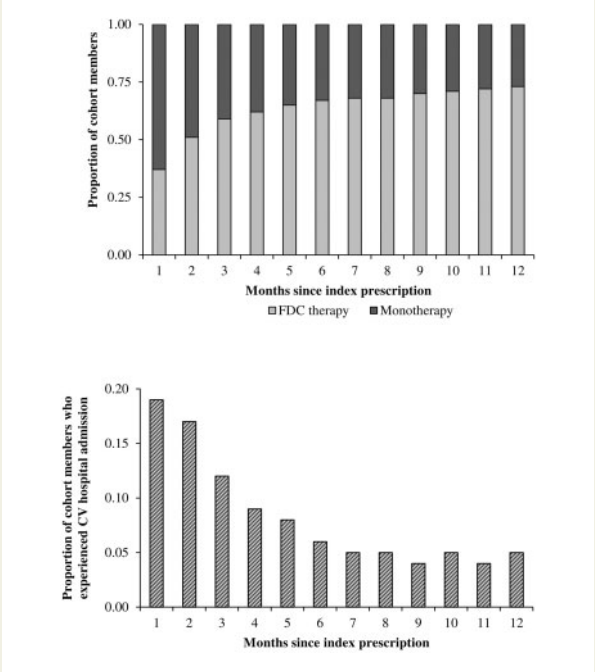

Figure 3 The top panel shows the monthly distribution of monotherapy or FDC therapy in the patients experiencing a CV event included in the self-controlled case series. The bottom panel shows the monthly distribution of the events. CV, cardiovascular; FDC, fixed-dose combination.

hospitalization for any CV event (-21%). This was the case for the risk of hospitalization for ischaemic heart disease (-39%) and atrial fibrillation (-37%). The hazard ratios were directionally similar also for cerebrovascular disease and heart failure, without, however, achieving statistical significance. Similar results were obtained when the HDPS was used to obtained an extended baseline matching between patients of the two treatment groups (*Table 3*). There was no significant between-group difference in the hospitalization for non-CV diseases. Mental disorders, for example, occurred in 2.7% of the hospitalized patients with initial monotherapy and 4.0% of those with initial combination treatment ($P = 0.17$). The corresponding figures for respiratory diseases were 6.6% and 7.9% ($P = 0.35$).

The results obtained from the analysis performed via the SCCS design, i.e. by the inclusion of 2212 patients who used monotherapy or FD two-drug combination therapy in different subperiods of the follow-up year and experienced at least one CV outcome, are shown in *Figure 2*. Compared to subperiods under monotherapy, the risk of any CV event was significantly and markedly reduced during the subperiods under combination therapy (-56%). This was the case also for the risk of ischaemic heart disease, cerebrovascular disease, heart failure, and atrial fibrillation (59%, 34%, 71%, and 59% respectively).

Additional analyses

Use of monotherapy and hospitalization for CV events was greater during the first months after the index prescription date (*Figure 3*). As shown in *Table 4*, upper part, for most CV events, the IRR was significantly less for subperiods on two-drug FDC than for subperiods on monotherapy both during the first 6 months after treatment initiation and in the later 6 months period, the Mantel–Haenszel estimates exhibiting similar values as those found in the main analysis. Furthermore, the incidence rate reduction associated with two-drug FDC treatment showed an attenuation but remained statistically significant after the time-trend adjustment provided by the inclusion of the self-controlled referent series (*Table 4*, lower part), except for cerebrovascular disease.

Discussion

Our study shows that among the NHS beneficiaries who live in Lombardy, initiation of antihypertensive treatment with a two-drug FDC led over the following year to a significant reduction (-21%, $P < 0.01$) of the risk of CV events compared to patients initiating

treatment with one drug only. Because patients starting treatment with a two-drug FDC exhibited a lower comorbidity index, a less frequent history of hospitalization for CV disease and, based on the rate of cotreatments, a lower prevalence of CV risk factors or cardiac disease, this could have been due to their lower baseline CV risk. Our study, however, provides evidence that this was not the only factor involved from three sets of results. First, in the group starting treatment with a fixed-dose two-drug combination a lower risk of CV events was seen after adjustment for the available baseline characteristics, including a sensitive predictor of mortality such as multisource comorbidity score, developed and validated for the Italian population.[25] Second, this was the case also when comparison was made between patients under mono or combination therapy who were matched for HDPS, obtained via a large number of pre-treatment variables. Third, and most importantly, during the year of follow-up, treatment with two-drug FDC was associated with a lower risk of CV events than monotherapy (-56%, $P < 0.01$) also when comparison was carried out within patients, i.e. by confronting the incidence of CV outcomes between periods on mono- or combination therapy in the same individuals. This removes the possibility that the between-group difference of CV risk was due to measured or unmeasured baseline differences (a key limitation of previous observations in favour of a greater CV protective effect of initial combination vs. single drug therapy[16,17]) and provides strong support to the conclusion that starting treatment with a two-drug FDC protects patients more effectively than starting treatment with one drug only because (i) the reduction of CV outcome associated with FDC treatment was marked and included in the SCCS series all specific CV outcomes and (ii) data were generated from the whole residentship of Lombardy, which suggest that the adoption of a two-drug FDC as the starting antihypertensive treatment step may offer a markedly greater protection and should thus be considered not just for some hypertensive subgroups (e.g. those with a high CV risk in the European hypertension guidelines[12]) but for the more general hypertensive population.

Our database does not explain why in real life initial two-drug FDC treatment is more protective than initial monotherapy despite the fact that initial one drug prescriptions are free to and, according by hypertension guidelines, should be upgraded to combination therapy in most patients.[12] This can find an explanation, however, in some observations made in previous studies.[3] First, although in the present study adherence to treatment was similar regardless the initial treatment strategy (presumably because to minimize confounding we excluded patients with treatment discontinuation and thus selected a more adherent cohort), initial combination treatment has been shown to favour, over the long-term, a better adherence to the prescribed treatment regimen,[10,37] perhaps because the more frequent and faster BP control that accompanies the assumption of two or more antihypertensive drugs increases patient's motivation[38] to continue with the BP lowering intervention.[3] Second, uptitration from mono to combination therapy may be delayed or prevented by physicians' inertia[14,15] or patients' reluctance to assume multiple drugs, which may be perceived as a marker of the severity of their disease. This may make overall BP control persistently less effective when monotherapy is the initial treatment strategy, a phenomenon that has been documented by the observation that, after 1 year, BP control is still less common with initial prescription of one drug as compared to two-drug combinations, either in a free or a single tablet format[13]. Compared to free combinations, however, administering two drugs in a single tablet allows a simplification of the treatment regimen that has been shown to have a pro-adherence effect,[39] possibly further enhancing the protective effect over initial monotherapy.

Our study has several elements of strength as well as limitations. The strengths are that our data provide information on antihypertensive treatment in real life, which is open to the influence of adverse factors which are minimized in clinical trials in which the organizational setting favours a much lower physicians' inertia to the need to upgrade treatment, a much better patients' adherence to the prescribed treatment regimen, and a reduction of the therapeutic errors that may occur in daily practice. They are also that the results were based on a large number of hospitalizations for CV events, which allowed analysis to extend to their cause specific nature (cerebrovascular disease, heart failure, coronary disease, and atrial fibrillation), with acceptable statistical power. Finally, an element of strength is represented by the results of the sensitivity analyses that allowed to verify the robustness of our main results by excluding a role of potential confounders in the interpretation of the data provided by the SCCS analysis. The limitations are those peculiar to the healthcare utilization databases,[19] i.e. the unavailability of BP (as well as serum cholesterol, blood glucose, and other CV variables) data which, in the present study, did not allow to determine whether the greater protective effect of initial combination treatment depends on an overall faster and better BP control or on other factors as well. In addition, our results did not include FDCs of current use, such as those based on blockers of the renin angiotensin system and calcium channel blockers because in 2010–2011 these FDCs were not reimbursed by the Italian NHS, and thus could not be part of the database. Finally, we could not compare the risk of CV events between initial fixed-dose and free drug combinations because use of the latter strategy as initial treatment was rare, i.e. only 1 out of 10 patients starting treatment with two drugs. This leaves the question whether in a real-life setting simplifying treatment by the FDC approach carries a substantial advantage unanswered.

A final comment is that in Lombardy initial two-drug combination treatment was much rarer than monotherapy (about 1 out of 5 patients) and that only in about 10% of the cases a free drug administration was employed. If this reflects what happens in other countries, another conclusion of our study is that, even in the FDC form, initial combination treatment is poorly employed in medical practice, and that, given its advantages, a substantial increase might be a desirable goal to try to increase in the future the effectiveness of antihypertensive treatment-related CV prevention.[3]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S; PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;**310**:959–968.
2. World Health Organization. *A Global Brief on Hypertension: Silent Killer, Global Public Health Crisis. World Health Day 2013*. Report, 1–39. Geneva, Switzerland: World Health Organization; 2013.
3. Mancia G, Rea F, Cuspidi C, Grassi G, Corrao G. Blood pressure control in hypertension. Pros and cons of available treatment strategies. *J Hypertens* 2017;**35**:225–233.
4. Mancia G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, Chazova IE, Puig JG. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. *J Hypertens* 2015;**33**:401–411.
5. Mancia G, Parati G, Bilo G, Choi J, Kilama MO, Ruilope LM. TALENT investigators. Blood pressure control by the nifedipine GITS-telmisartan combination in patients at high cardiovascular risk: the TALENT study. *J Hypertens* 2011;**29**:600–609. Erratum in: *J Hypertens* 2011;29:1022.
6. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. *Lancet* 2011;**377**:312–320.
7. Neutel JM, Mancia G, Black HR, Dahlöf B, Defeo H, Ley L, Vinisko R. TEAMSTA Severe HTN Study Investigators. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. *J Clin Hypertens (Greenwich)* 2012;**14**:206–215.
8. Kjeldsen SE, Sica D, Haller H, Cha G, Gil-Extremera B, Harvey P, Heyvaert F, Lewin AJ, Villa G, Mancia G. DISTINCT Investigators. Nifedipine plus candesartan combination increases blood pressure control regardless of race and improves the side effect profile: DISTINCT randomized trial results. *J Hypertens* 2014;**32**:2488–2498; discussion 2498.
9. Mancia G, Kjeldsen SE, Zappe DH, Holzhauer B, Hua TA, Zanchetti A, Julius S, Weber MA. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. *Eur Heart J* 2016;**37**:955–964.
10. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. *J Hypertens* 2014;**32**:1708–1715.
11. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens* 2008;**26**:819–824.
12. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;**31**:1281–1357.
13. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012;**59**:1124–1131.
14. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. *Hypertension* 2006;**47**:345–351.
15. Banegas JR, Segura J, Ruilope LM, Luque M, Garcia-Robles R, Campo C, Rodriguez-Artalejo F, Tamargo J; CLUE Study Group Investigators. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension* 2004;**43**:1338–1344.
16. Gradman AH, Paris H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. *Hypertension* 2013;**61**:309–318.
17. Corrao G, Nicotra F, Parodi A, Zambon A, Heiman F, Merlino L, Fortino I, Cesana G, Mancia G. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. *Hypertension* 2011;**58**:566–572.
18. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *Bmj* 2016;**354**:i4515.
19. Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases. *Hypertension* 2015;**65**:490–498.
20. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;**29**:610–618.
21. Corrao G, Rea F, Ghirardi A, Soranna D, Merlino L, Mancia G. Adherence with antihypertensive drug therapy and the risk of heart failure in clinical practice. *Hypertension* 2015;**66**:742–749.
22. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;**158**:915–920.
23. Hirakawa Y, Arima H, Webster R, Zoungas S, Li Q, Harrap S, Lisheng L, Hamet P, Mancia G, Poulter N, Neal B, Williams B, Rogers A, Woodward M, Chalmers J. Risks associated with permanent discontinuation of blood pressure-lowering medications in patients with type 2 diabetes. *J Hypertens* 2016;**34**:781–787.
24. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 2008;**168**:329–335.
25. Corrao G, Rea F, Di Martino M, De Palma R, Scondotto S, Fusco D, Lallo A, Belotti LMB, Ferrante M, Pollina Addario S, Merlino L, Mancia G, Carle F. Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy. *BMJ Open* 2017;**7**:e019503.
26. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;**61**:1234–1240.
27. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
28. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *Jama* 1996;**275**:1571–1576.
29. Emdin CA, Anderson SG, Salimi-Khorshidi G, Woodward M, MacMahon S, Dwyer T, Rahimi K. Usual blood pressure, atrial fibrillation and vascular risk: evidence from 4.3 million adults. *Int J Epidemiol* 2017;**46**:162–172.
30. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583–612.
31. Asplund K, Bonita R, Kuulasmaa K, Rajakangas A-M, Feigin V, Schaedlich H, Suzuki K, Thorvaldsen P, Tuomilehto J. Multinational comparisons of stroke epidemiology. Evaluation of case ascertainment in the WHO MONICA Stroke Study. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. *Stroke* 1995;**26**:355–360. Erratum in: Stroke 1995;26:1504.
32. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;**20**:512–522.
33. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 1995;**51**:228–235.
34. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;**25**:1768–1797.
35. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res* 2009;**18**:7–26.
36. Hallas J, Pottegård A. Use of self-controlled designs in pharmacoepidemiology. *J Intern Med* 2014;**275**:581–589.
37. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C, Merlino L, Mancia G. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens* 2010;**28**:1584–1590.
38. Düsing R. Adverse events, compliance, and changes in therapy. *Curr Hypertens Rep* 2001;**3**:488–492.
39. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;**23**:1296–1310.