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Adherence to Treatment by Initial Antihypertensive Mono and Combination Therapies

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BACKGROUND

Aim of our study was to compare adherence to antihypertensive drug therapy between newly treated patients in whom monotherapy or a 2-drug single-pill combination (SPC) was initially dispensed.

METHODS

The 63,448 residents of Lombardy Region (Italy), aged 40–80 years, who were newly treated with antihypertensive drugs during 2016, were identified and followed for 1 year after the first prescription. The outcome of interest was adherence to drug therapy that was measured according to the "proportion of days covered" (PDC) criterion, i.e., the ratio between the number of days in which the drug was available and the days of follow-up. Patients who had a PDC >75% and <25% were defined as highly and poorly adherent to drug therapy, respectively. Log-binomial regression models were fitted to compare the propensity to treatment adherence between the initial therapeutic strategies, after adjusting for baseline demographic and clinical covariates.

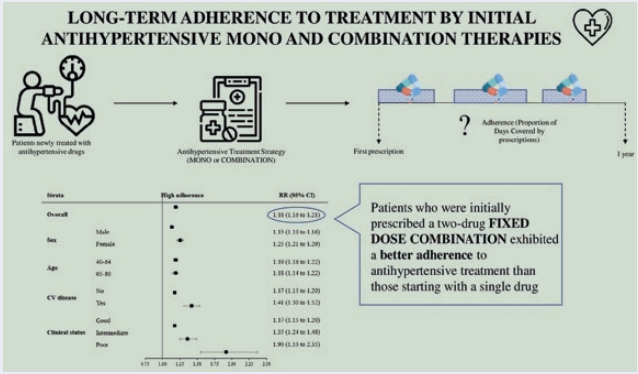
RESULTS

About 46% and 17% of patients showed high and poor adherence, respectively. Compared with patients under initial monotherapy (85%), those who were initially treated with a SPC (15%) had higher propensity to be highly adherent and a lower propensity to be poorly adherent to antihypertensive treatment (risk ratio: 1.18, 95% confidence interval 1.16–1.21; 0.42, 0.39–0.45, respectively). This was the case regardless the sex, the age, the patient clinical status, and with almost any type of SPC.

CONCLUSIONS

In a real-life setting, patients who were initially prescribed a 2-drug SPC exhibited more frequently a good adherence to antihypertensive treatment than those starting with a single drug.

GRAPHICAL ABSTRACT



Keywords: adherence; antihypertensive therapy; blood pressure; combination treatment; Healthcare Utilization Database; hypertension; monotherapy

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Hypertension guidelines have since long recommended antihypertensive treatment to be largely based on combinations of antihypertensive drugs[1–3] because drug combinations lower blood pressure (BP) much more effectively than monotherapies, if the combined drugs have complementary mechanisms of action.[4,5] Except for some subgroups of patients,[1] drug combinations have been recommended as second step treatment, i.e., after failure of monotherapy to reduce an elevated BP to target values. This has been modified, however, in recent guidelines which support use of dual drug combinations as first treatment step in most patients,[6–8] based on studies which suggest that initial dual combinations may oppose 2 barriers that minimize BP reduction in clinical practice, i.e., therapeutic inertia (no treatment uptitration when hypertension is not controlled)[9,10] and low adherence to the prescribed treatment regimen.[11–14] The European guidelines also recommend using single-pill combinations (SPCs) of the 2 drugs because of the evidence that reducing the number of daily pills is associated with a better long-term adherence to

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treatment.[15] Improving adherence to treatment is perceived as especially important because in hypertension low adherence is common[16–18] and associated with an uncontrolled BP[19] and an increased risk of outcomes.[20–24]

Aim of the present study has been to extend available information on the relationship between initial antihypertensive treatment strategy and subsequent adherence to treatment by comparing the odds of being highly or poorly adherent to antihypertensive drugs in patients starting treatment with 1 drug or a dual SPC. Comparisons included all dual SPCs approved for reimbursement by the Italian National Health Service (NHS) and specifically used for hypertension for which they are by far a more common form of initial combination treatment than separate administration of 2 drugs.[25]

METHODS

Setting

The data used in the present study were retrieved from the Healthcare Utilization Databases of Lombardy, a Region of Italy that accounts for almost 16% of its population (more than 10 million of residents). In Italy, the NHS provides healthcare virtually free of charge to all citizens and in Lombardy this has been associated since 1997 with an automated system of databases which provide information on all health services free of charge or reimbursable, including prescriptions to outpatients of a large number of drugs (according to the ATC classification system), hospitalizations (according to the ICD-9-CM classification system), and other healthcare-related items. These databases are linked by a unique individual identification code, which allows to trace the healthcare pathway of NHS beneficiaries. To preserve privacy, each identification code is automatically deidentified, the inverse process being only allowed to the Regional Health Authority upon request from judicial authorities. Further details on Healthcare Utilization Databases in pharmacoepidemiological studies are available in previous studies.[9,11,12,21,22]

Cohort selection

The target population consisted of residents (age 40–80 years) of Lombardy who were beneficiaries of the NHS and started to use antihypertensive drugs (see below) in year 2016. To ensure that selection did not include prevalent users, only residents in Lombardy since at least 10 years were included, which allowed absence of previous antihypertensive drug prescription to be documented over a long time. The date of the first drug prescription during the year 2016 was defined as the index date. The antihypertensive drugs prescribed in monotherapy included all types of diuretics (Ds), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), and calcium-channel blockers (CCBs). Antihypertensive drugs prescribed as SPC included ACEI + Ds, ARBs + Ds, ACEI + CCBs, ARBs + CCB, and BB + D. In addition to patients who received 1 or more antihypertensive drug prescriptions within the 10 years before the index date, exclusion involved patients (i) who were initially prescribed a free combination therapy; (ii) did not renew the initial drug prescription, i.e., no other antihypertensive drug prescription was received after the index date 1; and (iii) did not reach 1 year of follow-up because of emigration to another Italian Region, emigration to other countries or death. The remaining patients were included into the final cohort whose members were followed for 1 year after the index date. Members of the final cohort were classified by the initial treatment strategy, i.e., whether at the index date they were prescribed 2 drugs as SPC or monotherapy with 1 or the other combination component and analysis of subsequent adherence (see below) was conducted on an intention-to-treat basis.

Adherence to antihypertensive drug therapy

As mentioned above, our study focused on whether and how much initial therapy modified the subsequent adherence to antihypertensive drug treatment. Adherence was measured by the time covered by antihypertensive drug prescription during the 1-year follow-up, irrespectively of which drug or drugs were prescribed, and to this aim all antihypertensive drugs dispensed during the year after the index date were identified for each cohort member. The period covered by a prescription was calculated by dividing the total amount of the drug prescribed (available in our database) for the defined daily dose as reported on the WHO website at https://www.whocc.no/atc_ddd_index. The median (and interquartile range) of days availability for each medication class/drug combination is provided in Supplementary Table S1 online. For overlapping prescriptions, the patient was assumed to have taken all the drug(s) contained in the former prescription before using those from the latter prescription. Adherence to antihypertensive drug therapy was assessed by the ratio between the number of days in which 1 or more antihypertensive drug was available (irrespective of whether the drug or drugs were partly or totally different from the initial drugs initially prescribed) and the days of follow-up (i.e., 365 days), a measure referred to as "proportion of days covered" (PDC) by prescriptions.[26]

The primary goal of the study was to assess the favorable effect of SPC therapy by comparing the odds of patients of being highly adherent to treatment (PDC >75%) with initial SPC therapy vs. initial monotherapies. A secondary goal was to compare the odds of being poorly adherent to treatment (PDC <25%) in the 2 groups. These cutoff values were used because in previous studies on the Lombardy database these adherence levels showed a clear association with cardiovascular outcomes and mortality, which were markedly greater in the latter than in the former case.[21,22] Patients were followed for 1 year because previous studies have shown that major alterations in adherence (e.g., treatment discontinuation) occur within this time span.[27]

Covariates

Baseline characteristics included gender, age, initially employed antihypertensive therapy, comorbidities (previous hospitalization for cardiovascular disease, diabetes,

cancer, respiratory, and kidney diseases) and cotreatments (antidiabetics, antithrombotics, antiarrhythmics, lipid-lowering drugs, antidepressants, nonsteroidal anti-inflammatory drugs or NSAIDs, hypouricemic agents, and drugs for pulmonary diseases). The clinical status of the patients was further assessed by the Multisource Comorbidity Score, a multivariable prognostic score that has been shown to sensitively predict all-cause mortality and hospitalization in the Italian population.[28] Three categories of clinical status were considered: good ($0 \leq$ score ≤ 4), intermediate ($5 \leq$ score ≤ 14), and poor (score ≥ 15).

Data analysis

Standardized mean differences for binary covariates were used when appropriate to test differences between groups. Equipoise was considered to be reached when the between-group comparison of covariates had a mean standardized difference of <0.1. Log-binomial regression models were fitted to estimate the risk ratio, and its 95% confidence interval, of adherence to treatment in relation to the initial drug treatment strategy, using monotherapy as reference. Adjustments were made for the aforementioned baseline covariates. The association between the initial treatment strategy and adherence was also assessed after patient stratification for sex, age, previous hospitalization for cardiovascular disease and clinical status. Each available SPC (see Supplementary Table S2 online) was compared with either combination component prescribed as a single drug. For example, patients who started treatment with a SPC between an ACEI and a CCB were compared with subjects who were initially prescribed either an ACEI or a CCB as monotherapy. Although it was not required by the intention-to-treat analysis, calculation was also made of the changes (shift or addition) of other drug therapies from those prescribed at the index date.

Sensitivity analyses

Two sensitivity analyses were performed. First, because of the arbitrary nature of the PDC categorization, we used more permissive (70%) and restrictive (80%) categories of PDC to measure high adherence to treatment. Second, to account for the confounding effect of possible baseline demographic and clinical differences between patients prescribed a monotherapy and those prescribed combination treatment, data were also analyzed according to the high-dimensional propensity score matching approach.[29] The propensity score was obtained through a logistic regression model that included as covariates the abovementioned baseline data, all causes of hospitalization experienced by the patients, and all drugs prescribed to cohort members over the 2-year period prior to the index date. The 200 most predictive covariates were selected. Groups were matched 1:1 based on their propensity score, using a nearest neighbor matching algorithm without replacement.

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC) was used for the analyses. For all hypotheses tested, 2-tailed P values less than 0.05 were considered to be significant.

RESULTS

Patients

The distribution of the exclusion criteria is shown in Figure 1. Among the 1,738,402 patients who were treated with antihypertensive drugs during 2016, 63,448 subjects met the inclusion criteria and were included in the study. Of these, 53,702 (85%) started treatment with monotherapy and 9,746 (15%) with a 2-drug SPC, this being the case in the 12 Capitals of the provinces of the Region vs. more rural areas (14.0% vs. 15.7% initial prescriptions with a SPC). ACEIs were the most commonly used drugs in monotherapy, followed by BBs, ARBs, and CCBs. ACEI plus CCBs was the most commonly used SPC followed by ACEI or ARB plus D and ARB plus CCB (Supplementary Table S2 online).

The characteristics of the cohort members are shown in Table 1 according to the initial treatment strategy. In both initial monotherapy and SPC groups, mean age was 59 years and about 55% of the patients were men. Compared with patients under initial monotherapy, patients who were prescribed an initial SPC therapy showed less cotreatment with drugs for noncardiovascular diseases and fewer hospitalizations for several noncardiovascular comorbidities. There were also some other between-group baseline differences which were small and not statistically significant.

Initial monotherapy vs. initial combination therapy: pooled data

High adherence to treatment (PDC >75%) during the first year of drug therapy was observed in 28,909 patients (46%), of which 5,284 (54%) under initial SPC therapy and 23,625 (44%) under initial monotherapy. As shown in Figure 2, left panel, according to the log-binomial model, SPC therapy showed a beneficial effect on treatment adherence, the adjusted odds of being highly adherent being 1.18 (95% confidence interval, 1.16–1.21, $P < 0.001$). This was the case in all patient strata, i.e., males and females, younger and older patients, patients without and with previous hospitalization for cardiovascular disease (primary and secondary prevention) and patients with a good, intermediate, and poor clinical status. The odds of being highly adherent to treatment with an initial SPC was greatest among patients with a poor clinical status.

Poor adherence (PDC <25%) during the first year of drug therapy was observed in 10,469 patients (16.5%), of which 694 (7.1%) under initial SPC and 9,775 (18.2%) under initial monotherapy. Figure 2, right panel, shows that, compared with the data on high adherence, the data on the risk of being poorly adherent were invariably specular, i.e., in all patients as well as in different strata the risk of being poorly adherent was lower with initial SPC treatment than with initial monotherapy, the between-group difference being more marked than for the odds of being highly adherent.

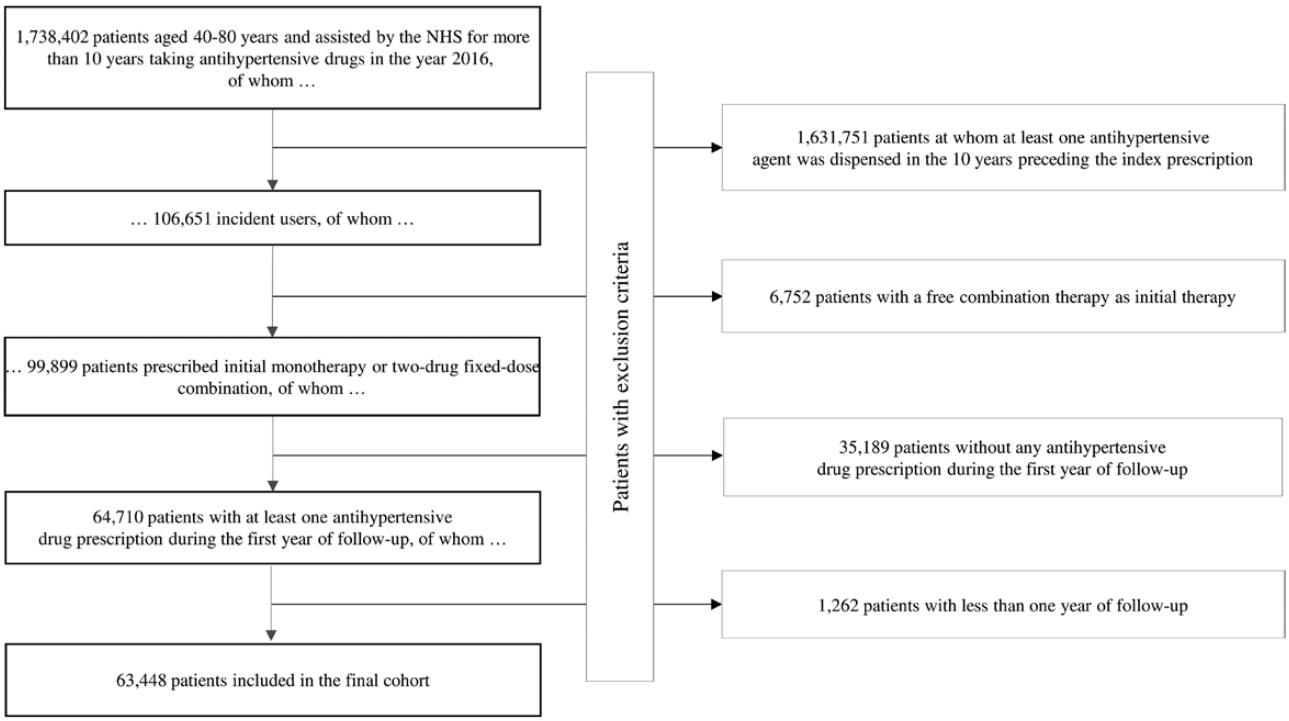

Figure 1. Flowchart of inclusion and exclusion criteria that were used to select the final cohort.

Initial monotherapy vs. combination therapy: different drugs

Figure 3, left panel, shows the adjusted odds of achieving high adherence to treatment according to the drugs prescribed as initial SPC. Compared with patients receiving initial monotherapy with 1 or the other combination components, the odds of being highly adherent to treatment increased with almost any type of initial SPC, ranging from 1.10 (95% confidence interval, 1.07–1.13) (ACEI + CCB vs. ACEI) to 2.32 (2.14–2.51) (ARB + D vs. D). The only exceptions were (i) the initial ARB + D SPC for which the adjusted odds of being highly adherent was not significantly different from initial ARB alone (P = 0.228), and (ii) the initial ACEI + D SPC for which the adjusted odds of being highly adherent was less than that seen with initial ACEI alone. A similar although specular pattern was seen for the odds of being poorly adherent to treatment (Figure 3, right panel).

A comparison between the available 5 SPCs is shown in Figure 4, left and right panels. Adherence to treatment (greater and smaller odds of being highly and poorly adherent, respectively) was similar between ACEI + CCB and ARB + CCB SPCs. Both ACEI + CCB and ARB + CCB SPCs were better than ACEI or ARB + D SPCs, the ARB + D SPC being superior to the ACEI + D SPC for the odds of being highly adherent. The odds of being highly or poorly adherent to treatment with the BB + D SPC were similar to the SPC of a renin–angiotensin system (RAS) blocker with D.

As shown in Supplementary Table S3 online, last line, shifts to other therapies were on average lower than 1 and less for almost all different SPCs vs. the corresponding combination components in monotherapy. The differences in shifts between SPC and monotherapies were more marked when monotherapies consisted of Ds or CCBs.

Sensitivity analyses

The results of the sensitivity analyses are shown in Supplementary Tables S4 and S5 online. The results described in the previous sections did not change by modifying the PDC categorization. This was the case also for the adoption of the high-dimensional propensity score algorithm to equalize baseline patients' characteristics between initial monotherapy and initial SPC therapy.

DISCUSSION

Our study confirms previous observations that in the real-life setting (i) adherence to antihypertensive drug treatment is low[16–18] and (ii) although recommended by the European guidelines as the preferred treatment strategy in the majority of hypertensive patients,[6] use of a drug combination as the starting antihypertensive therapy is still rare.[25] The main interest of our observations, however, lays in other findings. First, the chance of being highly adherent to antihypertensive drug prescriptions was significantly more common in patients starting treatment with 2 than in those starting treatment with 1 drug. Second, the risk of being low adherent to antihypertensive treatment was significantly less common in patients starting antihypertensive treatment with 2 vs. those starting treatment with 1 drug. Third, the above findings were shared by patients with different

Table 1. Baseline characteristics of cohort members according to the initial treatment strategy

	Monotherapy (*n* = 53,702)	Fixed dose combination (*n* = 9,746)	Standardized difference
Male gender	27,990 (52.1%)	5,352 (54.9%)	0.056
Age (years)			
40–64	35,101 (65.4%)	6,654 (68.3%)	0.062
65–80	18,601 (34.6%)	3,092 (31.7%)	
Comorbidities			
Cardiovascular disease	7,198 (13.4%)	577 (5.9%)	0.256
Diabetes	3,665 (6.8%)	517 (5.3%)	0.063
Kidney disease	242 (0.4%)	13 (0.1%)	0.060
Cancer	6,083 (11.3%)	869 (8.9%)	0.080
Respiratory disease	20,773 (38.7%)	3,249 (33.3%)	0.113
Cotreatments			
Antithrombotic drugs	7,788 (14.5%)	770 (7.9%)	0.210
Antiarrhythmic drugs	1,146 (2.1%)	50 (0.5%)	0.142
Lipid-lowering drugs	10,553 (19.7%)	1,535 (14.8%)	0.130
Antidiabetic agents	19,508 (36.3%)	3,092 (31.7%)	0.097
NSAIDs	30,098 (56.1%)	5,290 (54.3%)	0.036
Antigout drugs	1,616 (3.0%)	278 (2.9%)	0.006
Drugs for pulmonary diseases	3,560 (6.6%)	509 (5.2%)	0.059
Antidepressant drugs	9,925 (18.5%)	1,430 (14.7%)	0.102
Number of cotreatments			
0–1	18,980 (35.3%)	4,436 (45.5%)	0.261
2–3	14,617 (27.2%)	2,663 (27.3%)	
≥4	20,105 (37.4%)	2,647 (27.2%)	
Clinical status[a]			
Good	46,972 (87.5%)	9,165 (94.0%)	0.255
Intermediate	5,436 (10.1%)	499 (5.1%)	
Poor	1,294 (2.4%)	82 (0.8%)	

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]The clinical status was assessed by the Multisource Comorbidity Score (MCS) according to the hospital admission and the drugs prescribed in the 3-year period before the index date. Three categories of clinical status were considered: good (0 ≤ score ≤ 4), intermediate (5 ≤ score ≤ 14), and poor (score ≥ 15).

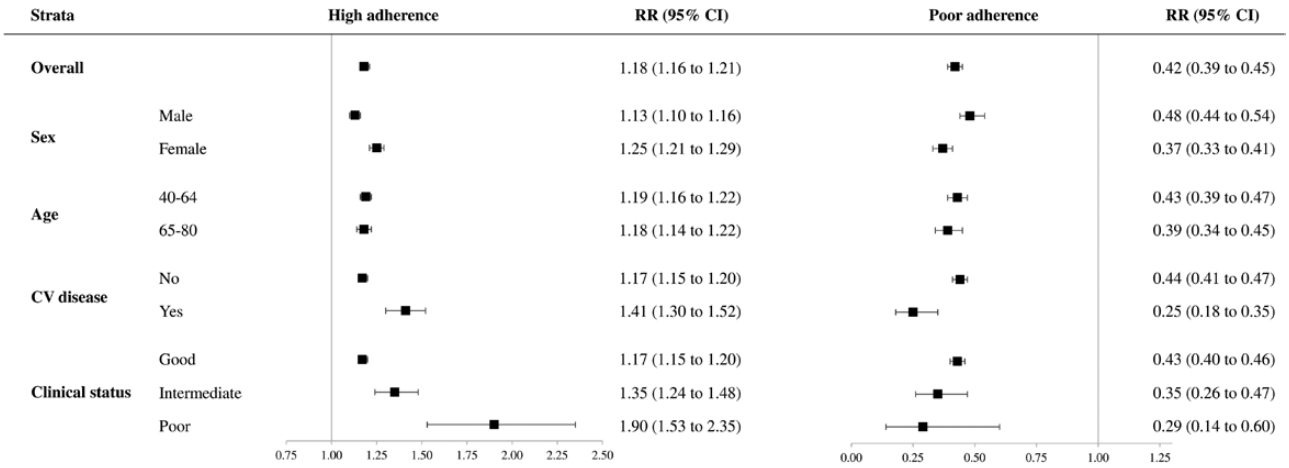

Figure 2. Adjusted odds of achieving high (>75% of a 1-year treatment duration) and poor (<25%) adherence to treatment in patients starting treatment with 1 drug (mono) or with a single-pill combination (SPC) of 2 drugs, according to baseline characteristics.

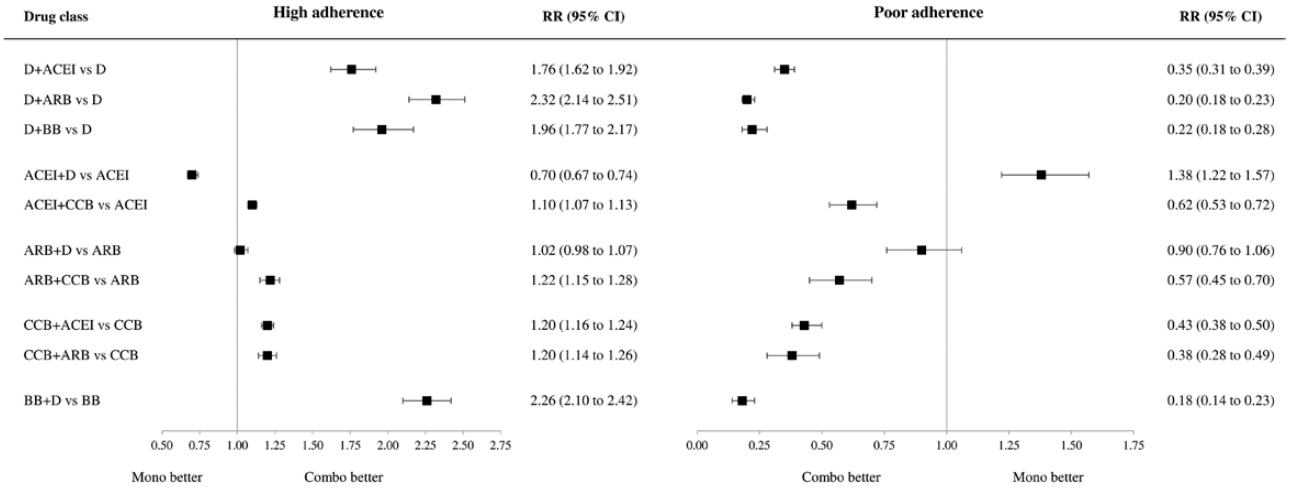

Figure 3. Adjusted odds of achieving high (>75% of a 1-year treatment duration) and poor (<25%) adherence to treatment in patients starting treatment with 1 drug (mono) or with a SPC of 2 drugs, one of which belonging to the drug class used in monotherapy. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium-channel blocker; D, diuretic; SPC, single-pill combination.

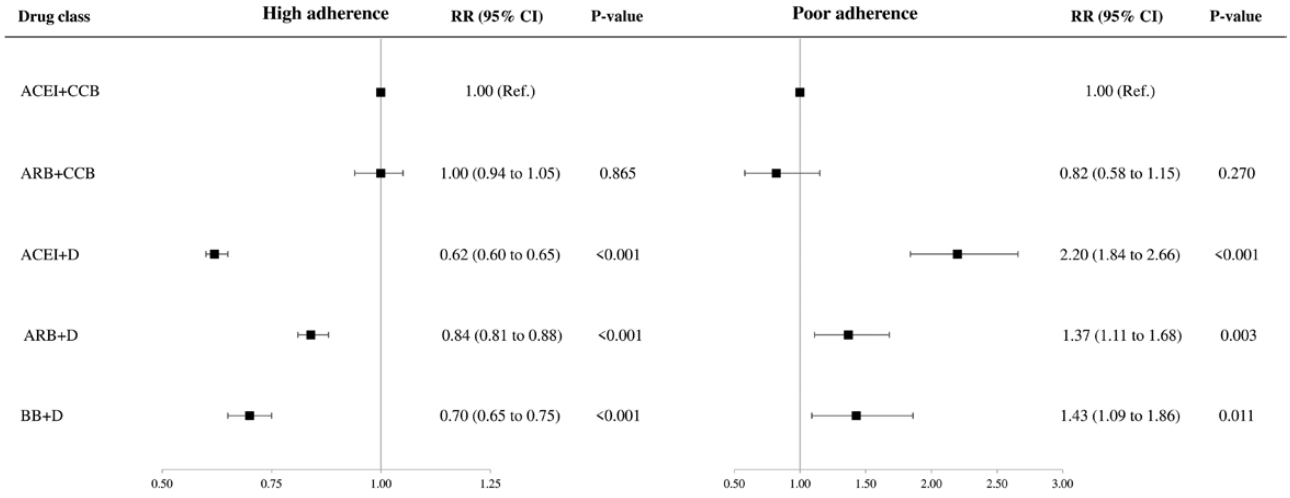

Figure 4. Adjusted risk of achieving high (>75% of a 1-year treatment duration) and poor (<25%) adherence to treatment by different SPCs used as initial therapy. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium-channel blocker; D, diuretic; SPC, single-pill combination.

demographic and clinical characteristics. Fourth, the differences in adherence were not related to difference in the rate of drug changes and additions to the initial treatment strategies because treatment shifts were similar in patients using initial monotherapy or SPC. Finally, and most importantly, compared with initial monotherapy, the improvement in adherence to treatment associated with initial SPC was by no means marginal. Overall, the chance of being highly adherent to antihypertensive treatment increased by 18% with an initial combination of 2 drugs, reaching increases of 41% and 90% in patients with previous hospitalization for cardiovascular diseases or with a poor clinical status, respectively. The improvement was even more evident for the risk of being a poorly adherent patient which decreased by an average of 58%, and by 75% and 71% in high cardiovascular risk patients (previous hospitalizations for cardiovascular disease) or patients with a poor clinical status, respectively. It can thus be concluded that initial combination treatment has major beneficial effects on adherence to antihypertensive treatment. This offers robust support to the guidelines recommendations to use combination treatment as the initial step in most hypertensive patients[6–8] because adherence to treatment bears a direct relationship with the rate of BP control[20,30,31] and the risk of cardiovascular events, which has been shown to be, respectively, smaller and greater in highly and poorly adherent individuals.[20–24] These 2 factors presumably account for the recent findings that, compared with initial monotherapy, starting treatment with 2 antihypertensive drugs is accompanied by a better long-term BP control,[32] and a lower risk of cardiovascular adverse events and mortality.[33–35]

In our patients, the increased chance of being highly adherent as well as the reduced risk of being poorly adherent offered by initial antihypertensive SPC treatment was seen

with most SPCs, including the D/BB SPC compared with D or BB monotherapy. This might have been generated by demographic and clinical differences between the monotherapy and combination therapy groups at baseline and/or by the fact that, while SPCs of antihypertensive drugs are prescribed for hypertension only, free use of these drugs extends to cardiac and renal diseases. However, the between-group differences in adherence were seen after adjustment for all baseline covariates. Furthermore, the results were not different when comparisons were done after equalization of baseline variables by the high-dimensional propensity score approach. Finally, adherence has been reported to be better when health conditions are more compromised, such as in cardiac or nephropathic patients.[36] Thus, a more likely explanation is that the better long-term adherence to antihypertensive drug prescription associated with initial SPC treatment is related to the advantages of this treatment regimen "*per se*," i.e., faster and more common BP control, earlier completion of the treatment titration phase, and treatment simplification.[25]

At variance from what was seen with all other SPCs, initial use of the ACEI/D or ARB/D SPC improved adherence markedly when compared with D monotherapy, but it did not show a favorable effect to treatment when compared with RAS blocker monotherapy. That is, adherence became worse when the RAS blocker monotherapy was an ACEI and did not show any improvement when the RAS blocker monotherapy was an ARB. It is important to mention that in our patients there was a relatively low number of treatments changes and that thus shift to or addition of other drugs was not responsible for this finding. Its explanation may thus be that the favorable effect of SPC on adherence to treatment also depends on the background adherence level provided by the combination components,[27] being greater when this is low (addition of a RAS blocker to D) and smaller when this is high (addition of D to a RAS blocker).[12,37] This may be consistent with the finding that Ds increased adherence to treatment (greater propensity for high adherence and lower risk of poor adherence) when added, as a SPC, to drugs with a high risk of treatment discontinuation such as BBs.[27]

Several other results of our study deserve mention. One, adherence was better for CCB + RAS blocker than for diuretic + RAS blocker SPCs. Two, CCB/ARB and CCB/ACEI SPCs had a comparable effect on adherence, which means that the better adherence reported for ARBs vs. ACEIs when these drugs are used in monotherapy[12,37] is no more visible when these drugs are combined with CCBs. Three, somewhat unexpectedly, the BB/D SPC performed much better than it might be predictable by the well-known poorer performance of these combination components in monotherapy. As a result, its effect on the odds of being highly and poorly adherent to treatment became comparable with that of the ACEI or ARB/D SPCs. Fourth, only slightly more than 50% of the patients under initial SPC exhibited an adherence to treatment that covered >75% of the follow-up, which means that even with SPC-based strategies adherence is not high and room for further improvement remains considerable. Finally, treatment changes involved only slightly more than 1 out of 2 patients and shifts were only modestly higher in patients starting treatment with 1 drug vs. those using an initial SPC. This presumably reflects the considerable amount of therapeutic inertia that characterizes clinical practice and makes changes of an initially selected treatment strategy difficult.[9]

Our study has several elements of strength. First, the investigation was based on a large and unselected population, which was made possible because in Italy a cost-free healthcare system involves virtually all citizens.[9,11,12,21,22] Second, the drug prescription database provided highly accurate data because pharmacists are required to report prescriptions in detail in order to obtain reimbursement, and incorrect reports have legal consequences. Third, patients were identified at the time of their initial antihypertensive drug therapy, a "new-user" approach that reduced the potential for selection bias.[38] Finally, the data provided by the main analysis were confirmed by sensitivity analyses. There are also limitations, however. First, our information is limited to drug prescription and we have no data on actual drug assumption by the patients. Second, our databases did not capture drugs prescribed outside the NHS. Finally, our study does not allow to suitably address the reasons for the differences in adherence to treatment between different SPCs, because in the Lombardy database some therapeutic information is not available (e.g., there are no data on the drug doses used in individual patients) and clinical information does not include BP and other cardiovascular risk factor values. We can confidently rule out, however, confounders such as differences in ethnicity or socioeconomic status because our population is largely Caucasian, antihypertensive drugs were available virtually free of charge, and income did not show any effect on adherence to treatment in a previous study.[39]

In summary, adherence to antihypertensive drug treatment is greater when therapy starts with a 2-drug SPC than with monotherapy. This is the case regardless of the age, sex, and patients' background clinical condition. It is also the case for different SPCs with the exception of those between diuretic and RAS blockers when compared with RAS blocker monotherapy. Our findings offer robust support to use dual SPC as the initial step in hypertensive patients in clinical practice and thus implement guidelines recommendations on a widespread basis. Because improving adherence to antihypertensive treatment increases the rate of BP control and reduces the risk of cardiovascular events, this may help to achieve an improvement of cardiovascular prevention.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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design of the study, the collection, analysis and interpretation of the data, or the decision to approve publication of the finished manuscript.

DISCLOSURE

G. Corrao received research support from the European Community, the Italian Agency of Drug, and the Italian Ministry of Education, University and Research. He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GlaxoSmithKline, Roche, AMGEN, and Bristol-Myers Squibb). He also received honoraria as member of Advisory Board from Roche. G. Mancia received honoraria for participation as speaker/chairman in national/international meetings from Boehringer Ingelheim, Ferrer, Medtronic, Menarini Int, Merck Serono, Recordati, and Servier. The other authors report no conflicts.

DATA AVAILABILITY

The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy Region upon reasonable request.

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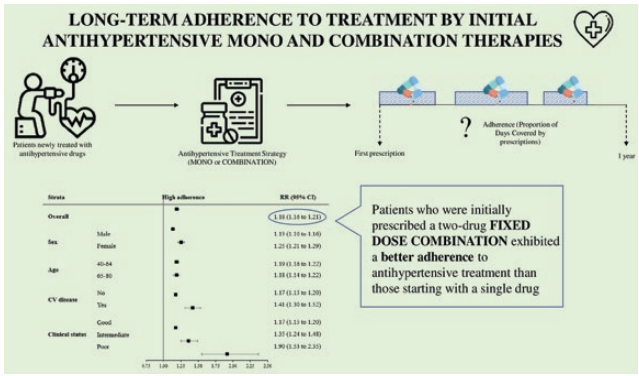

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