

Antihypertensive treatment in young adults and cardiovascular risk: a population-based cohort study

Federico Rea ^{1,2,*}, Gabriella Morabito ^{1,2}, Giovanni Corrao ^{1,2}, and Giuseppe Mancia ³

¹National Centre for Healthcare Research & Pharmacoepidemiology, at the University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, Milano 20126, Italy; ²Laboratory of Healthcare Research & Pharmacoepidemiology, Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, Milano 20126, Italy; and ³University of Milano-Bicocca (Emeritus Professor), Milan, Italy

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Abstract

Background and Aims The efficacy of antihypertensive drug treatment in reducing hypertension-related outcomes has been documented in old and middle age but never in younger individuals. The aim of this study was to assess the protective effect of antihypertensive drugs in young adults (18–39 years) by comparing the risk of nonfatal and fatal outcomes in patients with different adherence to antihypertensive drugs. Analysis was extended to middle-aged patients (40–55 years) for comparison.

Methods Using the healthcare utilization database of the Lombardy region (Italy), 286 751 residents, aged 18–55 years, who were newly prescribed antihypertensive drugs between 2009 and 2017 were identified. Adherence to drug therapy was measured by the proportion of the follow-up covered by antihypertensive drug prescription, and data were compared for adherent vs non-adherent patients, i.e. drug coverage $\geq 80\%$ vs $<80\%$ of the follow-up duration. The primary outcome was hospital admissions for cardiovascular (CV) events. Secondary outcomes were CV and all-cause death. Cox and the cause-specific hazard regression models were used to estimate hazard ratio (HR) and 95% confidence interval (CI).

Results Over a follow-up of about 6 years, the HR of hospitalization for a CV outcome associated with adherence to antihypertensive drugs was 0.78 (95% CI 0.65–0.94) and 0.80 (95% CI 0.76–0.84) among patients aged 18–39 and 40–55 years, respectively. Adherence to antihypertensive drugs was negatively associated with CV and all-cause mortality in the older group (–18%, 6–28%; –30%, 27–33%), while showing no significant effects on these outcomes in the younger one.

Conclusions In a real-life setting, adherence to antihypertensive drug treatment reduced CV risk in young adults as much as in middle-aged patients.

* Corresponding author. Tel: +39 02 64485859, Fax: +39 02 64485899, Email: federico.rea@unimib.it

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Structured Graphical Abstract

Key Question

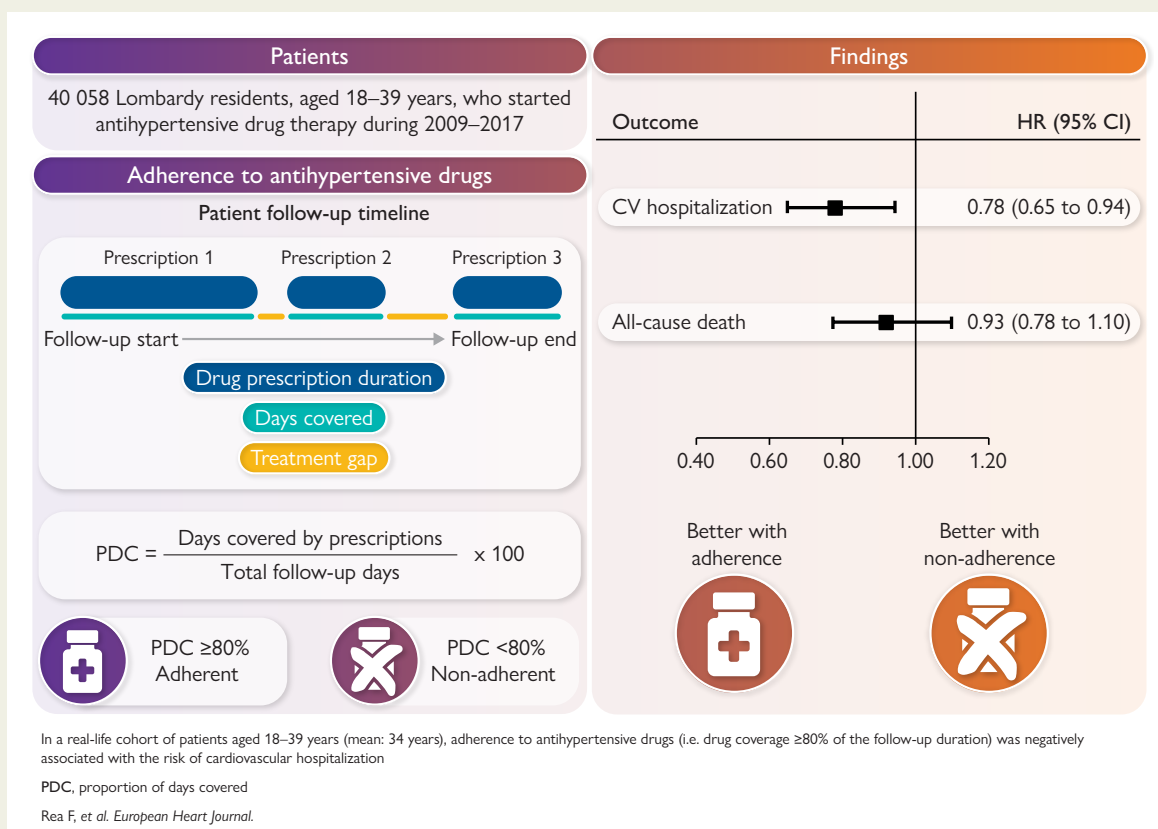
Does adherence to antihypertensive drug therapy reduce the risk of nonfatal and fatal outcomes in young adults?

Key Finding

In this cohort study of patients aged 18–39 years (mean: 34 years), adherence to antihypertensive drugs was associated with lower risk of cardiovascular hospitalizations.

Take Home Message

Antihypertensive drugs may have a beneficial effect also in young adults.



Keywords

Hypertension • Adherence • Clinical outcomes • Healthcare utilization databases • Population-based cohort studies

Introduction

High blood pressure (BP) is a major risk factor for cardiovascular (CV) morbid events and mortality in middle-aged and older individuals,¹ in whom trial-based evidence further shows that the risk can be markedly reduced by BP-lowering treatment.^{2,3} Evidence has also been provided that a BP increase is associated with CV outcomes in younger adults as well,^{4–8} but because of the low incidence of outcomes, at this younger age range, no evidence of the protective effect of treatment is available from trials,⁹ while data from the few available observational studies are non-univocal.^{4–7} Guidelines on hypertension acknowledge that in younger patients there is this important gap in knowledge but recommend BP-lowering treatment also in this age group based on extrapolation from the protective effect of treatment in middle-aged and older individuals.¹⁰

The aim of the present study was to evaluate the protective effect of antihypertensive drugs in young adults (18–39 years), using the data available

from the entire population of the Lombardy Region (Italy). The effect of drug treatment was assessed by estimating the association between high adherence to antihypertensive drugs and the onset of nonfatal and fatal outcomes compared with low adherence to antihypertensive drugs, an approach justified by the evidence that adherence is known to be inversely associated with the risk of CV outcomes and mortality. Data were collected over an average follow-up of about 6 years, and the analysis was extended to middle-aged patients (40–55 years) for comparison with an age range in which the benefit of treatment is well established.⁹

Methods

Setting

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, a region of Italy that accounts for almost

16% (about 10 million individuals) of its population. All Italian citizens have equal access to healthcare services as part of the National Health Service (NHS). Automated healthcare utilization databases allow the Lombardy Region to collect various information, including (i) demographic and administrative data on NHS beneficiaries; (ii) private and public hospital discharge records, including diagnoses and procedures coded according to the International Classification of Diseases, 9th Revision Clinical Modification (ICD-CM-9) classification system; (iii) outpatient drugs dispensing coded with the Anatomical Therapeutic Chemical (ATC) classification system; and (iv) death certificates (including the cause of death). Because a unique identification code was used for all databases, their linkage provided information on the complete care pathway supplied to NHS beneficiaries. To preserve privacy, each identification code is automatically converted into an anonymous code. Patient identification by the Regional Health Authority is only allowed upon request by judicial authorities. A detailed description of the healthcare utilization databases of the Lombardy region in the field of CV diseases is available in previous studies.^{11,12} Specific diagnostic and therapeutic codes used for the current study are given in [Supplementary data online, Table S1](#).

According to the rules of the Italian Medicines Agency,¹³ retrospective studies using administrative databases do not require protocol approval by the ethics committees.

Cohort selection and follow-up

The target population included Lombardy residents aged 18–55 years. Of these, those who received on distinct dates three dispensings for antihypertensive drugs within 6 months between 2009 and 2017 were identified and the date of the third prescription was defined as the *index date*. We considered that three prescriptions within 6 months are indicative of regular prescription and use. The antihypertensive drugs included all types of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium-channel blockers, dispensed in monotherapy as well as in combination. Patients were excluded if they (i) were not beneficiaries of the NHS for at least 5 years before the index date and (ii) received one or more antihypertensive drug prescriptions within the 5 years before the index date (to limit the analysis to newly treated hypertensive individuals). The patients recruited into the final cohort accumulated person-years of follow-up from the index date until the earliest date among clinical outcomes (see below), emigration, or 31 December 2019.

Adherence to antihypertensive medication

All antihypertensive drugs dispensed to cohort members during the follow-up were identified. The period covered by each drug prescription was calculated by dividing the total amount of the dispensed medication for the defined daily dose. For overlapping prescriptions, the individual was assumed to have exhausted the former prescription before starting the second one. Adherence to therapy was assessed as the cumulative number of days during which the medication was available divided by the number of days of follow-up, a quantity referred to as 'proportion of days covered' (PDC) by prescription.¹⁴ Patients with a PDC $\geq 80\%$ were defined as adherent to drug therapy, while those below this threshold (PDC 40–79 or <40 , see below) were considered non-adherent.

Clinical outcomes

The primary outcome was hospital admissions for CV events. The hospital discharge database was used to identify cohort members who experienced a hospitalization during follow-up in which stroke, myocardial infarction, or heart failure were listed as the primary diagnosis. The earliest date of hospital admission for these events was considered as the time of the CV event.

Secondary outcomes were CV and all-cause mortality.

Covariates

Characteristics assessed at the index date included sex, age, number of antihypertensive drugs, comorbidities (previous hospitalization for CV disease,

diabetes, kidney disease, cancer, and respiratory disease), and co-treatments (lipid-lowering drugs, antidiabetics, antithrombotics, antiarrhythmics, antidepressants, nonsteroidal anti-inflammatory drugs, hypouricemic agents, and drugs for pulmonary diseases). The clinical status of the patients was also assessed by the multisource comorbidity score, a multivariable prognostic score that has been shown to sensitively predict all-cause mortality and hospitalization in a large fraction (more than 20 million) of the Italian population.^{15,16} Four categories of clinical status were considered: good (score = 0), intermediate ($1 \leq \text{score} \leq 4$), poor ($5 \leq \text{score} \leq 9$), and very poor (score ≥ 10).

Data analysis

The probability of experiencing a specific outcome (i.e. stroke, myocardial infarction, and heart failure hospitalization, CV and all-cause death) was estimated through the cause-specific cumulative incidence function,¹⁷ a method that takes into account the competing nature of the considered outcomes. With this approach, a subject was assumed to experience the outcome only once, and the overall incidence at a given time was decomposed into a sum of the individual cumulative incidence functions for each type of outcome.

The cause-specific hazard regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between adherence to antihypertensive drugs and hospitalization for a CV event (i.e. myocardial infarction, heart failure, or stroke) and CV death,¹⁷ while the Cox model was used for all-cause death. Because adherence may change over time, the variable of adherence was included in the model as a time-dependent covariate. Adjustments were made for all the above-mentioned covariates. Analyses were stratified according to age, i.e. patients aged 18–39 and 40–55 years.

Sensitivity analysis

To verify the robustness of our findings, four sensitivity analyses were performed. First, because of the arbitrary nature of the PDC categorization, we used (i) more permissive (75%) and restrictive (85%) thresholds of PDC to define adherence to treatment and (ii) different adherence categories over the entire adherence spectrum (PDC $< 40\%$, from 40% to 79%, and $\geq 80\%$). Second, because young patients in treatment with antithrombotic drugs could be very different from the others, the analysis was repeated after removing these patients. Third, to investigate the possible presence of a 'healthy user' bias (patients adhering to antihypertensive drugs may also have a healthier lifestyle with a favourable effect on CV protection in general¹⁸), the association between adherence to antihypertensive drug therapy and outcomes presumably unrelated to hypertension or antihypertensive treatment^{19,20} was studied. These outcomes were the composite of hospital admissions for respiratory diseases, bacterial and skin infections, dental problems, diverticulitis, drug dependency, alcohol use, acute pancreatitis, herpes zoster, diphtheria urinary tract infections, foodborne bacterial infection, gall stones, gastrointestinal bleeds, gout, kidney stones, migraine, and sexually transmitted disease. In the case of a relationship between adherence to antihypertensive drugs and outcomes unrelated to hypertension (and thus of a possible 'healthy user' bias), further adjustment of the exposure-outcome association of interest for this quantified bias was planned. Briefly, the estimated bias (i.e. the HR of outcomes unrelated to hypertension associated with adherence to antihypertensive drugs) was subtracted to the main estimate (i.e. the HR of CV outcomes associated with adherence to antihypertensive drugs) in order to obtain an estimate of the exposure-outcome association of interest adjusted for the 'healthy user' bias, as described elsewhere.²¹ Fourth, in addition to adjusting the data for the available covariates (see above), further reduction of potential confounding was pursued by adopting the Monte Carlo sensitivity analysis,²² which adjusts the exposure-outcome association for an unmeasured confounder, set as to have a strong influence on clinical outcomes. We set the unmeasured confounder (i) to have a 10% or 25% prevalence in the study population, (ii) to increase CV risk by 1.5-

and 2-fold in patients exposed to the confounder compared to those not exposed to the confounder, and (iii) to be 1.5 and 2-fold less common in adherent patients than among non-adherent ones.

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA) was used for the analyses. For all hypotheses tested, two-tailed $P < .05$ were considered to be significant.

Results

Patients

Among the 539 214 patients aged 18–55 years receiving at least three consecutive antihypertensive drug prescriptions during 2009–17, 286,751 subjects met the inclusion criteria and were included in the study. Of these, 40 058 (14%) patients were aged 18–39 years (mean: 34 years) and 246 693 (86%) were aged 40–55 years (mean: 49 years) (Figure 1). About 80% of patients started treatment with one drug. The most frequent monotherapy was by far a renin-angiotensin system blocker, whereas a renin-angiotensin system blocker plus a diuretic was the most frequent two-drug combination (see Supplementary data online, Table S2).

The characteristics of the cohort members are shown in Table 1, separately for the two age groups. Almost half of the cohort members were women, one out of 10 patients was co-treated with antidepressant drugs and drugs for respiratory disease, and less than one out of 20 patients was hospitalized for CV diseases. About 30% and 44% of patients aged 18–39 years and 40–55 years, respectively, were adherent to antihypertensive drugs ($PDC \geq 80\%$) during the follow-up.

Clinical outcomes

Patients aged 18–39 years accumulated 251 384 person-years of observation (mean follow-up: 6.3 years) and generated 540 first hospital admissions for CV events (incidence rate: 2.1 cases every 1000 person-years), 89 CV deaths (0.4 cases every 1000 person-years), and 682 all-cause deaths (2.7 cases every 1000 person-years). Patients aged 40–55 years accumulated 1 487 923 person-years of observation (mean follow-up: 6.0 years) and generated 7009 first hospital

admissions for CV events (incidence rate: 4.7 cases every 1000 person-years), 931 CV deaths (0.6 cases every 1000 person-years), and 7449 all-cause deaths (4.9 cases every 1000 person-years). Cumulative incidences and incidence rates for specific CV events are reported in Figure 2 and Table 2.

Adherence with antihypertensive drugs and clinical outcomes

The association estimates between adherence to antihypertensive drugs and clinical outcomes are shown in Figure 3. The HR of hospitalization for a CV event associated with adherence to antihypertensive drugs was 0.78 (95% CI 0.65–0.94) and 0.80 (95% CI 0.76–0.84) among patients aged 18–39 and 40–55 years, respectively. There was no evidence that the association between adherence to antihypertensive drugs and hospitalization for a CV event differed between age groups ($P = .999$). The association between drug adherence and CV death was not assessed among patients aged 18–39 years because of the limited number of events (i.e. 89 CV deaths), while adherence to antihypertensive drugs was negatively associated with CV death among patients aged 40–55 years (HR 0.82, 95% CI 0.72–0.94). All-cause mortality was negatively associated with adherence in the older group (HR 0.70, 95% CI 0.67–0.73), while showing no significant difference in the younger one.

Sensitivity analyses

About 41% and 24% of patients aged 18–39 years and 40–55 years, respectively, showed a very low use of antihypertensive drugs ($PDC < 40\%$) during the follow-up. Figure 4 shows that the above results did not change by modifying the PDC categorization of adherence. Furthermore, there was a tendency for the HR of the risk of CV hospitalization to decrease progressively as adherence increased from the lowest to the intermediate and highest value. The main results did not modify by excluding patients prescribed antithrombotics (HR 0.73, 95% CI 0.60–0.89, $P = .002$). Adherence to antihypertensive drugs did not show any association with outcomes unrelated to hypertension or its treatment (see Methods) among patients aged 18–39 years (HR 0.94,

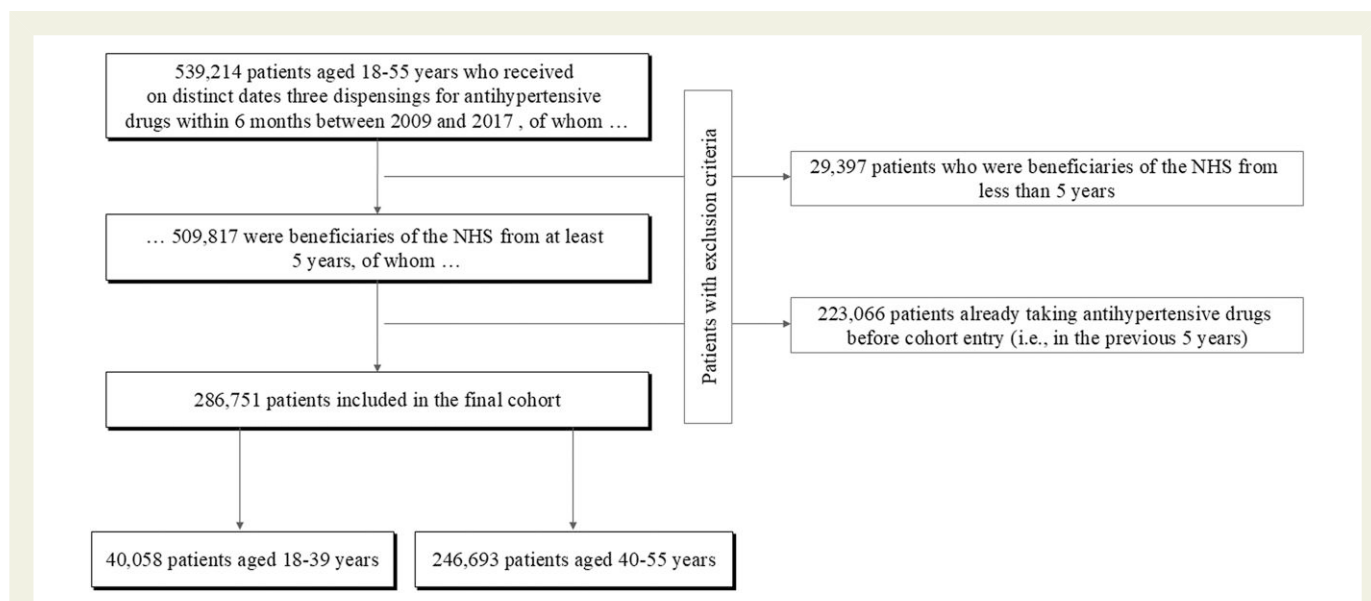


Figure 1 Inclusion and exclusion criteria used to select the final cohort

Table 1 Baseline characteristic of cohort members and adherence with antihypertensive drugs during follow-up in the two age groups

	18–39 years (n = 40 058)	40–55 years (n = 246 693)
Baseline		
Age (years): mean [SD]	34.1 [4.9]	48.7 [4.3]
Men	23 046 (57.5%)	142 595 (57.8%)
Antihypertensive drugs		
Monotherapy	32 807 (81.9%)	191 073 (77.5%)
Two drugs	6405 (16.0%)	49 698 (20.1%)
More than two drugs	846 (2.1%)	5922 (2.4%)
Other drugs		
Lipid-lowering agents	838 (2.1%)	14 218 (5.8%)
Antiarrhythmic agents	183 (0.5%)	1 119 (0.5%)
Antithrombotics	2785 (7.0%)	20 828 (8.4%)
Antidiabetic drugs	1008 (2.5%)	9147 (3.7%)
Hypouricemic agents	272 (0.7%)	1831 (0.7%)
Digitalis	7 (<0.1%)	69 (<0.1%)
Nitrates	8 (<0.1%)	163 (0.1%)
Nonsteroidal anti-inflammatory drugs	4730 (11.8%)	46 326 (16.2%)
Antimigraine drugs	1103 (2.8%)	5398 (2.2%)
Antidepressant drugs	3346 (8.4%)	22 016 (8.9%)
Drugs for respiratory disease	4817 (12.0%)	26 580 (10.8%)
Previous hospitalizations		
Ischaemic heart disease	898 (2.2%)	12 852 (5.2%)
Heart failure	380 (1.0%)	2238 (0.9%)
Cerebrovascular disease	388 (1.0%)	3777 (1.5%)
Venous thromboembolism	213 (0.5%)	945 (0.4%)
Cardiac valve	373 (0.9%)	1558 (0.6%)
Genetic thrombophilia and coagulation disorders	16 (<0.1%)	18 (<0.1%)
Diabetes	367 (0.9%)	3129 (1.3%)
Kidney disease	401 (1.0%)	1016 (0.4%)
Respiratory disease	1863 (4.7%)	8447 (3.4%)
Cancer	1520 (3.8%)	14 675 (6.0%)
Clinical status ^a		
Good	19 768 (49.4%)	120 139 (48.7%)
Intermediate	15 572 (38.9%)	96 174 (39.0%)
Poor	2661 (6.6%)	16 072 (6.5%)
Very poor	2057 (5.1%)	14 308 (5.8%)
During follow-up		
Adherence with antihypertensive therapy ^b		
Non-adherent	28 228 (70.5%)	138 141 (56.0%)
Adherent	11 830 (29.5%)	108 552 (44.0%)

SD, standard deviation.

^aClinical status was assessed by the multisource comorbidity score, and four categories were considered: good (score = 0), intermediate (score ≤ 1 to ≤ 4), poor (score ≤ 5 to ≤ 9), and very poor (score ≥ 10).^bAdherence was measured according to proportion of days covered, i.e. the proportion of days with antihypertensive drugs available with respect to the days of overall follow-up. Patients with a proportion of days covered ≥ 80% were defined as adherent to the drug therapy, while those below this threshold were considered non-adherent.

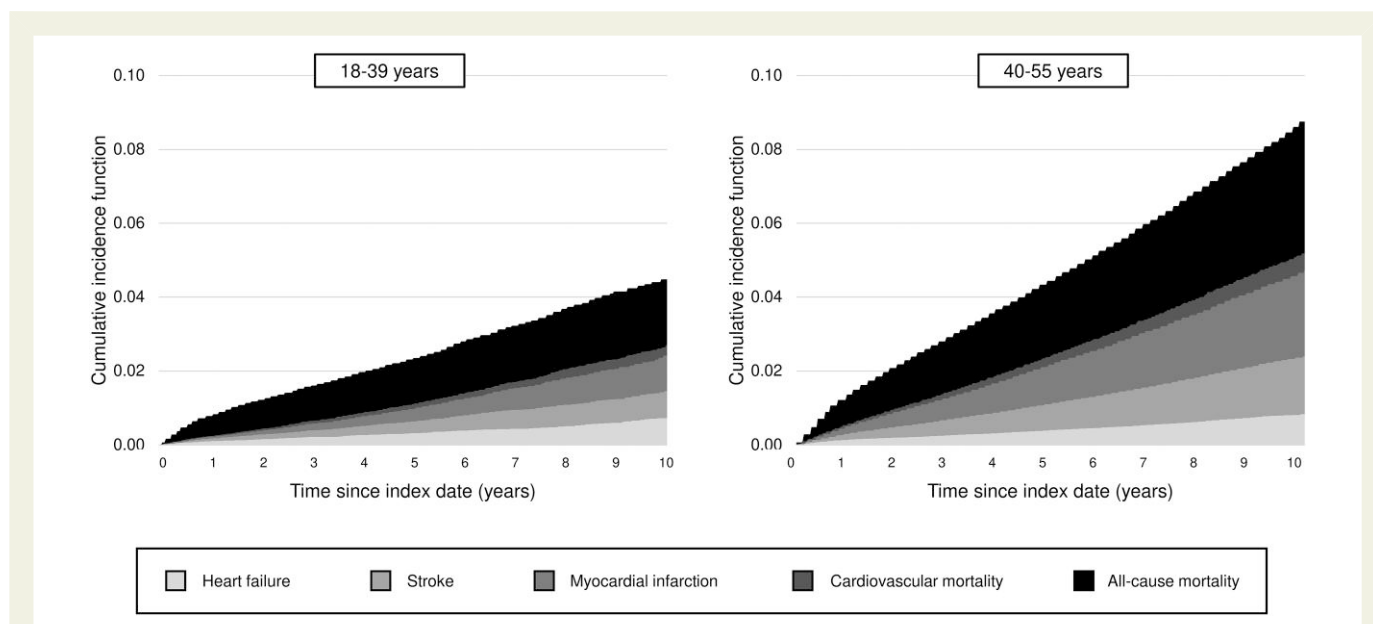


Figure 2 Cumulative incidence of hospitalization for cardiovascular outcomes or death according to age

Table 2 Incidence rates of clinical outcomes during follow-up according to age

Age	Outcome	Number of events	Rate (*1000 PY)
18–39 years	Any cardiovascular event	540	2.1
	Stroke	172	0.7
	Myocardial infarction	203	0.8
	Heart failure	165	0.7
	Cardiovascular mortality	89	0.4
	All-cause mortality	682	2.7
40–55 years	Any cardiovascular event	7009	4.7
	Stroke	2352	1.6
	Myocardial infarction	3389	2.3
	Heart failure	1268	0.9
	Cardiovascular mortality	931	0.6
	All-cause mortality	7449	4.9

PY, person-year.

95% CI 0.86–1.02, $P = 0.153$), while an association was seen in patients aged 40–55 years (HR 0.90, 95% CI 0.87–0.92, $P < .001$). In this older group of patients, the association between drug adherence and hospitalization for a CV event continued to remain significant after adjustment for the association between adherence and events unlikely to be related to hypertension (HR 0.90, 95% CI 0.85–0.96, $P = .001$).

The results of the Monte Carlo sensitivity analysis are shown in Figure 5. As expected, adjustment for the unmeasured confounder led to a lower estimate of the association between increased adherence and reduction of the risk of CV outcomes, the difference from the pre-adjustment value becoming more evident as the confounder–exposure relation became greater. However, the analysis shows that (i) the

confounder prevalence should reach 25% of the study population, and (ii) adherent patients should have a two-fold lower odds of exposure to the confounder than non-adherent individuals, with a two-fold increase of CV risk, to nullify the observed protective effect of adherence on the risk of hospitalization for CV outcomes.

Discussion

The present real-world study, based on almost 300 000 patients, shows that adherence to antihypertensive drugs was associated with a lower risk of hospitalization for CV events, which implies that antihypertensive

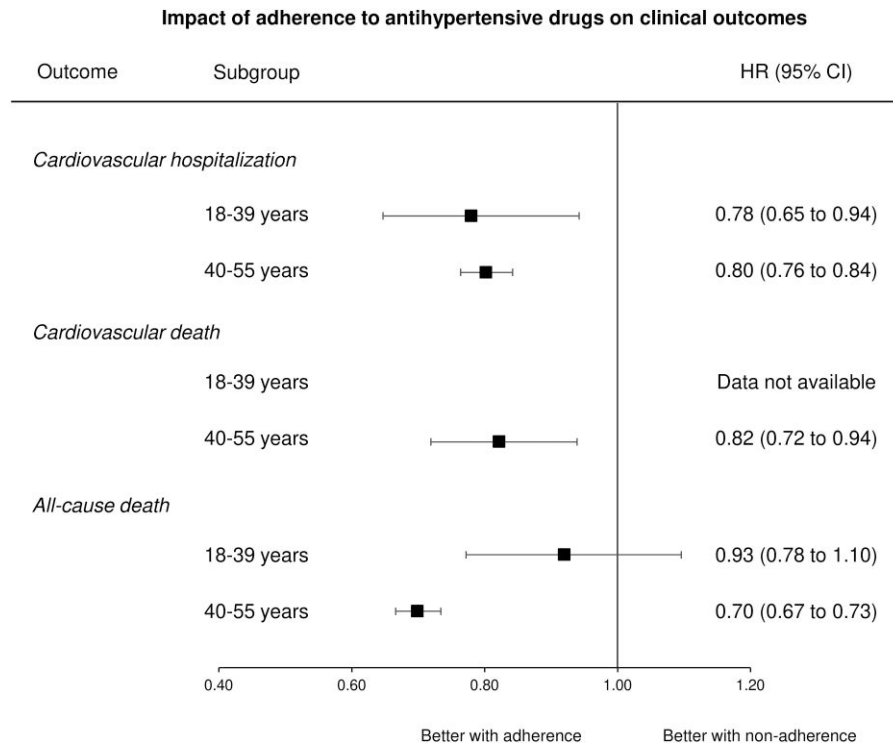


Figure 3 Hazard ratios and 95% confidence intervals for clinical outcomes (i.e. cardiovascular hospitalization, cardiovascular, and all-cause death) associated with adherence to antihypertensive drug therapy

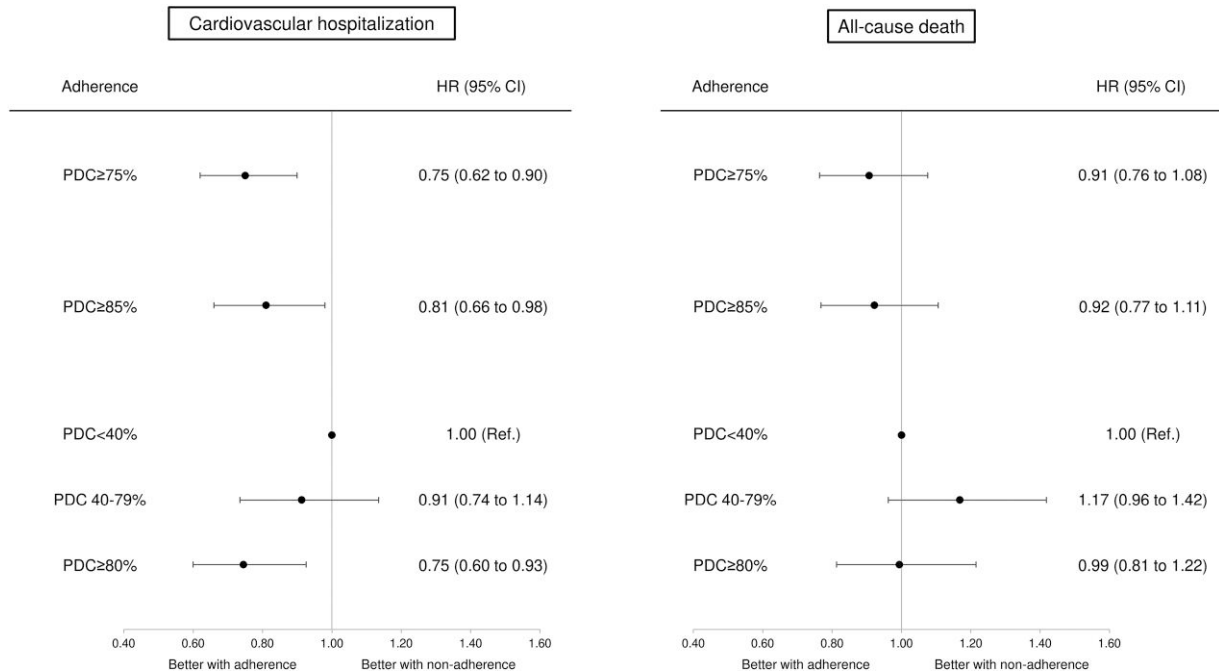


Figure 4 Hazard ratios and 95% confidence intervals for clinical outcomes (i.e. cardiovascular hospitalization and all-cause death) associated with adherence to antihypertensive drugs in patients aged 18–39 years by modifying the definition of adherence to antihypertensive drug treatment. Adherence was measured according to proportion of days covered, i.e. the proportion of days with antihypertensive drugs available with respect to the days of overall follow-up

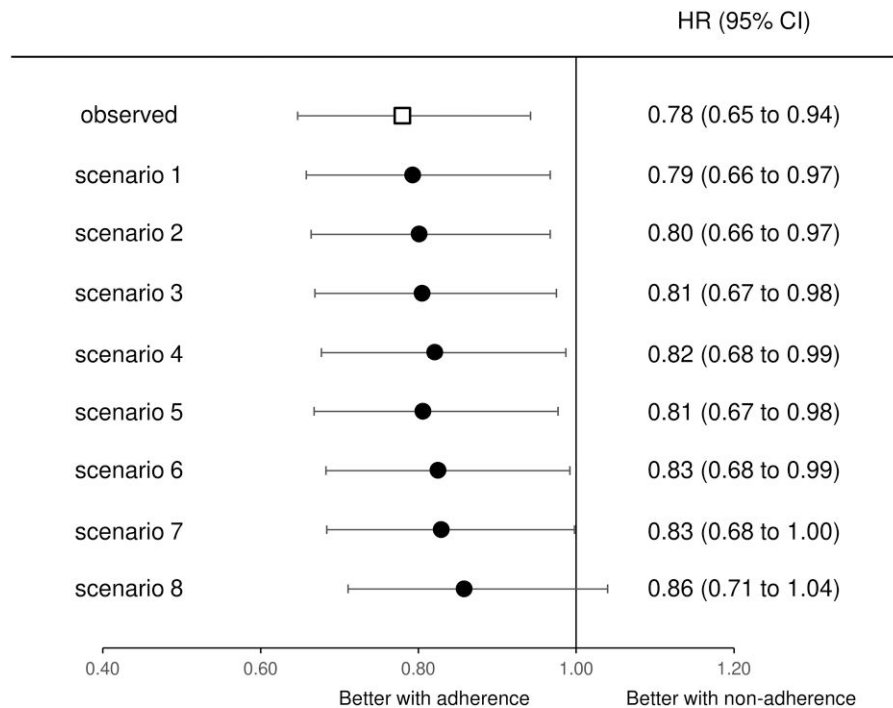


Figure 5 Influence of a confounder on the relationship between risk of hospitalization for cardiovascular disease (outcome) and adherence with antihypertensive drug treatment (exposure) in patients aged 18–39 years. The eight scenarios assumed the following value for the confounder's prevalence in the study population (P_C), confounder–(non)exposure association (OR_{CE}), and confounder–outcome association (RR_{CO}): (1) $P_C = 10\%$, $OR_{CE} = 1.5$, $RR_{CO} = 1.5$; (2) $P_C = 10\%$, $OR_{CE} = 2.0$, $RR_{CO} = 1.5$; (3) $P_C = 10\%$, $OR_{CE} = 1.5$, $RR_{CO} = 2.0$; (4) $P_C = 10\%$, $OR_{CE} = 2.0$, $RR_{CO} = 2.0$; (5) $P_C = 25\%$, $OR_{CE} = 1.5$, $RR_{CO} = 1.5$; (6) $P_C = 25\%$, $OR_{CE} = 2.0$, $RR_{CO} = 1.5$; (7) $P_C = 25\%$, $OR_{CE} = 1.5$, $RR_{CO} = 2.0$; and (8) $P_C = 25\%$, $OR_{CE} = 2.0$, $RR_{CO} = 2.0$

drug treatment had a beneficial effect. The novel finding, however, is that the benefit associated with adherence to antihypertensive drug treatment was visible not only in middle-aged patients, but also in young adults, namely, those aged 18–39 years (mean 34 years), in whom there was a 22% reduction in the risk of hospitalized CV events compared to non-adherent patients (see *Structured Graphical Abstract*). This extends the available evidence on the protective effect of antihypertensive drug treatment to a considerably younger age than that so far documented.⁹ In this context, it is also of interest to mention that (i) the benefit associated with adherence to antihypertensive treatment was similar in the younger and middle age groups of patients (20% and 22% reduction in the risk of hospitalization for CV events, respectively) and (ii) in middle-aged patients the protective effect of treatment included CV and all-cause mortality, while this was not the case in younger patients. This is likely not to originate from the inability of antihypertensive treatment to protect against fatal events in younger patients but rather from the considerably lower number of deaths available for analysis in the younger group, due to its much smaller size compared to the middle-aged group as well as to the fact that CV events rarely lead to death in young people. Indeed, the low number of CV deaths (i.e. 89, only 13% of the total number of deaths) prevented the evaluation of the beneficial effect of antihypertensive drugs with sufficient statistical power. This can make fatal events a suboptimal endpoint to assess the benefit of antihypertensive drugs (and, more in general, preventive treatments) in younger age ranges.

Several other aspects of our study deserve to be mentioned. First, although in the past the clinical value of adherence has been questioned by studies reporting similar effects of adherence to either active

treatment and placebo,¹⁸ the ability of increased adherence to protect against CV outcomes is since several years well documented not only for antihypertensive but also for lipid-lowering and antidiabetic treatment.^{23–26} This documentation is the background for the paramount importance given to adherence to treatment by policies and campaigns on CV prevention.²⁷ In this context, the present study provides further evidence that confounding explanations are responsible, including a health seeking behaviour that can make greater adherence a reflection of a healthier lifestyle or a better implementation of medical care in general. The further validation of this approach as a proxy of the protective effect of specific treatments supports its larger use especially in patients or conditions in which the benefits of treatment are not or cannot be documented by the trial approach. In addition to young hypertensive patients, this may be the case for very old patients, frail patients, and patients with special BP phenotypes or treatments of longer durations than the few year ones typical of trials.²⁸ Second, although the benefit associated with adherence to antihypertensive treatment was similar in the younger and middle age groups of patients, the absolute CV risk was lower among patients aged 18–39 years than among patients aged 40–55 years. Thus, the absolute risk reduction associated with adherence to antihypertensive drug therapy is expected to be lower among patients aged 18–39 years. Finally, because only 30% and 44% of young and middle-aged patients, respectively, had antihypertensive drugs available in more than 80% of the follow-up time, our study confirms the low long-term adherence to antihypertensive drug treatment previously documented for the general hypertensive population.^{12,29} It adds to previous evidence, however, that adherence to antihypertensive treatment may be particularly low in young people.

Our study has several strengths. First, the investigation was based on a large and unselected population because of the inclusion of virtually all residents in the database.¹¹ Second, the drug-dispensing database provided accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports have legal consequences.¹¹ Third, the adoption of the ‘user-only’ design (i.e. patients untreated were excluded) as well as of the ‘new-user’ approach (i.e. patients already taking antihypertensive drugs before cohort entry were excluded) reduced the potential for selection bias and confounding.^{30,31} Fourth, the robustness of our main findings was confirmed by several sensitivity analyses.

Our study has also limitations. First, despite the results of multiple sensitivity analyses, our results have the limitations inherent to the observational nature of the study, which means that our conclusion should find confirmation by bias-free randomized treatment trials. At present, a trial-based approach has not been possible because the low number of CV outcomes would require an unfeasible collection of data from an extremely large number of patients. Second, adherence to antihypertensive drugs was derived from drug dispensing, a widely used method to quantify adherence in population studies,¹⁴ which requires, however, the assumption that drug prescription reflects drug consumption by the patient, which may not be the case in all patients.¹¹ Third, due to the lack of the prescribed daily doses in our database, drug coverage was calculated according to a defined daily dose, leading to adherence misclassification in patients with higher or lower exposure to drugs than the predefined one. This, however, might have reduced rather than increased the outcome difference between adherence groups, thus underestimating the protective effect of drug treatment. Fourth, owing to privacy rules, the hospital diagnoses were not available for scrutiny, with a consequent lack of independent validation of hospital diagnosis.³² Fifth, in young adults, the limited number of events prevented the evaluation of the antihypertensive drug effect in important subgroups such as in women (only 142 hospitalizations), on specific CV events (only 172 hospital admissions for stroke), and on CV death (only 89 events) as well as to investigate differences between antihypertensive drug classes. Sixth, clinical characterization was probably not perfect because diseases not requiring hospitalization, such as mild-to moderate kidney disease, may have been underestimated in our study and covariates, included the number of antihypertensive drugs prescribed, were only assessed at baseline. Finally, because the Lombardy databases do not include some important clinical data (e.g. BP, serum cholesterol, blood glucose), lifestyle information (e.g. smoking status), and socio-economic and educational data, we cannot rule out the possibility that these unmeasured factors may confound the association between adherence to antihypertensive drugs and clinical outcomes. However, as far as socio-economic and educational data are concerned, income and educational status played no role in the use of antihypertensive drugs according to a previous study on the citizens of the Lombardy Region.³³ In addition, our data were adjusted for a large number of potential confounders, including treatment of several risk factors and CV diseases. Furthermore, one of the sensitivity analyses showed that, in order to nullify the observed association between drug adherence and hospitalization for CV events, an unmeasured confounder should be negatively associated with adherence and increase CV risk to such an extent to make the results explainable by unmeasured confounders unlikely.

In summary, in our real-life cohort of young adults, adherence to antihypertensive drugs reduced the risk of CV hospitalization as much as in middle-aged patients. This new finding supports the conclusion that antihypertensive drugs have a beneficial effect also in this age range. Given the observational nature of the study, randomized trial evidence is needed to confirm these findings.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

G.C. received research support from the European Community (EC), the Italian Medicines Agency (AIFA), the Italian Ministry of Education, University and Research (MIUR), and the Italian Ministry of Health. He took part to a variety of projects that were funded by pharmaceutical companies (i.e. Novartis, GSK, Roche, AMGEN, BMS, and Servier). He also received honoraria as member of Advisory Board from Roche. G.Ma. received honoraria for participation as speaker/chairman in national/international meetings from Bayer, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini Int., Merck, Novartis, Recordati, and Servier. Other authors declare that they have no competing interests.

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 licence 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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Ethical Approval

This study followed the principles of the Declaration of Helsinki. Data used in this study were anonymized before its use. According to Italian law, studies based entirely on registry data are exempt from patients informed consent and do not require approval from an ethics review board (General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on 10 August 2018; <https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/9124510>).

Pre-registered Clinical Trial Number

None supplied.

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