# Antihypertensive treatment changes and related clinical outcomes in older hospitalized patients

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**Abstract**

**Background:** Hypertension management in older patients represents a challenge, particularly when hospitalized.

Complete list of REPOSI Investigators and Giovani Internisti SIMI (GIS) is available in Appendix S2.

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**Objective:** The objective of this study is to investigate the determinants and related outcomes of antihypertensive drug prescription in a cohort of older hospitalized patients.

**Methods:** A total of 5671 patients from REPOSI (a prospective multicentre observational register of older Italian in-patients from internal medicine or geriatric wards) were considered; 4377 (77.2%) were hypertensive. Minimum treatment (MT) for hypertension was defined according to the 2018 ESC guidelines [an angiotensin-converting-enzyme-inhibitor (ACE-I) or an angiotensin-receptor-blocker (ARB) with a calcium-channel-blocker (CCB) and/or a thiazide diuretic; if >80 years old, an ACE-I or ARB or CCB or thiazide diuretic]. Determinants of MT discontinuation at discharge were assessed. Study outcomes were any cause rehospitalization/all cause death, all-cause death, cardiovascular (CV) hospitalization/death, CV death, non-CV death, evaluated according to the presence of MT at discharge.

**Results:** Hypertensive patients were older than normotensives, with a more impaired functional status, higher burden of comorbidity and polypharmacy. A total of 2233 patients were on MT at admission, 1766 were on MT at discharge. Discontinuation of MT was associated with the presence of comorbidities (lower odds for diabetes, higher odds for chronic kidney disease and dementia). An adjusted multivariable logistic regression analysis showed that MT for hypertension at discharge was associated with lower risk of all-cause death, all-cause death/hospitalization, CV death, CV death/hospitalization and non-CV death.

**Conclusions:** Guidelines-suggested MT for hypertension at discharge is associated with a lower risk of adverse clinical outcomes. Nevertheless, changes in antihypertensive treatment still occur in a significant proportion of older hospitalized patients.

**KEYWORDS**
antihypertensive drugs, cardiovascular events, hypertension, older patients, survival

## 1 | INTRODUCTION

Hypertension has a globally estimated prevalence of 20%–25% in the general population and a huge impact on health care systems.[1] The achievement of an appropriate blood pressure (BP) control strongly reduces cardiovascular (CV) morbidity and mortality.[2,3] Notably, the prevalence of hypertension increases with aging, with an estimated prevalence of ~60% in individuals older than 60 years[4] and of ~75% in those >75.[5] For many years, advanced age represented a barrier to the appropriate use of antihypertensive drugs, because of tolerability and safety concerns.[6] However, this conservative approach has been recently dismissed, as emphasized by the most recent European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines that contain special sections dedicated to patients older than 65 and 80 years (i.e., old and very old patients).[1]

This notwithstanding, the use of antihypertensive medicines still represents a clinical challenge in the elderly, for several reasons. First, older patients are more likely to be affected by numerous comorbidities—such as renal impairment,[7] chronic obstructive pulmonary disease (COPD),[8] diabetes and concomitant CV diseases[9,10]—and the treatment of these coexisting conditions may negatively interact with the safety and efficacy of antihypertensive medications. Furthermore, there are additional age-specific concerns (e.g., risk of postural hypotension,[11] limited life expectancy, dementia and metastatic malignancy), that make uncertain whether and to which extent

older patients might benefit from BP-lowering treatment in the context of their co-morbidities and reduced life expectancy.[5,7]

Typically, randomized controlled trials (RCTs) exclude very frail, dependent and postural hypotensive patients, thus limiting the quality of evidence-based treatment of hypertension in older patients, especially those needing hospitalization. Therefore, modifications of antihypertensive therapy are quite common during the acute phases of illness and many older patients are often undertreated after hospitalization.[7]

Therefore, the aim of this study was to investigate the impact of hospitalization on the modification of antihypertensive therapy in a cohort of older hypertensive patients and to characterize the clinical determinants of these changes as well as their association with clinical outcomes. To this end, we performed a subgroup analysis of the REPOSI register (REgistro POliterapie SIMI).

## 2 | METHODS

REPOSI, a multicentre, collaborative, observational register jointly held by the Italian Society of Internal Medicine (SIMI), the IRCCS Ca′ Granda Maggiore Policlinico Hospital Foundation and the IRCCS Mario Negri Institute of Pharmacological Research, is based on the participation of a representative network of internal medicine and geriatric wards in Italy. Full details about register design and specific aims have been previously reported.[12] Briefly, REPOSI was held for three non-consecutive years (2008, 2010 and 2012) and then annually from 2014 onwards. In each year, acute patients older than 65 years consecutively admitted to the participating medical wards were enlisted in the register over a period of 4 weeks on a quarterly basis (i.e., February, June, September and December). The study protocol was approved by the Ethics Committee of the Ca′ Granda Maggiore Policlinico Hospital Foundation and then by the local Committees of each participating site. REPOSI was conducted according to Good Clinical Practice recommendations and the Declaration of Helsinki. Concomitant diagnoses at hospital admission were coded according to the International Classification of Diseases—9th Edition (ICD-9) system. Medication use at admission and discharge was assessed according to the Anatomic Therapeutic Chemical (ATC) Classification System.

For the purpose of the present analysis, we considered 5671 patients enrolled from 2010 to 2016 with available follow-up data (Figure S1). At baseline, the presence of hypertension was defined by each investigator according to clinical history or use of antihypertensive drugs. To further define baseline clinical characteristics, the ICD-9 codes listed in the Supplementary Materials are used.

Polypharmacy was defined as the concomitant chronic use of 5 or more drugs.[12] Comorbidities were evaluated by means of the Cumulative Illness Rating Scale (CIRS) severity index (CIRS-SI) and comorbidity index (CIRS-CI).[13,14] The cognitive status was evaluated with the Short Blessed Test (SBT),[15] the presence of depression with the 4-item Geriatric Depression Scale (GDS-4)[16] and the functional status was evaluated with the Barthel index.[17] CIRS, SBT, GDS-4 and the Barthel index were collected from 2010 onwards, therefore they were available for 4714 REPOSI patients (80% of the study cohort).

### 2.1 | Evaluation of antihypertensive treatment

Antihypertensive treatment was assessed at admission and discharge. To understand its clinical impact in older subjects and to obtain a suitable model for the various index years, minimum treatment (MT) for hypertension was defined according to the 2018 ESC guidelines on hypertension[1]:

- an angiotensin converting enzyme-inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) in combination with a calcium channel blocker (CCB) and/or a thiazide diuretic and
- in subjects >80 years old, monotherapy with an ACE-I or ARB or CCB or thiazide diuretic.

### 2.2 | Follow-up and clinical outcomes

Follow-up data were collected at 3 and 12 months after hospital discharge through telephone interviews, except for the 2008 cohort for which only data at 3 months were available. For the cases who died, investigators in each participating ward collected information to evaluate cause and circumstances of death by interviewing the attending physicians or reviewing medical charts/discharge letters. For this study, death causes were classified as: (i) all-cause death; (ii) CV death and (iii) non-CV death. Data on re-hospitalization were collected during follow-up telephone interviews and classified according to the main reason for re-admission: (i) all-cause re-hospitalization and (ii) CV re-hospitalization. Moreover, two composite outcomes were also evaluated: (i) any death/re-hospitalization and (ii) CV-related death or re-hospitalization.

## 2.3 | Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQR) or mean and standard deviation (SD), with differences between groups evaluated according to the Mann–Whitney *U* test and Student's T test accordingly. Categorical variables were reported as counts and percentages and between groups differences were evaluated according to the chi-square test.

In order to identify factors associated with the discontinuation of MT at discharge, a univariate logistic analysis was performed, selecting the characteristics that were significantly different at the descriptive analysis, and all variables with a $p < .10$ were included in the multivariate models. We also performed two multivariate models: (i) one including health determinants and (ii) the second including clinical characteristics.

To evaluate the association between antihypertensive MT and clinical outcomes, a logistic regression analysis was performed employing both univariate and multivariate regression models. We compiled sequential multivariate models, as follows: (i) Model 1: adjusted for age, sex, body mass index (BMI); (ii) Model 2: as Model 1 plus CIRS-SI, CIRS-CI; (iii) Model 3: as Model 1 plus all comorbidities evaluated at baseline; (iv) Model 4: as Model 3 plus SBT, GDS-4, Barthel Index and (v) Model 5: as Model 4 plus polypharmacy.

Furthermore, we performed for each model the following sensitivity analyses: (i) patients categorized according to the use of antihypertensive drugs at admission and discharge; (ii) number of antihypertensive drugs at discharge and (iii) difference in number of antihypertensive drugs at discharge compared with admission. A two-sided *p* value <.05 was considered statistically significant. All analyses were performed using SPSS v. 25.0 (IBM, NY, USA). Reporting of the study conforms to broad EQUATOR guidelines.[18]

# 3 | RESULTS

Among the 5671 patients recruited in the register, 4377 (77.2%) were hypertensive at admission (Figure S1), and their baseline characteristics according to the presence or not of hypertension are reported in Table 1. Compared with normotensive patients, hypertensives were older ($p < .001$) and had a more impaired functional status according to a lower Barthel Index ($p = .008$), and higher CIRS-SI and CIRC-CI (both $p < .001$). Furthermore, they had a higher rate of comorbidities such as diabetes ($p < .001$), hypercholesterolemia ($p = .001$), coronary artery disease ($p < .001$), heart failure ($p < .001$) and chronic kidney disease (CKD) ($p < .001$) but the prevalence of tumours was higher in normotensive patients ($p < .001$) (Table 1). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were higher in hypertensive patients (both $p < .001$) (Table 1). Blood pressure values at discharge were available only for 4759 (83.9%) patients. SBP was significantly higher in hypertensive patients (mean [SD] 127.4 [15.7] mmHg vs. 122.8 [14.6] mmHg, $p < .001$), as well as DBP (72.2 [9.6] mmHg vs 71.0 [9.4] mmHg, $p < .001$, respectively).

Hypertensive patients had a higher rate of polypharmacy than normotensives ($p < .001$), with data on drugs prescription reported in Table S1; particularly, the prescription rate was higher for each of the analysed drugs, including antiplatelet agents, oral anticoagulants and proton-pump inhibitors, with more significant differences observed for ACE-I, ARBs, beta-blockers, CCB and diuretics.

## 3.1 | Hypertension minimum treatment and post-hospitalization changes

At hospital admission, a total of 2233 patients (51.0%) were on MT, while at discharge MT was reported for 1766 cases (40.3%). Hence, 197 patients (4.5%) prescribed MT at discharge were not on this regimen at admission, 664 patients (15.2%) on MT at admission were no longer prescribed at discharge. For 1569 patients (35.8%), MT was maintained at discharge, while 1947 patients (44.5%) did not receive MT at admission nor at discharge. The mean (±SD) number of antihypertensive drugs prescribed at admission was 1.05 (±0.83), while at discharge it was 0.84 (±0.83) with a mean change of −0.21 (±0.73). Compared with admission, the mean (±SD) change in drug number at discharge was −0.07 (±0.40) for patients not on MT at admission or discharge, −1.43 (±0.58) for patients on MT at admission but not at discharge, +1.20 (±0.48) for patients on MT at discharge but not at admission and − 0.05 (±0.45) for patients on MT both at admission and discharge.

At baseline (Table 2), patients no longer on MT at discharge had a higher CIRS-SI ($p = .017$), SBT ($p < .001$), GDS-4 ($p = .044$) and a lower Barthel Index ($p < .001$) than those who remained on MT. Both SBP and DBP values were lower in patients no longer on MT. Furthermore, patients no longer on MT at discharge had a higher prevalence of previous CKD ($p = .003$), low creatinine clearance at admission ($p < .001$) and dementia ($p = .001$) (Table 2). No differences were found in SBP and DBP values at discharge in patients who maintained and dismissed MT (data not shown).

**TABLE 1** Baseline characteristics according to the presence of hypertension

| ***N* = 5671** | **No Hypertension *N* = 1294** | **Hypertension *N* = 4377** | ***p*** |
|---|---|---|---|
| Age, *years* median [IQR] | 78 [72–84] | 80 [74–85] | <.001 |
| Female Sex, *n* (%) | 604 (46.7) | 2285 (52.2) | .001 |
| BMI, $kg/m^2$ median [IQR] *4947* | 24.2 [21.6–27.2] | 25.7 [23.0–29.1] | <.001 |
| SBP, *mmHg* mean (SD) *5614* | 127.9 (20.3) | 133.9 (22.5) | <.001 |
| DBP, *mmHg* mean (SD) *5614* | 72.6 (11.6) | 74.1 (12.0) | <.001 |
| CIRS-SI, median [IQR] *5650* | 1.46 [1.31–1.69] | 1.69 [1.46–1.92] | <.001 |
| CIRS-CI, median [IQR] *5650* | 2 [1–3] | 3 [2–5] | <.001 |
| SBT, median [IQR] *5022* | 6 [2–14] | 8 [2–14] | .0812 |
| GDS-4, median [IQR] *4662* | 1 [0–2] | 1 [0–2] | .072 |
| Barthel Index, median [IQR] *4173* | 94 [69–100] | 91 [67–100] | .008 |
| Smoking Habit, *n* (%) *5520* | 604 (48.0) | 1910 (44.8) | .049 |
| Alcohol Habit, *n* (%) *5491* | 577 (45.7) | 1829 (43.2) | .120 |
| Previous Admissions, *n* (%) | 414 (32.0) | 1502 (34.3) | .121 |
| Diabetes, *n* (%) | 250 (19.3) | 1364 (31.2) | <.001 |
| Hypercholesterolemia, *n* (%) | 55 (4.3) | 303 (6.9) | .001 |
| Coronary Artery Disease, *n* (%) | 152 (11.7) | 1005 (23.0) | <.001 |
| Myocardial Infarction, *n* (%) | 23 (1.8) | 157 (3.6) | .001 |
| PAD, *n* (%) | 42 (3.2) | 168 (3.8) | .321 |
| Heart Failure, *n* (%) | 151 (11.7) | 831 (19.0) | <.001 |
| Stroke/TIA, *n* (%) | 69 (5.3) | 329 (7.5) | .007 |
| Atrial Fibrillation, *n* (%) | 211 (16.3) | 1120 (25.6) | <.001 |
| Chronic Liver Disease, *n* (%) | 147 (11.4) | 320 (7.3) | <.001 |
| COPD, *n* (%) | 267 (20.6) | 981 (22.4) | .175 |
| Previous CKD, *n* (%) | 176 (13.6) | 1115 (25.5) | <.001 |
| CrCl, *mL/min* median [IQR] *5046* | 58.2 [41.0–76.5] | 50.0 [34.3–68.1] | <.001 |
| Dementia, *n* (%) | 132 (10.2) | 406 (9.3) | .318 |
| Neoplasm, *n* (%) | 225 (17.4) | 527 (12.0) | <.001 |
| Drugs administered, median number [IQR] *5487* | 4 [2–6] | 6 [4–8] | <.001 |
| Polypharmacy, *n* (%) *5487* | 505 (44.0) | 2966 (68.4) | <.001 |

Abbreviations: BMI, Body Mass Index; CI, Comorbidity Index; IRS, Cumulative Illness Rating Scale; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; CrCl, Creatinine Clearance; DBP, Diastolic blood Pressure; GDS, Geriatric Depression Scale; IQR, Interquartile Range; PAD, Peripheral Arterial Disease; SBP, Systolic Blood Pressure; SBT, Short Blessed Test; SI, Severity Index; TIA, Transient Ischemic Attach.

## 3.2 | Predictors of MT discontinuation between admission and discharge

To assess the clinical factors associated with MT discontinuation in those patients who were on MT at admission but not at discharge, we performed a logistic regression analysis, from which we excluded patients who were not on MT at admission but were on it at discharge. At univariate analysis, both clinical and functional status were significantly associated with MT discontinuation, with the worst functional status more likely to be associated with no MT at discharge. Furthermore, both the presence of diabetes and coronary artery disease were associated with lower chance of MT discontinuation, meaning that diabetics and/or patients with ischemic cardiac disease were more likely to be on MT for hypertension at discharge, while previous CKD, low creatinine clearance at baseline and a history of dementia were positively associated with MT discontinuation (Table 3), therefore patients with renal involvement or disease or affected by cognitive impairment were more likely to be discharged without MT for hypertension. In the multivariate analysis, none of the functional indexes did independently predict MT discontinuation at discharge. Instead, the multivariate model including comorbidities showed that patients with a history of diabetes were less likely to report MT discontinuation ($p = .022$), and that previous CKD, low creatinine clearance at baseline and

**TABLE 2** Baseline characteristics according to changes in antihypertensive treatment at discharge

| ***N* = 4377** | **Minimum Treatment Maintained *N* = 1569** | **Minimum Treatment Dismissed *N* = 664** | ***p*** |
|---|---|---|---|
| Age, *years* median [IQR] | 83 [80–87] | 83 [77–87] | .394 |
| Female Sex, *n* (%) | 900 (57.4) | 365 (55.0) | .297 |
| BMI, $kg/m^2$ median [IQR] *1940* | 25.7 [23.2–28.9] | 25.7 [22.8–28.7] | .376 |
| SBP, *mmHg* mean (SD) *2219* | 137.2 (22.5) | 131.7 (22.6) | <.001 |
| DBP, *mmHg* mean (SD) 2219 | 74.8 (11.8) | 72.8 (12.4) | <.001 |
| CIRS-CI, median [IQR] *2232* | 3 [2–4] | 3 [2–5] | .056 |
| SBT, median [IQR] *2004* | 8 [2–14] | 9 [4–16] | <.001 |
| GDS-4, median [IQR] *1867* | 1 [0–2] | 1 [0–2] | .044 |
| Barthel Index, median [IQR] *1646* | 92.00 [72.00–100] | 86.50 [54.75–100] | <.001 |
| Smoking Habit, *n* (%) *2177* | 613 (40.0) | 255 (39.7) | .895 |
| Alcohol Habit, *n* (%) *2158* | 632 (41.7) | 270 (42.1) | .843 |
| Previous Admissions, *n* (%) | 483 (30.8) | 185 (27.9) | .168 |
| Diabetes, *n* (%) | 501 (31.9) | 185 (27.9) | .057 |
| Hypercholesterolemia, *n* (%) | 113 (7.2) | 48 (7.2) | .982 |
| Coronary Artery Disease, *n* (%) | 374 (23.8) | 135 (20.3) | .071 |
| Myocardial Infarction, *n* (%) | 53 (3.4) | 28 (4.2) | .332 |
| PAD, *n* (%) | 63 (4.0) | 27 (4.1) | .955 |
| Heart Failure, *n* (%) | 273 (17.4) | 130 (19.6) | .221 |
| Stroke/TIA, *n* (%) | 121 (7.7) | 59 (8.9) | .352 |
| Atrial Fibrillation, *n* (%) | 400 (25.5) | 172 (25.9) | .839 |
| Chronic Liver Disease, *n* (%) | 82 (5.2) | 42 (6.3) | .300 |
| COPD, *n* (%) | 329 (21.0) | 125 (18.8) | .250 |
| Previous CKD, *n* (%) | 390 (24.9) | 206 (31.0) | .003 |
| CrCl < 30 ml/min, *n* (%) *1980* | 281 (19.3) | 165 (28.1) | <.001 |
| Dementia, *n* (%) | 126 (8.0) | 82 (12.3) | .001 |
| Neoplasm, *n* (%) | 163 (10.4) | 75 (11.3) | .526 |
| Polypharmacy, *n* (%) *5487* | 1116 (71.1) | 466 (70.2) | .653 |

*Note*: For acronyms, see Table 1.

a history of dementia were all positively and independently associated with higher odds of MT discontinuation (Table 4).

## 3.3 | Impact on outcomes

All patients on MT at discharge compared with those not on MT were included in the outcomes analysis. Cases not on MT at discharge (Table S2) experienced an increased rate of the composite outcomes hospitalization/all-cause death and CV hospitalization/death. In particular, all-cause death, CV death and non-CV death rates were all increased in patients not on MT at discharge (Table S2). In the sequential logistic multivariate analysis models, MT at discharge was found associated in all models with a lower risk of both the composite outcomes as well as with the risk of all death outcomes, with model 5 showing a reduction of the risk ranging from 40% to 54% (Table 4).

Furthermore, several sensitivity analyses were carried out in order to understand the impact of MT at discharge and the number of antihypertensive drugs on the clinical outcomes (Table S3). Hence, in a fully adjusted multivariate model (Model 5 in the main analysis) the use of MT, both at baseline and discharge or only at discharge, were associated with a lower risk of all the examined outcomes.

Similarly, a higher number of antihypertensive drugs at discharge was again associated with a lower risk of outcomes, as well as the difference in number of drugs between admission and discharge was associated with a lower risk of hospitalization/all-cause death, all-cause death, non-CV death occurrence (Table S3). Moreover, being no longer on MT was associated with an increased risk for all-cause and non-CV death.

**TABLE 3** Logistic regression analysis for changes in minimum treatment at discharge

| | Univariate | | Multivariable Model 1 | | Multivariable Model 2 | |
|---|---|---|---|---|---|---|
| | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| CIRS-SI | 1.50 (1.14–1.97) | .004 | 1.48 (0.60–3.65) | .391 | | |
| CIRS-CI | 1.06 (1.01–1.11) | .016 | 0.97 (0.83–1.14) | .726 | | |
| SBT | 1.02 (1.01–1.04) | <.001 | 0.99 (0.98–1.01) | .498 | | |
| GDS-4 | 1.10 (1.01–1.19) | .033 | 1.09 (0.98–1.21) | .098 | | |
| Barthel Index *(by 10 point)* | 0.92 (0.89–0.95) | <.001 | 0.96 (0.91–1.02) | .228 | | |
| Diabetes | 0.82 (0.67–1.01) | .057 | | | 0.77 (0.62–0.96) | .022 |
| Coronary Artery Disease | 0.82 (0.65–1.02) | .071 | | | 0.84 (0.66–1.07) | .168 |
| Previous CKD | 1.36 (1.11–1.66) | .003 | | | 1.30 (1.02–1.67) | .035 |
| CrCl < 30 mL/min | 1.58 (1.26–1.99) | <.001 | | | 1.38 (1.07–1.77) | .013 |
| Dementia | 1.61 (1.20–2.17) | .001 | | | 1.58 (1.15–2.18) | .003 |

Abbreivations: CI, Confidence Interval; OR, Odds Ratio; for other acronym, see Table 1.

**TABLE 4** Logistic regression analysis for adverse outcomes

| | **Minimum Treatment vs. No Minimum Treatment** | | | | | |
|---|---|---|---|---|---|---|
| | **Univariate** | | **Multivariable Model 1** | | **Multivariable Model 2** | |
| | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| Hospitalization/All-Cause Death | 0.55 (0.47–0.63) | <.001 | 0.51 (0.43–0.61) | <.001 | 0.54 (0.45–0.64) | <.001 |
| All-Cause Death | 0.38 (0.31–0.48) | <.001 | 0.31 (0.24–0.40) | <.001 | 0.33 (0.25–0.42) | <.001 |
| CV Hospitalization/Death | 0.53 (0.41–0.68) | <.001 | 0.44 (0.33–0.58) | <.001 | 0.47 (0.35–0.62) | <.001 |
| CV Death | 0.37 (0.26–0.52) | <.001 | 0.32 (0.21–0.47) | <.001 | 0.34 (0.23–0.50) | <.001 |
| Non-CV Death | 0.44 (0.34–0.57) | <.001 | 0.35 (0.27–0.46) | <.001 | 0.35 (0.27–0.47) | <.001 |
| | **Multivariable Model 3** | | **Multivariable Model 4** | | **Multivariable Model 5** | |
| | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| Hospitalization/All-Cause Death | 0.54 (0.46–0.63) | <.001 | 0.59 (0.48–0.73) | <.001 | 0.60 (0.49–0.75) | <.001 |
| All-Cause Death | 0.36 (0.28–0.45) | <.001 | 0.46 (0.34–0.62) | <.001 | 0.46 (0.34–0.62) | <.001 |
| CV Hospitalization/Death | 0.54 (0.41–0.70) | <.001 | 0.60 (0.42–0.86) | .005 | 0.61 (0.42–0.87) | .006 |
| CV Death | 0.43 (0.30–0.61) | <.001 | 0.57 (0.35–0.92) | .021 | 0.57 (0.35–0.93) | .024 |
| Non-CV Death | 0.41 (0.30–0.56) | <.001 | 0.52 (0.35–0.77) | .001 | 0.53 (0.35–0.78) | .002 |

*Note*: Model 1 = adjusted for age, sex, BMI, SBP at baseline, DBP at baseline; Model 2 = adjusted for previous covariates plus CIRS-SI, CIRS-CI; Model 3 = adjusted for Model 1 plus diabetes mellitus, hypercholesterolemia, CAD, PAD, heart failure, stroke/TIA, atrial fibrillation, chronic liver disease, COPD, CKD, dementia, neoplasm; Model 4 = adjusted for Model 3 plus SBT, GDS-4, Barthel Index; Model 5 = adjusted for Model 4 plus polypharmacy; for acronyms, see previous tables.

## 4 | DISCUSSION

In this retrospective analysis, derived from the nationwide database of older inpatients included in the REPOSI register, we confirmed a high prevalence of hypertension in the elderly and that hypertensive patients were older, with a more impaired clinical status and more burdened with multimorbidity and polypharmacy. While at admission more than a half of patients were on MT according to clinical practice guidelines, at discharge this proportion did decrease to 40%. Patients who discontinued MT had a more impaired clinical and functional status at admission, even if the functional indexes were not associated with discontinuation. On the other hand, such comorbidities as dementia, diabetes and CKD were independent predictors of discontinuation. Finally, subjects still on MT

at discharge had a lower risk for all the clinical outcomes examined (Figure 1).

Pertaining to the role of comorbidities in determining treatment modifications, in our population CKD appeared to play a significant role, perhaps because of concerns regarding the adverse renal effects of antihypertensive drugs. In agreement with previous findings,[19] dementia was associated with a higher probability of MT discontinuation in our population. Conversely, the present findings emphasize the role of diabetes in determining MT confirmation or even intensification, because of the relevant impact of the coexistence of diabetes and hypertension on the risk of outcomes.[20] Judgement on treatment needs to be based on a combined evaluation of clinical and functional status and presence of comorbidities, rather than on a single condition. Our findings support that none of the various domains is more important in influencing management approach, emphasizing that all dimensions are important and that a multidimensional approach is needed to manage older patients and tackle their significant complexity and frailty.[21]

In keeping with this multidimensional approach, another concern regards in-hospital drugs management. It is well established that a comprehensive evaluation performed during hospitalization and the resulting drug treatment revision and reconciliation have a great impact on clinical outcomes in older patients. Indeed, previous reports identified hospitalization as a major factor that induced antihypertensive treatment modifications or discontinuation mainly due to adverse reactions.[22,23] Therefore, the correct management of any pharmacological therapy should be a balance between the correct prescription and the avoidance of adverse effects, and this seems to be particularly important in older subjects during in-hospital stay and pharmacological reconciliation process.

However, notwithstanding the fact that an algorithm has been proposed to evaluate hospitalized patients with high BP,[24] there are no RCTs on hospitalized hypertensive patients and no guidelines specifically address this situation. Treatment and BP endpoints in daily clinical practice in hospitalized hypertensive patients remain a gap in evidence, resulting in a non-standardized approach with difficulties in applying guidelines recommendations, mainly tailored on outpatients, to the in-hospital setting. Our research clearly underlines that further studies are required to address this clinical need.

## 4.1 | Comparison with the available evidence

A major strength of this study is that it is the first register-based real-world study investigating the associations between antihypertensive drug treatment, in-hospital treatment changes and survival in older patients hospitalized in internal medicine and geriatric wards. We observed that maintaining an antihypertensive MT according to guidelines was associated with a significant clinical benefit in older hypertensive cases and that MT maintenance was associated with a survival advantage. Presently, there are few data on hospitalized hypertensive older patients and scanty data are available regarding treatment changes at hospital discharge, with no specific indications in the American[25] nor European[1] guidelines. In them, cut-offs values stem from randomized controlled trials based on office BP measurements, whereas cut-offs stemming from inpatients have not been used. One of the most important randomized clinical trials on BP treatment targets is the Systolic Blood Pressure Intervention Trial (SPRINT). It compared the outcome of patients at high CV risk treated

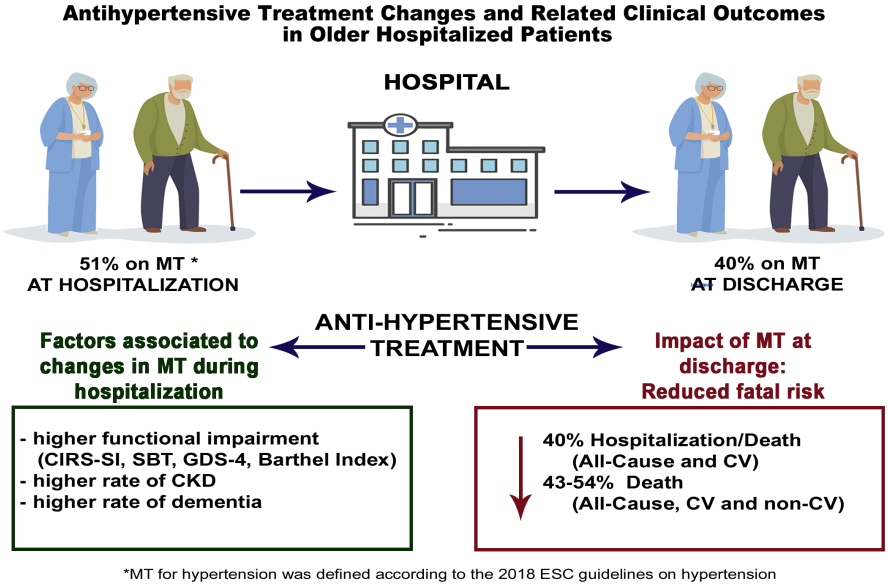


**FIGURE 1** Antihypertensive treatment changes and related clinical outcomes in older hospitalized patients. CKD, Chronic Kidney Disease; CIRS-SI, Cumulative Illness Rating Scale Severity Index; CV, Cardiovascular; GDS, Geriatric Depression Scale; SBT, Short Blessed Test; MT, Minimum Treatment; this figure has been designed using images from Freepik.com.

to a target of systolic BP of 120 mmHg with that of patients with a target of 140 mmHg.[26] In SPRINT, the analysis of the subgroup of subjects aged 75 or more[27] showed that an intensified BP treatment was able to reduce fatal and non-fatal major CV events and death from any cause also in this age group, thus emphasizing that these subjects can benefit from antihypertensive drug therapy.

In a previous study, Anderson et al.[28,29] reported a 14% increase in antihypertensive drug prescription after hospital discharge for non-CV diseases, due to the recording of a high BP during hospitalization in patients with previously well controlled outpatient BP. However, the observed prescription intensification was not associated with a reduction in CV events or BP at 1 year, but was instead associated with an early increased risk of adverse outcomes (i.e., readmissions and serious adverse events within 30 days).[28] On these findings, Anderson et al suggested that drug intensification should be generally avoided, particularly in patients with well controlled outpatient BP. A possible explanation for the negative finding by Anderson et al is that transiently elevated BP is a common occurrence in patients hospitalized for reasons other than hypertension—e.g., anxiety, volume overload, failure to administer the patient usual antihypertensive therapy, inability to assume oral medications[30]—and that this may result in unnecessary and sometimes harmful treatment intensification. In this context, the present study shows instead that the achievement and maintenance of a guideline-adherent MT is associated with positive clinical outcomes. However, when compared with Anderson's findings some differences should be acknowledged. First, they performed a retrospective cohort study, while the present findings are based on data from a register. Furthermore, their evaluation of hypertension drug treatment was based on recommendations from different guidelines.[1,25] In addition, even if both studies did evaluate patients older than 65 years of age, their population was younger than that of the present study.

### 4.2 | Study limitations

Due the observational nature of this register, BP values were not collected according to a standardized method for BP measurement. Also, we could not analyse the relationship of MT according to newly diagnosed/established hypertension. Furthermore, the original study was not designed nor powered to examine the specific subgroups reported in this analysis. However, observational studies are suitable to describe the natural history of a disease and to generate or confirm new pathophysiological hypothesis.[31] Another limitation is that the outcomes were not centrally adjudicated but reported by investigators. Finally, while the nationwide impact of the REPOSI makes these data relevant, the fact that the register study was carried out exclusively in Italy suggests caution to generalize these results to global hypertensive subjects.

## 5 | CONCLUSIONS

In this observational study on hypertensive older inpatients, we found a significant decrease after hospitalization in the use of a guideline-adherent antihypertensive MT. This prescription change is associated with the clinical status, and some specific comorbidities are independently associated with MT discontinuation. After hospital discharge, maintaining an antihypertensive guideline-adherent MT is associated with a lower risk of major clinical outcomes, particularly with a marked reduction of all cause, CV and non-CV mortality risk.


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### CONFLICT OF INTEREST

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