Compendium on the Pathophysiology and Treatment of Hypertension

Two-Drug Combinations as First-Step Antihypertensive Treatment

Giuseppe Mancia, Federico Rea, Giovanni Corrao, Guido Grassi

Abstract: **Blood pressure (BP) control in patients with hypertension is variable worldwide, and in general, it results largely unsatisfactory. Factors responsible for this phenomenon include insufficient national cardiovascular healthcare policies for prevention, poor patient compliance with prescribed treatment schedules, and the reluctance of physicians to modify treatment strategies when BP is still elevated, that is, the so-called therapeutic inertia. A further important factor favoring poor BP control is the limited use of combination drug treatment, despite evidence of its superior ability to control BP in patients with difficult-to-treat hypertension. In addition, combination treatment allows to achieve BP control more easily (and more quickly) as compared with monotherapy. This article, after briefly examining the main features of BP control, will review the importance in the treatment of hypertension of the drug combination strategy, based on the recommendations of the 2018 European Society of Cardiology/European Society of Hypertension guidelines. Empahsis will be given to the drug combination treatment as first step of the antihypertensive therapeutic intervention. The potential drawbacks and barriers to combination drug treatment as initial therapeutic strategy will also be briefly discussed. (*Circ Res*. 2019;124:1113-1123. DOI: 10.1161/CIRCRESAHA.118.313294.)**

Key Words: blood pressure ■ cardiology ■ cardiovascular risk ■ drug combinations ■ humans ■ hypertension ■ treatment adherence

There is general agreement that perhaps the most important problem faced by hypertension today is the low rate of blood pressure (BP) control achieved by treatment in medical practice, that is, the high number of hypertensive patients who fail to reach the BP values recommended by guidelines as the ones maximizing patients' protection by antihypertensive treatment. This rate is highly heterogeneous between countries, but overall, no more than 15% to 20% of the world hypertensive population has been shown to achieve BP control when the target BP is set at <140/90 mm Hg,[1,2] with a further striking reduction when lower BP control values are indicated,[3] such as in the past for diabetic patients[4] and, currently, for a large fraction of the hypertensive population.[5,6] Because, compared with hypertensive patients achieving BP control, uncontrolled patients exhibit a marked persistent elevation in the risk of cardiovascular events and death,[7] low rate of BP control is regarded as a major reason why hypertension remains the main cause of death for the world population,[8] thereby representing a fundamental problem for public health.

This article will address some of the factors responsible for the widespread inability to control an elevated BP in real life. The conclusion will be reached that this does not depend on the available therapeutic armamentarium but rather on its inappropriate use in the context of the treatment strategies recommended in the past. Arguments will be provided against the time-honored initial monotherapy and in favor of initial combination treatment, preferably by 2 drugs in a single pill, to oppose 2 major barriers to successful BP-lowering treatment; that is, low adherence to the prescribed treatment regimen and therapeutic inertia.

Strategies Based on Initial Monotherapy

Decades of research have offered antihypertensive treatment a large number of medicaments that can effectively reduce an elevated BP. Used alone or in combination with one another, the available medicaments can control BP in the vast majority of the hypertensive population, limiting the fraction in which no BP control can be achieved, that is, resistant hypertension, to about 5% to 10% of all hypertensive individuals.[6,9–12] Thus, the problem of poor BP control in real life does not originate from lack of suitable antihypertensive agents but from other factors that prevent them from expressing their therapeutic potential. As discussed by the recent guidelines of the European Society of Cardiology and the European Society of Hypertension, a most important factor can be the treatment strategies recommended in the past, because of their common foundation on initial monotherapy.[6]

Monotherapy at Increasing Doses

The guidelines that first addressed the treatment of hypertension in the late seventies and the eighties advised treatment

From the University of Milano-Bicocca, Italy (G.M.); Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research and Pharmacoepidemiology, Unit of Biostatistics, Epidemiology, and Public Health (F.R., G.C.) and Department of Medicine and Surgery Clinica Medica (G.G.), University of Milano-Bicocca, Italy; and IRCCS Mutimedica, Sesto San Giovanni, Milan, Italy (G.G.).

Correspondence to Professor Giuseppe Mancia, University of Milano-Bicocca, P.za dei Daini, 4 – 20126 Milano, Italy. Email giuseppe.mancia@unimib.it

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
BP	blood pressure
HOPE-3	Heart Outcomes Prevention Evaluation-3
VALUE	Valsartan Antihypertensive Long-Term Evaluation

to fully exploit the BP-lowering potential of monotherapy, by progressively increasing the dose of the initially prescribed drug until no further incremental BP response was obtained.[13,14] It is now clear, however, that, although the BP reduction may become somewhat greater, a progressive increase in the drug dose frequently leads to a substantial increase in the drug-related side effects, this being particularly the case for classes of common use, such as diuretics, β-blockers, and calcium channel blockers.[15] Because (1) side effects are the most important cause of treatment discontinuation[16] and (2) treatment discontinuation is associated with an increased cardiovascular risk,[17] this treatment strategy has been abandoned by subsequent guidelines and today finds no place in the management of hypertension, even in selected groups of patients.

Sequential Monotherapy

Sequential monotherapy has never been formally recommended by guidelines but is a widely used treatment strategy in medical practice. It refers to the switching from one monotherapy to another in the attempt to find the single medicament that controls the elevated BP. As discussed in a previous report,[18] this has some therapeutic rationale because, within a given patient, the magnitude of the BP reduction may vary from one drug class to another.[19] Furthermore, changing monotherapy is required when serious (but in some patients even nuisance) side effects to the initially prescribed drug occur. However, sequential monotherapy is a time-consuming strategy, which may generate patients' frustration, loss of confidence in the doctor, and, ultimately, treatment discontinuation. Furthermore, no matter which drug or drug dose is used, monotherapy cannot control BP in many hypertensive patients, its BP-lowering ability being particularly limited in important clinical subgroups, such as in patients with isolated systolic hypertension, advanced organ damage, or diabetes mellitus.[20–22]Thus, rather than being an asset, large use of the sequential monotherapy strategy may represent an important cause of poor BP control in real life.

Step-Care Treatment

Initial monotherapy followed by the addition of a second, a third, or even a fourth or fifth drug, commonly known as step-care treatment, has been the main treatment strategy recommended by the hypertension guidelines issued in the last 2 to 3 decades.[4,23–29] This strategy has a clear pathophysiological rationale because (1) hypertension is almost always due to a variety of pathogenetic factors and (2) BP is a multiregulated variable, with neural, humoral, and local mechanisms working in concert or against each other to change or defend a given BP value. This makes the multiple BP-lowering mechanisms made available by the combination of different drugs much more effective than one or few. Full support comes from the evidence that compared with increasing the dose of the initial drug, adding a second drug can increase by about 5× the chance of achieving BP control[30] regardless which drug is used initially and which is added. It further comes from the evidence that only about 40% of the patients respond to monotherapy (and only about 30% reach BP control), whereas 75% to 80% of the patients respond to 2 drugs and 90% to 95% to ≥3 drugs.[15,30] Thus, in principle, moving from initial monotherapy to the sequential prescription of ≥2 drugs if BP remains uncontrolled represents a good treatment strategy whose ability to protect hypertensive patients from their high cardiovascular risk has been repeatedly documented by its adoption in virtually all outcome-based randomized trials. The problem, however, is that the highly controlled environment of a trial favours a high adherence to the treatment prescription,[31] as well as a limited inertia,[32] to the adoption of progressive treatment steps, at striking variance from real life in which adherence is low and inertia to treatment uptitration high. In a large number (about 800 000) of residents of Lombardy (a region of Northern Italy) newly treated with antihypertensive drugs, >60% showed, over the years, ≥1 episodes of prolonged treatment discontinuation as documented by the failure to renew antihypertensive drug prescription for ≥3 months. Furthermore in the whole study population, patients adherent to antihypertensive drugs for >75% of the follow-up time were only 24%[33,34] (Figure 1). As to therapeutic inertia, it is well known that in a large number of patients, treatment is not upgraded when, at a given visit, BP is found to be uncontrolled.[35,36] The important adverse role of inertia for BP control is also demonstrated by the persistent prevalence of patients under antihypertensive monotherapy in most countries (Figure 2), against the recommendation of guidelines to move to combination treatment in at least 3 of 4 patients to achieve BP control.[28]

Combination Treatment as the First Step

Both the 2003 American[24] and the 2007 and 2013 European Society of Cardiology/European Society of Hypertension guidelines[4,28] advised initial use of 2 antihypertensive drugs in selected hypertensive groups of patients. For the American guidelines, an initial 2-drug combination was recommended when baseline BP was at least 20/10 mm Hg (systolic/diastolic) above the target of <140/90 mm Hg, thus being ≥160/100 mm Hg. For the European guidelines, it was also recommended in the absence of an especially marked BP elevation if patients had a high or very high cardiovascular risk, such as when there is a history of cardiovascular or renal event. It was argued that under these circumstances, BP may have to be lowered to <130/80 mm Hg, rather than to <140/90 mm Hg as in the general hypertensive population—a goal that can be beyond the BP-lowering potential of a single antihypertensive drug. It was also argued that the faster BP reduction associated with initial use of 2 antihypertensive drugs[37,38] might provide a more timely protection in patients in whom a high or very high cardiovascular risk makes an early cardiovascular event possible.

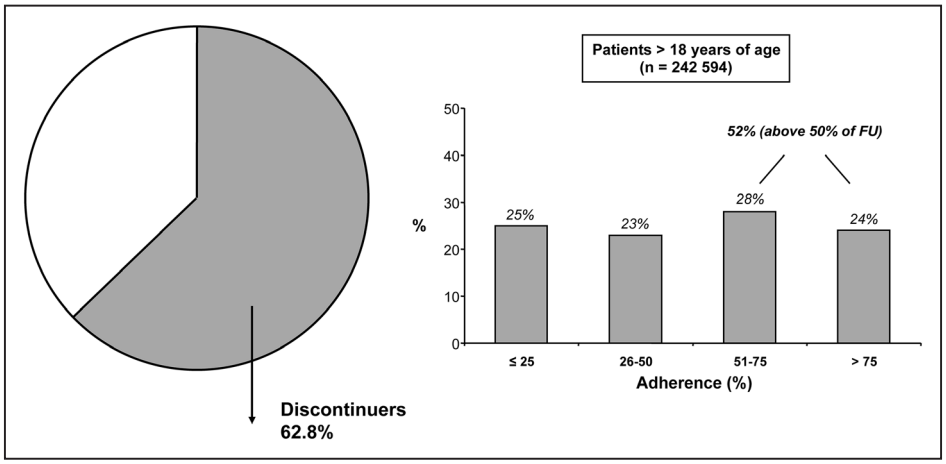

Figure 1. Percentage of patients newly treated with antihypertensive drugs who exhibited ≥1 periods of treatment discontinuation (left) and average adherence to antihypertensive treatment of the newly treated cohort during a several year follow-up (FU; right). Discontinuation was defined as ≥3 mo under no prescription. Average adherence was quantified as percentage of the FU time covered by antihypertensive drug prescriptions. The database includes all residents (10 million) of a Northern Italian Region (Lombardy). Data derived from Corrao et al.[33,34]

The hypertension guidelines recently issued in the United States and Europe[5,6] have expanded on these previous recommendations and now advise initial use of 2 antihypertensive drugs in most hypertensive patients. This because new evidence has shown that initial combination treatment not only extends to an earlier time window the protection of high cardiovascular risk individuals but it has additional short-term and even long-term advantages in the more general hypertensive population (Table). Initial use of 2 antihypertensive drugs is followed not only by a prompter BP reduction but also by a reduced heterogeneity of the BP response between patients. It is characterized by a steeper relationship between the doses of the combination components used and the BP effect that makes subsequent uptitration of treatment easier, faster, and more frequently successful.[6] Except for some hypertension categories, such as the elderly and the frail, older patients, the risk of excessive hypotension is only slightly greater than that accompanying initial monotherapy or placebo even in patients with a modest initial BP elevation (grade 1 hypertension) as documented by a recent randomized trial.[39] Most importantly, evidence has been obtained that initial combination treatment may be associated with long-term advantages of crucial clinical relevance that appear to involve the hypertensive population at large. Figure 3 shows that, compared with initial monotherapy, patients belonging to the National Health and Nutrition Examination Survey and starting treatment with either free or single-pill combinations of drugs exhibited a more frequent BP control (BP <140/90 mm Hg) 1 year later.[40] This may result from an attenuation of the 2 main barriers to long-term BP control, that is, low adherence to the prescribed treatment and therapeutic inertia. Figure 4 (top) shows that in a large number (about 440 000) of residents of the Lombardy region initiating antihypertensive treatment with a single drug, the risk of treatment discontinuation varied markedly according to the drug prescribed, the highest and lowest discontinuation rate being shown by diuretics and angiotensin receptor antagonists, respectively.[41] It further shows, however, that treatment initiation with drug combinations was associated with a much lower discontinuation rate than initial monotherapy, regardless whether the drugs were given separately or a in a single-pill format (Figure 4, bottom).[41] This was the case also when, in 2 similarly large cohorts (about 440 000 patients each) a comparison was made between (1) initial treatment with combinations including a diuretic versus a diuretic monotherapy or (2) initial treatment with combinations without a diuretic versus a monotherapy other than a diuretic.[41,42] We can speculate that the prompter BP response to initial combination treatment may have a positive psychological impact on the patients, namely that it may increase their motivation to continue treatment on a prolonged basis. Whatever the reasons, however, a long-term increase in adherence to treatment has important therapeutic effects because increasing adherence to antihypertensive treatment is positively related to the achieved BP values, with an increase in the rate of BP control.[43] Furthermore, a large body of evidence is available that adherence to antihypertensive treatment is related to the incidence and risk of cardiovascular events either in the context of randomized trials and in real-life medicine.[31,44–47] In the Lombardy population, for example, increasing adherence to antihypertensive drugs from <25% to >75% of the overall treatment time was found to be associated with a progressive reduction in the risk of hospitalization for ischemic heart disease, cerebrovascular disease, and heart failure, this being the case both in the general hypertensive population and in its elderly fraction, including patients >85 years of age.[42,44–46]

Recent evidence is also available that, compared with initial monotherapy, initial 2-drug combination treatment can effectively bypass therapeutic inertia. This is illustrated in Figure 5, which refers the antihypertensive drugs prescribed to patients starting treatment with 1 or 2 antihypertensive drugs, 6 months and 1, 2, or 3 years after treatment initiation. In patients initiating treatment with 1 drug, monotherapy continued to remain by far the prevailing prescription (Figure 5A), with a marked difference in the use of combination treatment with the group initially treated with 2 drugs for the whole 3-year follow-up (Figure 5B).[48] These observations also document that in medical practice, (1) therapeutic inertia can be extremely common and (2) an inertial therapeutic

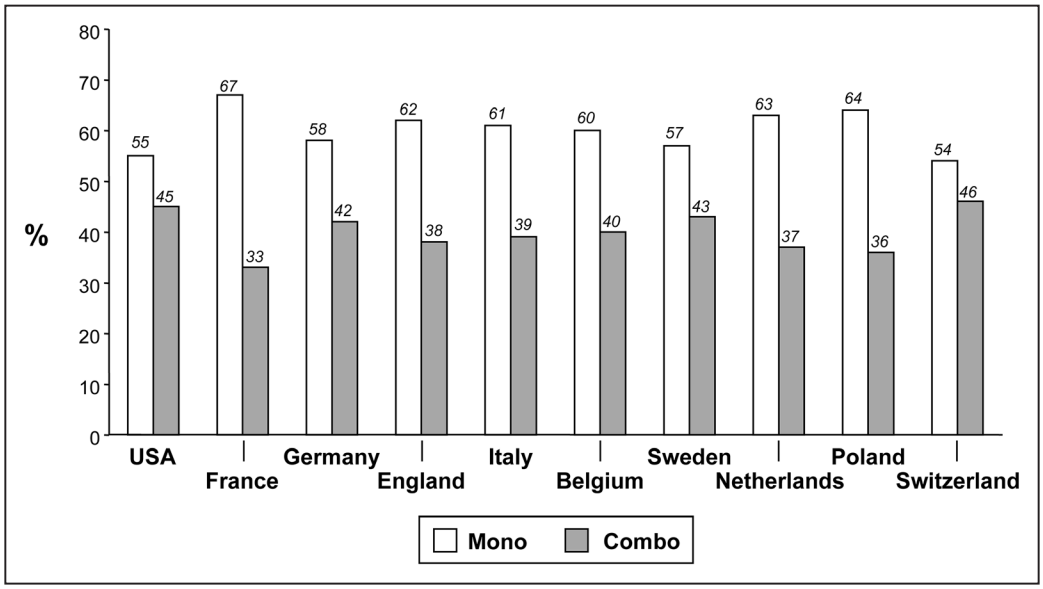

Figure 2. Percentage of hypertensive patients under monotherapy (open bars) or under combination drug treatment (closed bars) in a number of European and extra-European countries.

attitude involves also patients starting treatment with 2 drugs in whom prescriptions of ≥3 antihypertensive drugs remained substantially below the percentage (≥25%) shown by trials to be required for BP control. In these patients, however, the initial choice of 2 drugs bypassed the monotherapy problem, presumably allowing control the elevated BP to be much more effectively achieved.

An additional important question is whether the initial 2-drug combinations should be administered separately or as a single, fixed-dose tablet. Fixed-dose combinations may make uptitration to effective treatment less flexible. However, a large number of studies has shown that reducing the number of daily pills is associated with an improved adherence to the prescribed antihypertensive treatment regimen[49–52] regardless the background level of cardiovascular risk, the treatment duration, and the patients' age and comorbidities.[53,54] This has made guidelines almost invariably favorable to this type of treatment. The 2018 European guidelines[6] recommend the initial treatment strategy to make use, whenever possible, of single-tablet, 2-drug combinations, taking advantage of the availability of many combinations (eg, a blocker of the renin-angiotensin system with a calcium channel blocker or a diuretic) in ranges of doses of the combination components, thus favoring treatment flexibility.

Initial 2-Drug Combination Treatment and Cardiovascular Protection

In the HOPE-3 trial (Heart Outcomes Prevention Evaluation-3), patients with grade 1 hypertension (140–159 mm Hg, average 154 mm Hg systolic BP) exhibited, compared with placebo, a 24% reduction in the risk of cardiovascular outcomes with a treatment based on the initial administration of 2 antihypertensive agents (candesartan+hydrochlorothiazide).[39] However, this proved the ability of initial combination treatment to protect hypertensive patients while providing no information on whether, in patients starting treatment with a drug combination, cardiovascular protection is greater than in those starting treatment with 1 drug and moving to a combination later, the initial combination treatment strategy thereby being superior to the stepwise treatment approach. To date, this question has not been addressed by an outcome-based trial with a controlled randomized design, and we doubt that this would provide a meaningful answer to the above question because, as already mentioned, the advantages of initial combination treatment versus initial monotherapy, that is, improved adherence to treatment and reduced therapeutic inertia, important as they may be in real-life conditions, are minimized by the controlled medical environment of randomized trials. An example is provided by the trials which have looked via a double-blind design to the long-term BP-lowering effect of an initial 2-drug administration versus the administration of the combination components in monotherapy followed by the addition of the second drug few months later. Predictably, the initial combination treatment was associated with a faster BP reduction, but, after the addition of the second drug, the monotherapy groups caught up and no between-group BP difference was anymore visible at the end of the treatment period.[37,38]

Randomized trials apart, many outcome-based observational studies, including those performed in conditions closer to real life, support, indirectly or directly, the conclusion that, compared with initial monotherapy, initial combination treatment may be associated with a lower incidence and risk

Table. Rationale for Initial 2-Drug Combination Therapy

Greater blood pressure reduction vs monotherapy
Steeper dose–blood pressure response relationship
No/small increase in hypotensive episodes
More frequent blood pressure control
Better adherence to drug treatment
Reduced therapeutic inertia

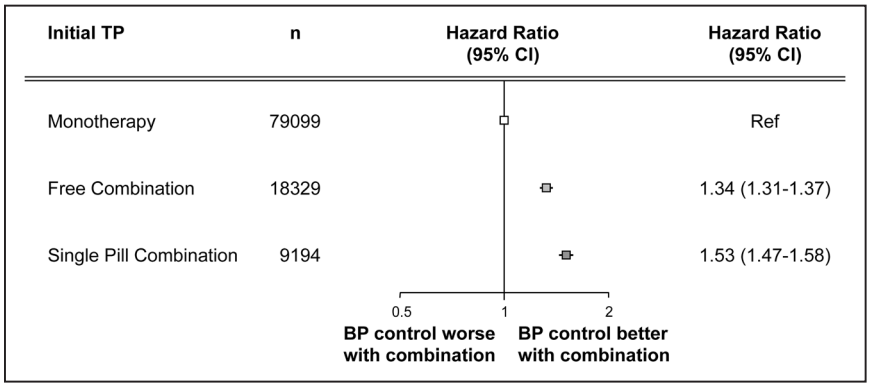

Figure 3. Multivariable hazard ratios (and 95% CIs) of obtaining blood pressure (BP) control 1 y after initiating treatment with monotherapy, free 2-drug combination therapy, or single-pill 2-drug combination therapy. Combination of 2 drugs as initial treatment strategy was associated with a greater chance of achieving BP control than monotherapy. TP indicates therapy. Data derived from Egan et al.[40]

of cardiovascular morbid and fatal events. A post hoc analysis of the hypertensive, high-cardiovascular-risk patients of the VALUE trial (Valsartan Antihypertensive Long-Term Evaluation) has shown that in patients in whom treatment achieved BP control within few months (a goal easier to be achieved with initial 2-drug combinations, see above), cardiovascular outcomes were less than in patients in whom BP control was achieved at a later time.[55] Similar data have been reported by a post hoc analysis of the hypertensive patients of the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) and ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) in which achieving BP control within few months was more protective than achieving BP control later.[56,57] Finally, in a study of about 1700 hypertensive patients, Gradman et al[58] have shown that (1) initial combination treatment lead to a better BP control than initial monotherapy over the following 2 years and (2) this difference translated into a cardiovascular events difference, with a significantly lower risk of combined cardiovascular events (−38%), as well as of heart failure (−36%) and stroke (−21%).

This has been more recently shown also in 3 studies that have used the administrative database of the residents of Lombardy (about 10 million), thereby addressing the issue in the context of real-life medical practice. Of the 2 million patients who were found to be on antihypertensive drugs, those starting and continuing treatment with drug combinations exibited the lowest risk of cardiovascular events. This resulted in an about 20% reduction of hospitalization for coronary disease, stroke, or heart failure compared to those treated with initial and subsequent monotherapy, initial combination therapy followed by monotherapy, and even initial monotherapy followed by combination therapy[42] (Figure 6A). Furthermore, in the study in which patients started antihypertensive treatment with a single drug and largely remained on monotherapy because of therapeutic inertia (see above), hospitalization for combined and cause-specific cardiovascular events was significantly greater than that of patients starting treatment with 2 drugs (Figure 6B).[48] Finally, in patients in whom the risk of hospitalization for cardiovascular events was assessed for 1 year after treatment initiation, patients starting treatment with 2 drugs showed less cardiovascular events compared with patients starting treatment with 1 drug only (Figure 6C).[59] It is important to emphasize that in the last 2 studies, data analysis was performed by the propensity score approach. This equalizes a large number of variables involved in the cardiovascular risk of the 2 groups at baseline, minimizing the well-known limitation of comparing nonrandomized groups, that is, that the results originate from initial clinical differences rather than from the subsequent treatment strategies. Because

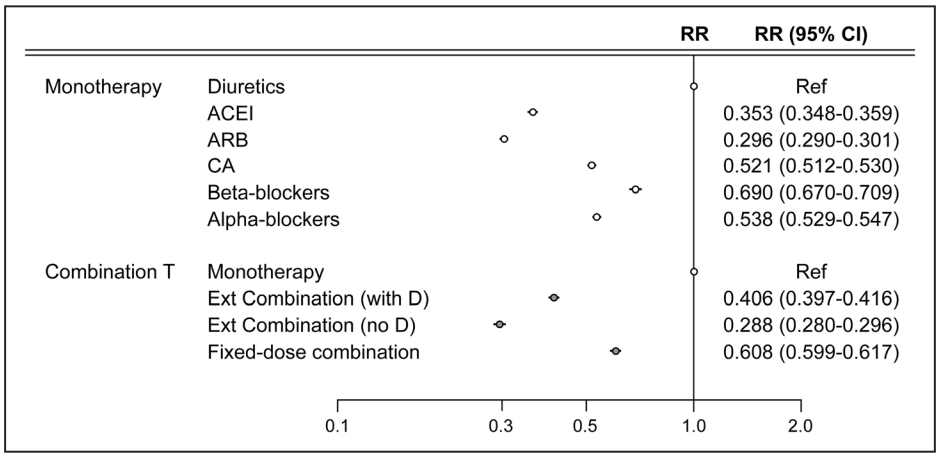

Figure 4. Monotherapy shows the risk of discontinuation of antihypertensive drug treatment according to the class of antihypertensive drugs used as initial monotherapy. Combination refers to the risk of drug treatment discontinuation in patients initially treated with drug combinations, in the free or fixed-dose form. Discontinuation of treatment in patients under initial monotherapy (average of all monotherapies) was taken as reference. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CA, calcium antagonists; D, diuretics; Ext, extemporaneous; RR, relative risk; and T, therapy. Data derived from Mancia et al.[41]

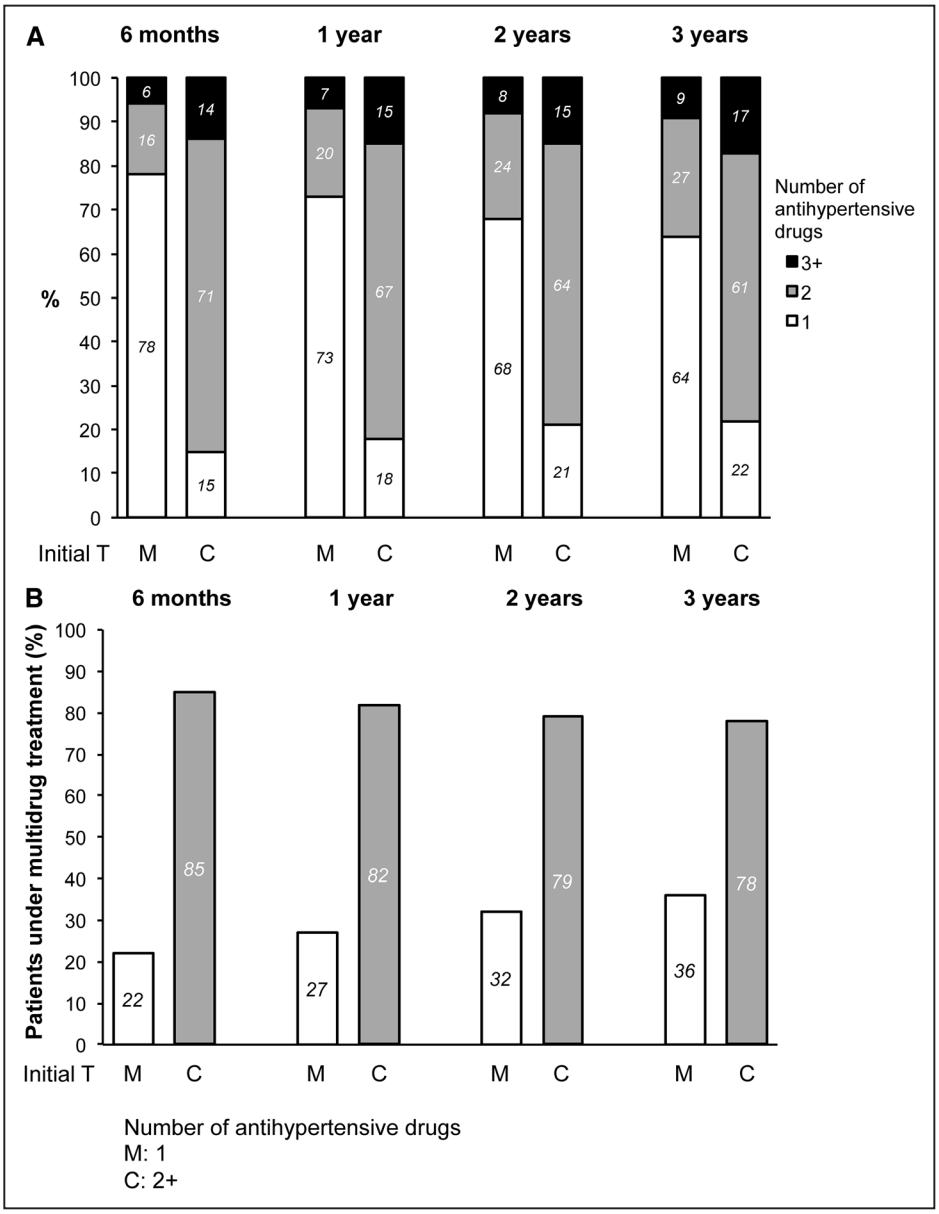

Figure 5. Percentage of patients prescribed 1, 2, ≥3 (A, top), or ≥2 antihypertensive drugs after initial prescription of monotherapy or 2 antihypertensive drugs (B, bottom). C indicates combination therapy; M, monotherapy; and T, therapy. Data refer to a 3-year follow-up and are derived from Rea et al.[48]

propensity score analysis does not eliminate initial inequalities resulting to unmeasured variables, this was further addressed by a within-patient comparison approach, using the 3500 patients of the last study who experienced a cardiovascular outcome and were prescribed, during the follow-up period, combination therapy for a subperiod and monotherapy for another (Figure 7A).[59] The risk of hospitalization for cardiovascular outcomes was significantly and markedly less (−56%) during the subperiod when patients were on combination therapy than during the subperiod when they were on monotherapy. This was the case also when cause-specific outcomes were considered, the outcome reduction seen during the combination as compared with monotherapy period being 71% for heart failure, 59% for coronary disease, 34% for stroke, and 59% for new atrial fibrillation. Even in the absence of randomized trials, a rather convincing evidence seems to be available that initial treatment with 2 antihypertensive drugs provides an earlier and long-lasting greater protection than initial monotherapy, the within-patient analysis excluding between-group differences in baseline clinical characteristics and cardiovascular risk as a confounding responsible factor. This justifies, on a scientific basis, the choice of American and European guidelines to abandon initial monotherapy and recommend initial 2-drug combination treatment in the majority of the hypertensive population. In the European guidelines, this is accompanied by the recommendation to use, whenever possible, single-pill, 2-drug combinations because (1) treatment simplification is accompanied by an increased adherence to treatment[60,61] and (2) the large availability of 2-drug combinations with dose ranges of combination components favours

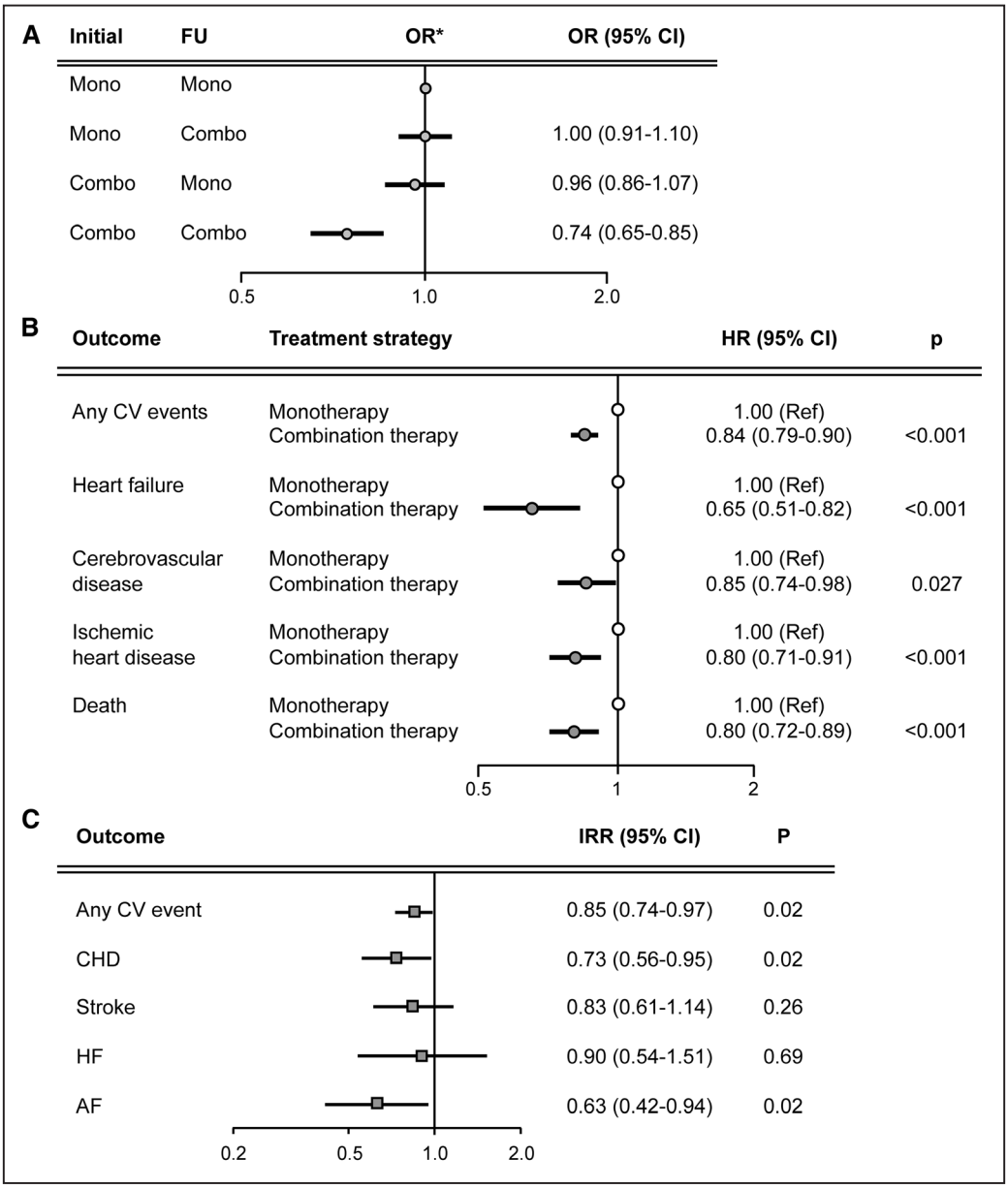

Figure 6. A, Risk of hospitalization for cardiovascular (CV) outcomes according to initial treatment strategy, ie, 2-drug combination (combo) or monotherapy (mono) in large cohorts taken from the Lombardy region database. A, The treatment strategies consisted of initial and subsequent monotherapy (reference), initial monotherapy followed by combination therapy, initial combination therapy followed by monotherapy, and initial and subsequent combination therapy. Data were adjusted for potential confounders. Compared with the other treatment strategies, the initial and subsequent combination therapy was associated with a significant reduction in the risk of hospitalization for CV events. **B**, The risk of hospitalization for CV events during a 3-year follow up (FU) in patients on initial combination of 2 antihypertensive drugs was less than that of patients on initial monotherapy. Data from the patients of Figure 5, in whom therapeutic inertia prevented patients on initial monotherapy from subsequent treatment uptitration to drug combinations. To minimize between-group differences of baseline CV risk, data were analyzed according to the propensity score approach. **C**, One-year risk of hospitalization for CV events in another cohort of patients from the Lombardy database initiating antihypertensive treatment with a 2-drug combination as compared to initial monotherapy. Data were adjusted for potential confounders and similar results were obtained by the propensity score analysis approach. Hospitalization for CV events refers to stroke, CHD, and HF. AF indicates atrial fibrillation; CHD, coronary heart disease; HF, heart failure; HR, hazard ratio; IRR, incidence risk ratio; and OR, odds ratio. From Corrao et al[42] and Rea et al.[48,59]

treatment flexibility and uptitration. Although at present, the most widely available combinations consist of a blocker of the renin-angiotensin system (ACE [angiotensin-converting enzyme] inhibitor or angiotensin II receptor antagonist) with a calcium channel blocker or a diuretic, other combinations have been successfully tested in outcome-based trials[6] and are thus suitable for therapeutic use, especially for specific clinical conditions. Single-pill, 2-drug combinations other than those between a renin-angiotensin blocker and a calcium channel blocker or a diuretic will probably be made available in the future.

Initial Combination Treatment—Drawbacks and Barriers

Large use of initial combination treatment will inevitably lead to patients taking 2 drugs when 1 would be enough to

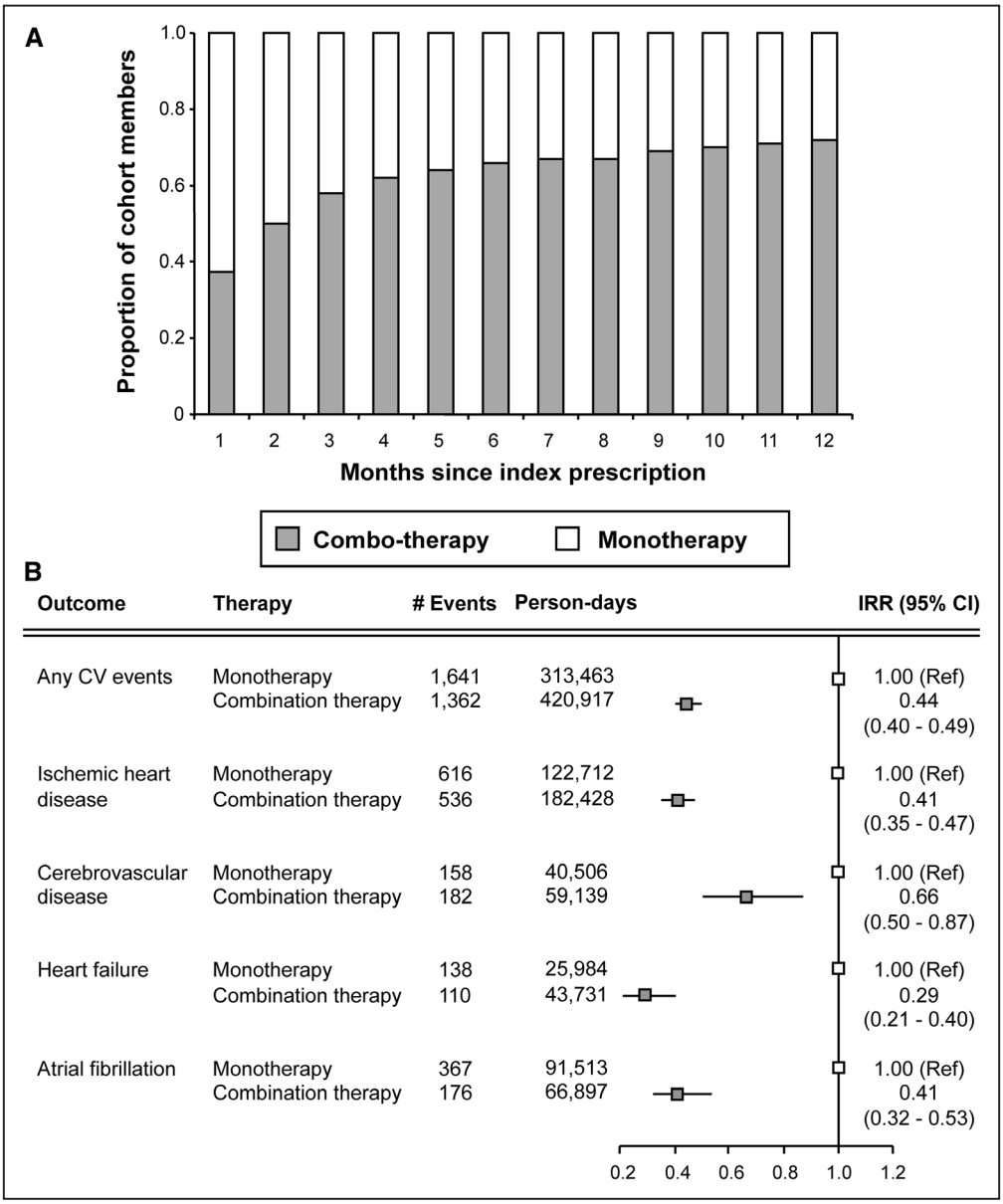

Figure 7. Risk of hospitalization for cardiovascular (CV) events in the 2212 patients who experienced an event during the 1-year follow-up after treatment initiation and were prescribed, during the year, either monotherapy or 2-drug combination therapy. A, Monthly distribution of mono or combination therapy; **B**, incidence risk ratio (IRR) for CV outcomes in the period of the year under combination therapy vs the period under monotherapy, which is taken as reference. Data refer to the cohort shown in Figure 6C and are derived from Rea et al.[59]

control their BP elevation. The potential economical disadvantage, however, is marginal because in most instances, the cost of 2 drugs is only slightly greater than that of a monotherapy. This is the case also for single-pill combinations, which is almost always similar if not less than the cost of the drugs separately administered. Also to be considered is that a combination of 2 drugs does not necessarily mean a greater risk of side effects because drug combinations allow their components to be given at lower doses, with a favorable rather than unfavorable effect on their tolerability profile.[15] There are, however, other less favorable aspects, such as, for example, that in case of adverse reactions, it may not be easy to identify, in individual patients, the guilty versus the innocent drug. Initial combination treatment should probably also be discouraged in some patient subgroups. According to the European guidelines,[6] initial monotherapy rather than combination therapy should be preferentially used in patients with a high-normal BP (130–139/85–89 mm Hg) in whom a very high cardiovascular risk (history of cardiovascular events) calls for BP-lowering treatment because under this circumstance, a limited BP reduction is needed to reach the recommended BP target (<130/80 mm Hg). This goal is achievable by a single BP-lowering drug, which may also be associated with little risk for BP to fall to levels such as <120/70 mm Hg at which, according to the reports of registries and post hoc analysis of large trials,[6,62–67] vital organ perfusion may be compromised, leading to a J-curve–like increase of cardiovascular risk.[68] For the same reasons, initial monotherapy may be considered in patients with grade 1 hypertension whose baseline systolic BP is closer to 140

mm Hg. Finally, initial monotherapy should definitively be the treatment of choice in old, frail or very old patients because in these patients, the mechanisms defending BP homeostasis are frequently impaired,[69] leading to an excessive BP fall that may damage renal and other vital organ function. Acute hypotensive episodes[70] may also be more frequent, leading to injurious falls that in the elderly may have dramatic consequences even for survival. In this context, it should not be forgotten that these inconveniences are invariably more frequent in real life than in trials. In elderly patients of the Lombardy database initiating antihypertensive drug treatment, the risk of hospitalization for hip fracture (assumed to have a relationship with hypotensive injurious falls) in the following 30 days was significantly greater for a number of drug classes compared randomly selected conditions in which no drugs were taken or to control patients.[71] This is an important reason why European guidelines do not recommend initial triple therapy under any circumstance.[6]

Finally, barriers to large use of initial combination treatment may also be erected by Regulatory Agencies and National Health Care Systems, often not especially sensitive to the long-term advantages of novel treatment strategies and more concerned on their possible short-term negative impact on costs.

Disclosures

G. Mancia has received honoraria for participation as speaker/chairman in national/international meetings from Boehringer Ingelheim, Ferrer, Medtronic, Menarini Int, Merck Serono, Recordati, and Servier. 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 in a variety of projects that were funded by pharmaceutical companies (ie, Novartis, GSK, Roche, AMGEN, and BMS). He also received honoraria as a member of Advisory Board from Roche. G. Grassi has received honoraria for participation as speaker/chairman in national/international meetings from Astra-Zeneca, Medtronic, Merck Serono, and Recordati. The other authors report no conflicts.

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