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DO ANTIHYPERTENSIVE DRUGS COMBINATIONS IN SINGLE-PILL COMBINATION IMPROVE CARDIOVASCULAR OUTCOMES?

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Abstract

Recommendations and guidelines propose to combine antihypertensive drugs to improve BP control, highlighting the advantages of single-pill combinations (SPCs) to improve treatment adherence. It is speculated that, compared with free-dose combinations (Free-DCs), SPC should achieve a reduction in cardiovascular (CV) events and mortality through better adherence and BP control. However, there is little information in this regard. For this reason, the objective of this review was to provide a descriptive analysis the differences in CV outcomes between SPCs antihypertensive drugs treatments vs. Free-DCs treatments. Ten studies were found and none had a randomized controlled design. Medication adherence was higher with SPCs, but outcomes were not adjusted for the adherence/persistence. When groups were compared according to similar adherence degrees, the statistical significance in favor of SPCs disappeared. Thus, randomized controlled studies are necessary to evaluate if SPCs have any effect beyond the improvement of the adherence to hypertensive treatment.

Key words: arterial hypertension, hypertension treatment, single-pill combinations, cardiovascular outcomes

Resumen

¿Las combinaciones de medicamentos antihipertensivos en un solo comprimido mejoran los resultados cardiovasculares?

Las recomendaciones y las guías proponen combinar fármacos antihipertensivos para mejorar el control de la presión arterial, destacando las ventajas de las combinaciones en un solo comprimido para mejorar la adherencia al tratamiento. Se especula que, en comparación con las combinaciones en varios comprimidos, deberían lograr una reducción de los eventos cardiovasculares y de la mortalidad a través de una mejor adherencia y control de la presión. Sin embargo, hay poca información al respecto. Por esta razón, el objetivo de esta revisión fue proporcionar un análisis descriptivo de las diferencias en los resultados cardiovasculares y la mortalidad entre los tratamientos con combinaciones de antihipertensivos en un solo comprimido vs. combinaciones de los mismos grupos de fármacos en varios comprimidos. Se encontraron diez estudios, pero ninguno tenía un diseño controlado aleatorio. La adherencia a la medicación fue mayor con las combinaciones en un comprimido, pero los resultados no se ajustaron por la adherencia/persistencia. Cuando se compararon los grupos según grados de adherencia similares, la significación estadística a favor de las combinaciones en un comprimido se perdió. Por lo tanto, son necesarios estudios controlados aleatorios para evaluar si las combinaciones de antihipertensivos en un comprimido tienen algún efecto más allá de la mejora de la adherencia al tratamiento.

Palabras clave: hipertensión arterial, tratamiento de la hipertensión, combinaciones en un comprimido, resultados cardiovasculares

KEY POINTS

- A central problem of arterial hypertension is to improve blood pressure control rates to reduce the disease burden.
- Combinations of antihypertensives in a single-pill (SPCs), also called "fixed-dose combinations", have been shown to improve adherence and persistence to medication compared to the administration of the same antihypertensives but in several pills, also called "free-dose combinations".
- However, there are no randomized controlled studies showing that SPCs reduce cardiovascular events and mortality compared with free-dose combinations in patients without differences in adherence/persistence.

Elevated blood pressure (BP) continues to be the leading cause of death worldwide[1], causing around 10.4 million deaths each year, and it is estimated that this situation may worsen after the COVID-19 pandemic[2]. On the other hand, control rates are low worldwide, particularly in low- and middle-income countries[3], a situation that is also likely to worsen as a result of COVID-19[4].

For these reasons, measures that help to improve arterial hypertension control are likely to have a favorable impact on the burden of this disease. In this sense, current recommendations and guidelines for the treatment of arterial hypertension[5-7] propose to combine antihypertensive drugs to improve BP control, highlighting the potential advantages of antihypertensive drugs combinations in a single pill (SPCs), also known as "fixed-dose combinations".

Although SPCs improve adherence and persistence[8], they have some disadvantages; it could hinder the dosage adjustments, leading to potential overdosing or underdosing[9], and may reduce the ability to identify the cause of an adverse event related to one of the components. Furthermore, SPCs could produce therapeutics mistakes such as duplication in the prescription of some drugs[10]. Finally, although this kind of treatment could reduce per hospitalization cost, the direct cost in pharmacy may be higher than the individual use of antihypertensive drugs in two or more pills, also named "free-dose combinations" (Free-DCs)[11]. Indeed, SPCs has problems for social security coverage in many countries as Argentina where a recently published multicentric study did not find a better level of adherence in patients who used fixed-dose antihypertensive combinations[12].

Although it can be speculated that SPCs, through better adherence compared with Free-DCs, should reduce even more cardiovascular (CV) events and mortality, there is little information regarding this issue. For this reason, the aim of this review was to provide a descriptive analysis the differences in CV outcomes between SPCs antihypertensive drugs treatments vs. Free-DCs treatments.

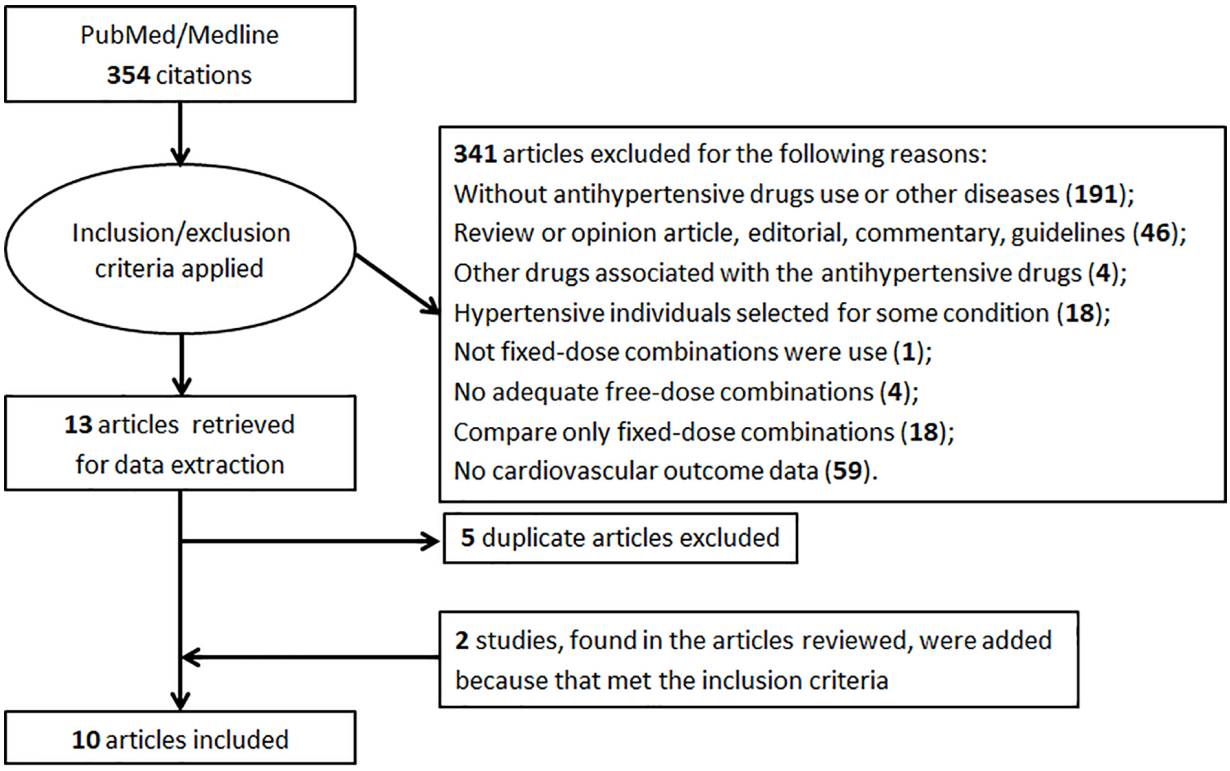
Methods

We performed a review of the full text articles published in PubMed in the period February 1, 2011, to Abril 30, 2023, which compared CV outcomes in hypertensive patients treated with antihypertensive drugs in SPCs vs. Free-DCs. The search terms were: fixed-dose combinations; single-pill combinations; cardiovascular outcomes, fixed-dose combinations; cardiovascular outcomes, single-pill combinations; clinical outcomes, fixed-dose combinations; clinical outcomes, single-pill combinations; cardiovascular outcomes, fixed-dose combinations, antihypertensive; cardiovascular outcomes, single-pill combinations, antihypertensive; clinical outcomes, fixed-dose combinations, antihypertensive; clinical outcomes, single-pill combinations, antihypertensive.

The inclusion criteria for the studies to be reviewed were the following: a) being studies carried out in hypertensive patients, b) comparing treatments with antihypertensive drugs in SPCs vs. combinations of similar numbers and classes of antihypertensive drugs in ≥ two pills (Free-DCs) and, c) analyze cardiovascular events and/or mortality. Studies carried out in hypertensive patients but selected for some conditions (chronic kidney disease (CKD), ischemic heart disease, diabetes mellitus, resistant hypertension, etc.), and those studies that, in addition to antihypertensive, also contain other drugs (statins, aspirin, polypill, etc.), were excluded.

With the search terms previously mentioned 354 studies were identified, 341 articles excluded for the reasons detailed in Figure 1. After removing duplicates, 8 studies remained for revision [15-22]; 2 studies[13, 14], that were found in the references of other articles, were also added

Figura 1 | Flowchart of included studies



to the analysis (Fig. 1). Results of each study on characteristics, adherence, BP levels, achieved target BP and CV outcomes were summarized in a narrative analysis.

Analyzed studies

The characteristics of the 10 studies are shown in Table 1. None of them had a randomized controlled design. Most studies compared combinations of two antihypertensive drugs[14-20], two compared combinations of two or more antihypertensives[13, 22] and, another study, combinations of three antihypertensives[21]. Most of the combinations were of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) + calcium channels blockers (CCBs)[14,17-19, 22] or combinations of ARBs or ACEIs + diuretics [15,16,20].

Belsey JD[13] investigated CV event-free survival in an observational study on a retrospective cohort in United Kingdom subjects. Combination of acute myocardial infarction (AMI), stroke, mortality, heart failure (HF), acute coronary syndrome, transient ischemic attack, bypass, and percutaneous coronary angioplasty were the events considered over a minimum follow-up period of 5 years after initiation of therapy. Authors compared patients treated with SPCs of two or more any antihypertensive drugs of different classes (n = 9929) with another group (n = 18 665), with two or more antihypertensive drugs of different classes in Free-DCs. The groups remained unbalanced after matching. There were 2173 events in SPCs group (21.9%) and 6285 in Free-DCs group (33.7%); Higher CV event-free survival in the SPCs group was observed, 27% risk reduction in the crude data (HR 0.73, 95% CI 0.70-0.76) and 26% in the adjusted model (HR 0.74, 95% CI 0.70-0.77). It is important to note that both before and after treatment the BPs were higher in the Free-DCs group: before treatment Free-DCs 159.7 ± 17.4 mmHg / 91.5 ± 9.1 mmHg vs SPCs 154.9 ± 24.3 mmHg / 90.5 ± 12.8 mmHg ($p > 0.001$); after treatment Free-DCs 148.2 ± 13.0 mmHg / 82.7 ± 7.1 mmHg vs SPCs 147.8 ± 12.5 mmHg / 82.4 ± 7.5 mmHg ($p = 0.011$ for systolic BP, $p = 0.001$ for diastolic BP). Furthermore, target achievement (BP ≤ 140/90 mmHg) was also worse in Free-DCs group (23.8% vs. 24.9%, $p = 0.04$). Adherence was not reported in this study.

Ferrario CM et al[14] in a retrospective observational cohort study compared three cohorts: 1-SPCs of amlodipine + olmesartan (n = 4864), 2- SPCs of amlodipine + benazepril (n = 12 051), and 3- Free-DCs of amlodipine +

Tabla 1 | Characteristics of the studies which evaluated cardiovascular outcomes and mortality with single-pill antihypertensive drugs combinations versus free-dose combinations

Study	Design	Regimen		Sample size		Mean age, years		Sex, female %		Follow-up, months
		SPCs	Free-DCs	SPCs	Free-DCs	SPCs	Free-DCs	SPCs	Free-DCs	
Belsey[13]	Retrospective cohort study	Two or more of different classes	Free-DCs Two or more of different classes	9929	18 665	61.2 (11.3)	62.5 (11.1)	66	56.6	≥60
Ferrario[14]	Retrospective observational study	CCB + ARB CCB + ACEI	CCB+ARB	4864 12 051	7748	53.8 (11.2) 56.0 (11.9)	60.7 (12.5)	41.9 43.8	49.2	Mean SPCs 18.1; Mean Free-DCs 19.5 Mean SPCs 20.8
Ho[15]	Retrospective cohort analysis	ACEIs or ARBs + diuretic	ACEIs or ARBs + diuretic	13 176	4392	58.79 (13.48)	58.98 (13.80)	47.1	46.4	Mean SPCs 29.6; Mean Free-DCs 27.7
Sicras Mainar[16]	Observational multicenter study	ACEIs or ARBs + diuretic	ACEIs or ARBs + diuretic	1112	493	68.7 (12.1) 67.8	70.7 (12.0)	55.2	56.2	24
Simons[17]	Randomized database analysis	CCB + ACEI	CCB + ACEI	9340	3093	(67.6-68.1)*	71.5 (71.0-71.9)*	51	54	48
Tung[18]	Retrospective database analysis	CCB + ARB	CCBs + ARBs	3301	13 204	60.30 (12.53)	60.37 (13.09)	47.7	48.0	Mean 15.2
Tung[19]	Retrospective database analysis	CCBs +ARBs	CCBs +ARBs	1136	4544	60.28 (14.56)	60.70 (14.89)	45.69	45.20	Mean 25.2
Verma[20]	Retrospective cohort study	ACEIs or ARBs + diuretic	ACEIs or ARBs + diuretic	6675	6675	71 (68±77)**	71	55.1	53.8	Median 60.9
Wang[21]	Retrospective cohort study	Various combinations of 3 drugs (one pill)	Various combinations of 3 drugs (three pill)	336	10 030	70.73 (8.49)	(68±77)**	44.4	54.8	12
		Various combinations of 2 drugs + third agent (two pill)		470		72.54 (9.01)	72.32 (9.53)	40.7		
Schmieder[22]	Retrospective cohort study	Various combinations of 2 or 3 drugs (one pill)	Same drugs in various pills	28 999	28 999	64.9 to 71.6	64.7 to 71.3	48,2 to 59.2	48.4 to 58.6	12

SPCs: single pill combinations; Free-DC: free-dose combinations; CCBs: calcium channel blockers; ARBs: angiotensin receptor blockers; ACEIs: angiotensin converting enzyme inhibitors

** 95% CI. ** interquartile range (IQR)*

ARBs (n = 7748). Means ages were different, 53.8 ± 11.2, 56.0 ± 11.91 and 60.7 ± 12.52 years old for cohort 1, 2 and 3, respectively (p < 0.001 between cohorts). Mean days follow-up were also different, 543.0 ± 113.7, 625.4 ± 133.1 and, 585.3 ± 132.4, p < 0.001. They found 35% higher risk (HR 1.35, 95% CI 1.15-1.59) in the primary combination outcome of HF, stroke, AMI, diagnosis of ischemic heart disease [IHD] and surgery related to AMI and IHD with Free-DCs compared to SPCs of amlodipine + olmesartan. Significant differences were observed in HF (HR 1.32, 95% CI 1.09-1.60), stroke (HR 1.64, 95% CI 1.49-2.36) and AMI/IHD-related surgery (HR 1.43, 95% CI 1.01-2.03). It should be noted that there was a higher percentage (44.12%) of days covered [PDC] with medication > 80% (good-adherence indicator) in SPCs amlodipine + olmesartan group compared with those in the SPCs amlodipine + benazepril (36.46%, p < 0.001) and Free-DCs (19.53%, p < 0.001). The study does not report BP values or percentage of patients who achieved treatment goals.

Ho CT et al[15] conducted an observational real-world study from the National Health Insurance Research Database of Taiwan. Patients newly diagnosed with hypertension, and prescribed with SPCs (n = 13 176) versus Free-DCs (n = 4392) of ACEIs or ARBs + thiazide diuretic were compared. Propensity score matching to eliminate differences in baseline characteristics of the two groups was performed. Primary endpoint was the combination of all-cause mortality, AMI, stroke, and coronary revascularization. Secondary endpoints included hospitalization for HF, a new diagnosis of CKD and the start of dialysis. All patients were followed up for at least one year or till the occurrence of clinical endpoints, whichever came first. Mean duration of follow-up were 887.89 (456.09) days and 830.22 (462.50) days (p < 0.001) for SPCs and Free-DCs groups, respectively. SPCs reduced 15% the primary endpoint (HR 0.85, 95% CI 0.74-0.97), and also the hospitalization for HF (HR 0.76, 95% CI 0.6-0.95) and initiation of dialysis (HR 0.69, 95% CI 0.53-0.89) compared with Free-DCs regimens. Percentage of patients with good-adherence (PDC > 80%) was higher in SPCs group (35.4%) compared with Free-DCs group (28.2%) (p < 0.001). It is important to note that the benefit in CV and renal outcomes observed with SPCs, compared to Free-DCs, disappears when both groups are compared but with a PDC > 80%. Unfortunately, BP values and the percentage of patients that reached BP goals are not reported.

Sicras Mainar A et al[16] performed a multicenter observational study on hypertensive patients > 30 years old, from six primary care centers and two hospitals, in Cataluña. The authors investigated the relationships between CV events incidence and compliance, persistence, and BP control level. Patients were followed for two years and treated with SPCs of ACEIs or ARBs + diuretics (n = 1112) vs. Free-DCs from the same classes of antihypertensive drugs (n = 493).

Those with Free-DCs treatments, compared with SPCs treatments, were older (70.7 ± 12.0 vs. 68.7 ± 12.1 years old, p <0.001) and had more IHD (13.2% vs. 9.1%, p = 0.044), organ failure cardiac, hepatic or renal (12.8% vs. 8.6%, p = 0.042), and diabetes mellitus (30.6% vs. 28.3%, p = 0.013). Cumulative incidence of ischemic or hemorrhagic stroke and transient ischemic attack in Free-DCs was 4.6% vs. 2.4% in SPCs (p = 0.041). SPCs treatment, compared with Free-DCs, showed better therapeutic good-adherence (PDC ≥ 80%: 56.3% vs. 41.8%, p <0.001), longer treatment persistence (62.1%, 95% CI 56.3-67.9 vs. 49.7%, 95% CI 38.5-60.9) and higher BP control (48.9%, 95% CI 43.0-54.8 vs. 46.7%, 95% CI 35.6-57.8). Patients with SPCs also had a significant reduction in systolic and diastolic BP between the beginning and the end of the study (139.6 ± 16.0 vs. 136.9 ± 17.6 mmHg, p = 0.030, and 79.1 ± 10.1 vs. 77.1 ± 10.5 mmHg, p < 0.001). In contrast, those with Free-DCs only significantly reduced the diastolic BP (139.0 ± 18.3 versus 138.1 ± 16.4 mmHg, p = NS, and 78.5 ± 9.8 versus 77.6 ± 10.6 mmHg, p = 0.046).

Simons EL et al[17] in an observational study of 12 433 Australians, found 4-year mortality of 8% in the group initially treated with SPCs of amlodipine + perindopril (n = 9340) and 18% in the group initially treated with the same drugs in Free-DCs (n = 3093). In the follow-up period, witching to similar classes of antihypertensive drugs (calcium channel blockers + ACEIs or ARBs) was accepted. It should be noted Free-DCs group had a higher risk due to older age (71.5 vs. 67.8 years old, p < 0.001), longer duration of antihypertensive treatment before the study, greater evidence of diabetes mellitus (20% vs. 16%, p < 0.001) and hyperlipidemia (51% vs. 43%, p < 0.001). In the Free-DCs group mortality risk was higher than in the SPCs group (HR 2.81, 95% CI 2.42-3.26 in the univariate model; HR 1.83, 95% CI 1.55-2.16 in the adjusted multivariate model). Although SPCs group had higher median persistence than Free-DCs (42 months, 95% CI 33 to > 43 months vs. 7 months, 95% CI 5-9, respectively), mortality risk was not adjusted for persistence time. Authors acknowledge that this very large difference in mortality was unexpected and is likely to be an overestimate, possibly due to residual confounding by other unmeasured variables. This study also does not provide BP values or report the percentage that achieved BP targets.

Tung YC et al[18] in a retrospective analysis of 16 505 Asians from Taiwan, compared two hypertension treatment strategies: a SPCs of amlodipine + valsartan

(n = 3301) vs. Free-DCs of ARBs + CCBs (n = 13 204). To identify an appropriate Free-DCs combination group, propensity score matching was utilized. After a mean follow-up of 15.2 months, SPCs group had significantly lower hospitalization rates (14.57% vs. 18.43%, p < 0.001). SPCs group also had a better CV event-free survival (HR 0.83, 95% CI 0.73-0.94) at expense of a decrease in HF rates (2.12% vs. 3.26%, p < 0.001), malignant dysrhythmia (0.18% vs. 0.42%, p = 0.021), and percutaneous coronary intervention (0.76% vs. 1.26%, p = 0.015), but not from AMI, stroke and coronary artery bypass grafting. Although SPCs group, compared with Free-DCs group, had higher PDC (80.35% vs. 72.57%, p < 0.001) and better persistence (266 vs. 225 days, p < 0.001), CV outcomes were not adjusted for adherence/persistence. This study does not provide information about BP values or the percentage of patients who achieved BP goals.

Using National Health Insurance Research Database of Taiwan, Tung YC et al[19], compared patients taking SPCs of ARBs + CCBs (n = 1136) vs. Free-DCs (n = 4544). Propensity score matching was performed to balance the potential difference in the two study groups. Mean follow-up duration was 2.1 years. SPCs were associated with a higher percentage of patients with good-adherence (PDC ≥ 80%: 64.97% vs. 56.88%, p < 0.001). Similarly, medication persistence was better in SPCs group than in Free-DCs group (293.8 vs. 275.1 days, p < 0.001.). SPCs group had a 28% reduction in the risk of the primary CV event (HR 0.72, 95% CI 0.54-0.95), that was a combination of total mortality, AMI, stroke, coronary revascularization, hospitalization for unstable angina, and sudden cardiac arrest resuscitation. SPCs was also associated with better CV event-free survival (log-rank p = 0.021) but lost statistical significance when groups were compared according to similar adherence levels. At the secondary endpoints, SPCs group was associated with 29% lower risk for HF hospitalization (HR 0.71, 95% CI 0.51-0.99). There were no differences between the two groups in risks of a new diagnosis of CKD or the start of dialysis. This study does not provide BP records.

In a Canadian observational study with a median follow-up of 1826 days, Verma AA et al[20] used a high-dimensional propensity score matching to identify comparable groups[23] in a retrospective cohort of hypertensive patients. They found, in the intention-to-treat analysis, 11% reduction in the risk (HR 0.89, 95% CI 0.81-0.97) of reaching the primary event (combination of death or hospitalization due to AMI, HF, or stroke) when were used SPCs of ARBs or ACEIs + hydrochlorothiazide (n = 6675) vs. Free-DCs of the same classes of antihypertensive drugs (n = 6675). Risk reduction was due to a 15% decrease in the risk of death (HR 0.85, 95% CI 0.77-0.94). There were no significant differences in risk of AMI, stroke, and HF. The PDC was significantly higher in the group with SPCs than in the group with Free-DCs (70%, IQR 19 ± 98 and 42%, IQR 11 ± 91, respectively, p < 0.01). It should be noted that the statistical significance of the reduction in primary outcome does not hold when only the adherent individuals of the groups are compared. This study does not provide BP values or report the percentage of subjects who achieved BP targets.

Wang X et al[21], in a retrospective cohort of 10 836 elderly hypertensive subjects from Texas Medicare Advantage Plus, evaluated the risk of hospitalization for CV events in patients treated with a triple combination of antihypertensive drugs. The follow-up period was one year. The study comparing any triple SPCs therapy (n = 336) with any double SPCs plus a third agent (n = 470), and any free-dose triple combination therapy (n = 10 030). Risk of hospitalization for CV events was higher in the double SPCs plus a third agent, and free-dose triple combination therapy groups (HR 3.82, 95% CI 1.80-8.12 and HR 3.65, 95% CI 1.43-9.31, respectively). It should be noted that in patients treated with triple SPCs numerous variables associated with the risk of hospitalization were less frequent (diabetes, HF, depression, hyperlipidemia, history of previous hospitalization, neuropathy). In this study, adherence was not significantly associated with a lower risk of hospitalization for CV disease, although the time at which it was evaluated (6 months) could be considered inappropriate. Unfortunately, the authors do not provide BP values or the percentage that reached BP goals.

The recently published START study, by Schmieder RE et al[22], have provided further evidence in favor of SPC. In this retrospective cohort study, data from hypertensive patients ≥18 years from a German statutory health fund (AOK PLUS) treated with renin-angiotensin system combinations given as single pill or identical multipills covering the years 2012 to 2018 were compared after 1:1 propensity score matching. More than 160 000 patients with hypertension and who received one of the following four antihypertensive combination ramipril/amlodipine, candesartan/amlodipine, valsartan/amlodipine, or valsartan/amlodipine/hydrochlorothiazide were identified. After propensity score matching, data from 28 999 hypertensive patients with one of the 4 SPCs combinations were compared to 28 999 hypertensive patients with identical drug combinations given as Free-DCs. Differences in incidence of outcomes and time to first respective event were reported as incidence rate ratios (IRRs) and hazard

ratios (HRs). In all 4 comparisons between SPCs and Free-DCs, the authors found a lower mortality rate in the SPC: valsartan/amlodipine IRR, 0.761 (95% CI, 0.683–0.848); candesartan/amlodipine IRR, 0.538 (95% CI, 0.284–0.980); candesartan/amlodipine IRR 0.526 (95% CI, 0.463–0.596); valsartan/amlodipine/hydrochlorothiazide IRR, 0.515 (95%CI 0.375-0.709). Furthermore, patients treated with any of the 4 SPCs analyzed had a lower risk for a predefined composite outcome consisting of all-cause death and all-cause hospitalization, lower than Free-DCs ($p < 0.001$). Regarding the specific cardiovascular endpoints, a significant lower event rate was observed in 15 out of 20 comparisons performed. Comparing the 4 drug combination groups, patients on SPCs had a significantly lower incidence ($P<0.05$) of coronary artery disease and heart failure. However, only ramipril/amlodipine showed superiority in SPC to prevent AMI, but this combination had no advantages in the prevention of cerebrovascular disease. Cardiovascular mortality was not communicated. The percentage of patients that were persistent to antihypertensive drug combinations 1 year after start of observation was significantly higher under SPCs. Compared with the respective SPC group, the proportion of patients who were persistent using Free-DC was 20% less in the valsartan/amlodipine group, 30% less in the candesartan/amlodipine with Free-DCs, 24% less in the candesartan/amlodipine group, and 49% less in the valsartan/amlodipine/hydrochlorothiazide group with Free-DC. Since no adjustment by adherence/persistence was made, the benefit observed could be related to the improvement in these variables. Unfortunately, the authors do not provide BP values or the percentage that reached BP goals.

Discussion and conclusions

Despite the "advice" of the guidelines on arterial hypertension about the convenience of using SPCs, several observations should be considered concerning the CV outcomes and mortality.

First, no appropriate size, controlled and randomized trials have been carried out that compare primary or secondary prevention of CV events and mortality with similar numbers and classes of antihypertensive drugs in SPCs vs. Free-DCs. The information available comes only from observational studies, databases or retrospective cohorts. Despite the matching of groups and adjustments for confounding variables, there is no doubt that biases or hidden confounding variables may persist in these types of studies.

Second, the important role played by better adherence/persistence of treatment with SPCs use, which has been recently revised[8], seems clear in reducing CV events. To such a point that studies showed a lower risk of mortality and CV events with SPCs do not reach to statistical significance when only adherent patients are included in the comparisons or after stratifying the groups by similar adherence levels[15, 19, 20].

Third, it would be expected that the groups with better adherence would have not only lower BP values and higher percentages of hypertension control, but also better coverage and/or health systems. Thus, use of SCPs could be a marker of social advantage and this association explains the reduction in all-cause mortality observed in some studies. Unfortunately, eight of the ten studies do not report BP values or the percentage of individuals who achieved BP goals with treatment. Furthermore, one of the two studies that showed the BP values and the percentage of patients who reached the target BP[13], does not describe how BP was measured. The other study[16] found in the group with SPCs better adherence and persistence, significant BP decrease, better BP control, and lower incidence of stroke, but did not adjust the outcomes for adherence.

Supporting the relationship between SPCs use and CV event reduction, a prospective open-label study showed that a triple SPC therapy, containing in a single pill ACEI + diuretic + CCB, was more effective than Free-DCs in left ventricular mass index reduction and left ventricular hypertrophy regression[24], although this is a small study.

Therefore, with the information available to date, it is not possible to confirm a relationship, although there probably exists, between SPCs use, greater adherence, greater BP decrease, better BP control and reduction in CV events and mortality.

Finally, the use of SPCs does not necessarily ensure good-adherence. Other predictors of non-adherence to treatment with antihypertensive drugs should also be considered, such as low educational level[12], young age[25], female sex[24], number of medications[25] and use of diuretics[12, 25]. In consequence, measures to improve adherence

to treatments[5] and hypertension control should be added to the use of SPCs, such as self-monitoring of BP at home, telemonitoring, reminders, elimination of barriers to medication access (as direct costs) and multidisciplinary approaches including nurses, pharmacists and community health workers[25].

In conclusion, randomized and controlled studies are necessary to evaluate if SPCs of antihypertensive drugs reduce CV events and mortality, beyond the improvement of the adherence to antihypertensive treatment. Furthermore, there is also no evidence that the sequence SPCs → greater adherence → greater BP decrease → better BP control → reduction in CV events and mortality is fulfilled. Thus, to reduce CV outcomes, it seems prudent not only to advise for a wide use of SPCs, but also strongly recommend more comprehensive measures that can improve the adherence to chronic treatments.

Conflict of interest: None to declare

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