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Benefit of treatment based on indapamide mostly combined with perindopril on mortality and cardiovascular outcomes: a pooled analysis of four trials

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Objective: The aim of this study was to assess the reduction in all-cause death and cardiovascular outcomes associated with the administration of the thiazide-like diuretic indapamide monotherapy or in combination with perindopril as a blood pressure lowering drug in randomized controlled trials (RCTs).

Method: Aggregate data from four published RCTs conducted versus matching placebo were pooled: PATS, a 2-year study (indapamide), and PROGRESS, a 4-year study (indapamide and perindopril), both in patients with a history of stroke or transient ischemic attack; ADVANCE, a 4-year study in patients with type 2 diabetes and cardiovascular risk factor (single-pill combination perindopril/indapamide) and HYVET, a 2-year study in very elderly hypertensive individuals (indapamide and an option of perindopril). The pooled effect (fixed and random) estimate (hazard ratio) was reported with corresponding 95% confidence intervals and *P* values. Treatment discontinuations were also analysed to assess the net benefit of the treatment.

Results: The population involved 24 194 patients (active: 12 113, placebo: 12 081). The fixed-effects meta-analysis of the three mortality endpoints found low statistical heterogeneity ($I^2 = 0$). Statistically significant risk reductions in the indapamide with or without perindopril-treated patients as compared to placebo were observed for all-cause death (−15%), cardiovascular death (−21%), fatal stroke (−36%) and all strokes (−27%). Other cardiovascular outcomes were improved (risk reduction, 22 to 36%). As expected, discontinuation rates for safety (two studies) were higher in the active group (6.4 vs. 3.9%), while they were similar when discontinuation for any reason is concerned (18.4 vs. 18.0%).

Conclusion: Across medium to high cardiovascular risk population, long-term indapamide, mostly combined with perindopril-based treatment, provided evidence of benefit on mortality and morbidity.

Keywords: blood pressure lowering trials, cardiovascular event reduction, hypertension, indapamide, indapamide ± perindopril, meta-analysis, randomized controlled trials, thiazide-like diuretics, treatment discontinuations

Abbreviations: ACE, angiotensin-converting enzyme; ADVANCE, Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HYVET, Hypertension in the Very Elderly Trial; IRIS, Institut de Recherches Internationales Servier; NHMRC, National Health and Medical Research Council of Australia; PATS, Post-stroke Antihypertensive Treatment Study; PROGRESS, Perindopril pROtection aGainst REcurrent Stroke Study; RCT, randomized controlled trial; VA, Veterans Administration

INTRODUCTION

Since the first Veterans Administration (VA) Cooperative trial published in 1967 [1], diuretics have been regarded as fundamental drugs for the treatment of patients with an elevated blood pressure (BP), and their use both as the initial treatment step and/or in combination with other antihypertensive agents has been recommended in almost all hypertension guidelines [2–11]. Reasons are that diuretics effectively lower an elevated BP both in monotherapy [12,13] and in combination with other antihypertensive drugs [14], the BP-lowering effect of diuretics is accompanied by a substantial reduction of cardiovascular outcomes in trials against placebo or a control group [15–20], and in BP-lowering trials in which the BP reduction was

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similar between differently treated groups, the protective ability of diuretics did not significantly differ from that seen with other antihypertensive drug classes [16,18].

Among the diuretics recommended for antihypertensive treatment, some guidelines express a preference for chlorthalidone and indapamide because of the evidence that, compared with thiazides, these thiazide-like diuretics have a longer duration of action and a greater BP lowering ability [8,21–24]. Other guidelines [4,25], however, emphasize that a randomized trial-based reduction of cardiovascular risk has been documented not only for thiazide-like but also for thiazide diuretics, including hydrochlorothiazide, different diuretics have been compared in the setting of observational but never in head-to-head randomized outcome trials, and even if not all data are univocal [26,27], some thiazide-like diuretics (e.g. chlorthalidone) have been associated with a greater risk of side effects [28], that is the main cause of treatment discontinuation [29], which is known to be associated with a rebound increase of outcomes [30,31]. They thus consider thiazides, chlorthalidone and indapamide, all suitable for initial and maintenance of antihypertensive treatment both in monotherapy and in combination with other BP-lowering agents such as a blocker of the renin-angiotensin system.

Among the diuretics mentioned by guidelines, indapamide has been used in large-scale trials, which have addressed the protective effect of BP-lowering treatment, either alone or more often in combination with the angiotensin-converting enzyme (ACE) inhibitor, perindopril, in clinically important patient categories such as postischemic or posthaemorrhagic stroke [Poststroke Antihypertensive Treatment Study] (PATS) [32,33] and [the Perindopril pROtection aGainst REcurrent Stroke Study] (PROGRESS) [34,35], diabetes [The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation] (ADVANCE) [36] and old age with systo-diastolic or isolated systolic hypertension [the Hypertension in the Very Elderly Trial] (HYVET) [37]. In the present study, we have analysed these four trials to provide a detailed comparison of their individual results as well as of their pooled effects on clinical outcomes. Pooling these four large trials has never been done before, although previous meta-analyses have presented some partial results with indapamide [15,18,20,38]. Side effects leading to treatment discontinuation were also analysed to assess the net benefit of indapamide with or without perindopril-based treatment, that is the benefit shown after balancing protective against adverse consequences.

MATERIALS AND METHODS

Baseline patient demographics, clinical outcomes and hazard ratios with their 95% confidence intervals (CIs) were extracted for each of the four above-mentioned randomized placebo-controlled trials: PATS [32,33], PROGRESS [34,35], ADVANCE [36] and HYVET [37], using the original publications. Only the aggregate data from these studies were used, and the authors of the original studies were contacted to provide additional data where needed. For the analyses of treatment discontinuation due to side effects (which are available only for PROGRESS and ADVANCE), we used the data from two additional publications [31,39]. The literature was scrutinized to ensure that no other randomized event-based trial conducted with an indapamide-based treatment was available.

Endpoints and definitions

The definition of outcomes reported in the original publications was retained. Here, we analysed only the endpoints with a similar definition across the studies and focused our analyses on the fatal and nonfatal endpoints. More specifically, the considered fatal events were all-cause death, cardiovascular death [death due to stroke, to coronary disease (including sudden death) and to heart failure] and stroke death. Fatal and nonfatal events were any haemorrhagic or ischemic stroke, myocardial infarction and heart failure, major cardiovascular events [cardiovascular death, nonfatal myocardial infarction (MI) and nonfatal stroke), major coronary events [death due to coronary heart disease (including sudden death) and nonfatal MI]. Transient ischemic attacks were not considered. Mortality data and any stroke events were available for the four studies. Strokes were the primary endpoint in three studies, while other events were only assessable in two or three studies, depending on the event.

Data on permanent treatment discontinuations for any reason and for safety reasons (including hypotension/dizziness, cough and serious adverse events) were extracted. In addition, data on conditions requiring additional treatment with an ACE inhibitor and/or a diuretic not authorised by the protocol are provided for each study.

Statistics

Inverse variance-weighted fixed and random-effects meta-analysis was performed for each endpoint (DerSimonian and Laird methodology). Between-study heterogeneity was characterized using the I^2 statistic. Sources of heterogeneity derived from the clinical characteristics of patients enrolled to each study were examined. The results of fixed-effect model are presented except when meaningful between-study heterogeneity was present. In this case, the random-effects model was preferred. The pooled effect estimate (hazard ratio) was reported with corresponding 95% CIs and P values (two-tailed, with type I error of 0.05).

RESULTS

Between-trial differences and similarities

The main features of the four RCTs are presented in Table 1. Common characteristics of all trials were patients having at least one cardiovascular risk factor, having mortality and cardiovascular outcomes as a primary endpoint (assessed by an independent adjudication Committee blinded to treatment allocation), and having an active treatment based on indapamide or indapamide plus perindopril, with a control group on placebo. All four trials fulfil the 'high quality' criteria according to the classification proposed by the Cochrane Collaboration [40] (Supplemental Table S1, http://links.lww.com/HJH/C124) or, the more specific, hypertension-oriented classification of Thomopoulos *et al.* [40]. These criteria were randomization generation sequence, double-blind design, loss to follow-up less than

TABLE 1. Main features of the four studies

	PATS (1995) [32]	PROGRESS (2001) [34]	ADVANCE (2007) [36]	HYVET (2008) [37]
	Secondary prevention		Primary prevention	
Countries (centres)	China	10 countries: Asia, Australasia and Europe	20 countries: Europe, China, Asia, Australasia & Canada	13 countries: Europe, China, Australasia abd Tunisia
Inclusion criteria	Poststroke (stroke or TIA) with or without HTN	Poststroke (stroke or TIA) with or without HTN	Type 2 diabetes, age ≥55 years + risk factor with or without HTN	Very elderly (>80 years old) + HTN
Run-in period	2-week placebo with cessation of any BPL	4-week with perindopril	6-week with low-dose perindopril/indapamide	8-week placebo with cessation of any BPL
Intervention group	Indapamide 2.5 mg	Perindopril 4 mg alone or + Indapamide 2.5 mg (2 mg Japan) + standard additional therapy	SPC perindopril 4 mg/ Indapamide 1.25 mg + standard additional therapy	Indapamide SR 1.5 mg ± perindopril (2 or 4 mg)
Comparator group	Matching placebo	Matching placebo + standard additional therapy	Matching placebo + standard additional therapy	Matching placebo
BP-lowering treatment	Not to be modified	Additional Tx authorized[1]	Additional Tx authorized[3]	No additional Tx authorized
Primary endpoint	Stroke recurrence (fatal or nonfatal)	Stroke recurrence (fatal or nonfatal)	Composite endpoint: major micro- and major macro-vascular events[a]	Any stroke (fatal or nonfatal)
Years of follow-up (range)	2 years, median (0–3.8)	3.9 years, mean (0–4.5)	4.3 years, mean (0–5.6)	1.8 years, median (0–6.5)

BP, blood pressure; HTN, hypertension; SPC, single-pill combination; TIA, transient ischemic attack; Tx, open-label prescription.
[a]1° composite: major macrovascular and microvascular events, defined as death from CVD, nonfatal stroke or nonfatal MI, and new or worsening renal or diabetic eye disease.

10% and therapy discontinuation less than 10% per year of follow-up; and a rate of at least 60% of hypertensive individuals at baseline, representing at least 5000 patient-years and the presence of four or more types of outcomes reported in each individual trial [41]. Of note, two trials (PATS and HYVET) were prematurely terminated for ethical reasons (significant 29 and 41% decrease in stroke compared with placebo, respectively).

Overall, the four studies (Table 2) involved 24 194 patients of whom 14 684 (60.7%) were treated with the dual therapy (indapamide and perindopril or dual placebo). Twelve thousand, one hundred and thirteen patients received the active treatment that included indapamide (i.e. only the combination treatment group of the PROGRESS study is reported here) and 12 081 received placebo. Although all four studies were conducted vs. placebo, had data on cardiovascular outcomes and included a majority of hypertensive patients, there was a certain amount of diversity. The cardiovascular risk of the overall study population ranged from medium to high. Baseline BP varied from normotension to grade 3 hypertension, and the burden of comorbidities differed considerably, as did the age ranges, the sex ratio and the ethnic profiles.

Unlike in HYVET and PATS, in which the BP-lowering treatment of interest was given to patients who were untreated or in whom current treatment had been discontinued, in ADVANCE and PROGRESS, the study treatment was given on top of conventional antihypertensive drug treatment, which could be modified during follow-up at the discretion of the responsible physician. In ADVANCE, at study end, 74 and 83% of the patients in the active and placebo groups, respectively, received additional BP-lowering agents, including calcium channel blockers in 32 and

TABLE 2. Mean (±SD) baseline characteristics of patients in each study

	PATS (1995) [32]	PROGRESS (2001) [34]	ADVANCE (2007) [36]	HYVET (2008) [37]
Total participants	5665	3544[a]	11 140	3845
Active[b]	2841	1770	5569	1933
Placebo	2824	1774	5571	1912
On combined therapy	0%	100%	100%	73.4% (active group) 85.2% (placebo)
Mean age (years)	60 ± 8	63 ± 9	66 ± 6	84 ± 3
History of HTN	NA	50% treated HTN	75% treated HTN	90% with 65% treated HTN
Baseline SBP (mmHg)	154 ± 24	149 ± 19	145 ± 22	173 ± 8
Baseline DBP (mmHg)	93 ± 13	87 ± 11	81 ± 11	91 ± 9
Severity of HTN (mmHg)	84% with SBP or DBP ≥140 or 90 and 57% with SBP or DBP ≥160 or 95	54% with SBP≥160 or DBP≥90)	59% with 68% SBP or DBP ≥140 or 90	100% (SBP≥160)
Female patients	28%	29%	43%	60.5%
Diabetes	Missing	12%	100%	7%
Coronary heart disease	Missing	18%	12% (MI)	3% (MI)
History of stroke	100%	100%	9%	7%

HTN, hypertension; MI, myocardial infarction; NA, not available.
[a]*N*: 3544 patients planned to receive combination therapy with indapamide ± perindopril among the whole cohort (*N* = 6105).
[b] Active, Indapamide with or without perindopril.

TABLE 3. Mean SBP and DBP blood pressure decreases (mmHg) for each study

	Follow-up (years)	Mean baseline SBP/DBP (SD)	Concomitant BP-lowering drugs at the end of follow-up	Placebo-corrected mean BP decrease Mean (SE)	
		SBP/DBP		SBP	DBP
PATS	2	154 (23) / 93 (13)	none	−6.8 (95% CI, 5.3–8.3)	−3.3 (95% CI, 2.4–4.1)
PROGRESS	3.9	149 (19) / 87 (11)	NA (50% at baseline)	−12.3 (0.5)	−5.0 (0.3)
ADVANCE	4.3	145 (22) / 81 (11)	74 vs. 83%[a]	−5.6 (0.2)	−2.2 (0.1)
HYVET	2.0	173 (8) / 91 (9)	none	−15.0 (NA)	−6.1 (NA)

95% CI, 95% confident interval; NA, not available.
[a]Active vs. placebo groups.

43% of the patients, respectively. Such data are not available for the PROGRESS combined group.

Blood pressure endpoints

Considering the difference in baseline BP, the potential concomitant use of other BP-lowering agents in ADVANCE and PROGRESS and to a lesser extent the different dose of indapamide (1.25–2.5 mg), the effect of the indapamide with or without perindopril-based treatment was different between the four studies (Table 3). The mean differences in placebo-corrected SBP/DBP reductions varied from −5.6/−2.2 mmHg in ADVANCE and −6.2/−2.9 mmHg in PATS compared with −12.3/−5.0 mmHg in PROGRESS and −15/−6.0 mmHg in HYVET.

Treatment discontinuation for safety reasons

Permanent treatment discontinuation rates were available in two studies (PROGRESS and ADVANCE) and are presented for each study and in the pooled analysis in Table 4. In both studies, treatment discontinuation for any reason was similar in the active and placebo groups, whereas treatment discontinuation for safety reasons (including hypotension, dizziness and cough) was numerically higher in active compared with placebo-treated patients.

In the pool of PROGRESS and ADVANCE studies ($n = 14\,684$ patients of whom 64% were receiving background BP-lowering therapy), 18.2% discontinued treatment permanently, the proportion being similar in the active (18.4%) and placebo (18.0%) groups. Discontinuation for safety reasons, including for hypotension/dizziness and for cough, was approximatively twofold higher in the active-treated patients compared with placebo.

Major cardiovascular and mortality outcomes

Over a median follow-up of 1.8–4.3 years, there were fewer deaths in the active treatment group (7.5%) as compared to the placebo group (8.7%), mostly of cardiovascular origin (4.0 and 5.0%, respectively), while deaths attributed to stroke occurred in 1.5 and 2.3%, respectively. The statistical heterogeneity was low ($I^2 = 0$) for all mortality outcomes. The indapamide with or without perindopril-based regimen was associated with a significantly lower cumulative incidence of all-cause mortality (risk reduction −15%) as well as cardiovascular deaths (−21%) and fatal stroke (−36%) when compared with placebo. Forest plots showing all-cause mortality endpoint and the cardiovascular mortality endpoint are presented in Fig. 1.

Results for these mortality and the other cardiovascular endpoints are presented in Table 5 and supplemental Table S2, http://links.lww.com/HJH/C124 for individual trial data. High heterogeneity in the treatment effect between the studies was observed for all other endpoints, including total stroke (no effect in ADVANCE), which was also significantly lower in the active group (hazard ratio 0.73, 95% CI 0.57–0.94, $P = 0.015$). However, all these cardiovascular morbidity outcomes were numerically improved with a risk reduction varying from 22 up to 36% as compared with placebo (−22% for major coronary events, −25% for major cardiovascular events, −26% for MI, −27% for stroke and −36% for heart failure).

DISCUSSION

The patient population ($n = 24\,194$) pooled in our analyses not only comprised (62%) individuals with hypertension but also normotensive individuals with at least one

TABLE 4. Rates of permanent discontinuation for safety reasons in each study and in their pooled analyses

	PROGRESS [34]		ADVANCE [31,36]		Pool PROGRESS + ADVANCE [39] [a]		
Discontinuation for	Active[c]	Placebo	Active[c]	Placebo	Total	Active[c]	Placebo
N patients	1770	1774	5569	5571	14 684	7339	7345
Safety reason:	8.5%	7.0%	5.7%	2.8%	753 (5.1%)	471 (6.4%)	285 (3.9%)
Hypotension/dizziness	1.6%	1.0%	1.2%	0.4%	138 (0.9%)	98 (1.3%)	40 (0.5%)
Cough	1.0%	0.2%	3.3%	1.3%	277 (1.9%)	202 (2.8%)	75 (1.0%)
Serious adverse events	NA	NA	1.2%	1.2%	–	–	–
Conditions requiring Rx[b]	2.0%	3.3%	0.6%	0.8%	–	–	–

[a]These data are based on analyses first published in a previous study by Atkins 2017 [39].
[b]Treatment requiring open-label treatment with an ACE inhibitor and/or a diuretic.
[c]Active, Indapamide combined with perindopril; NA, not available for the PROGRESS combination therapy group.

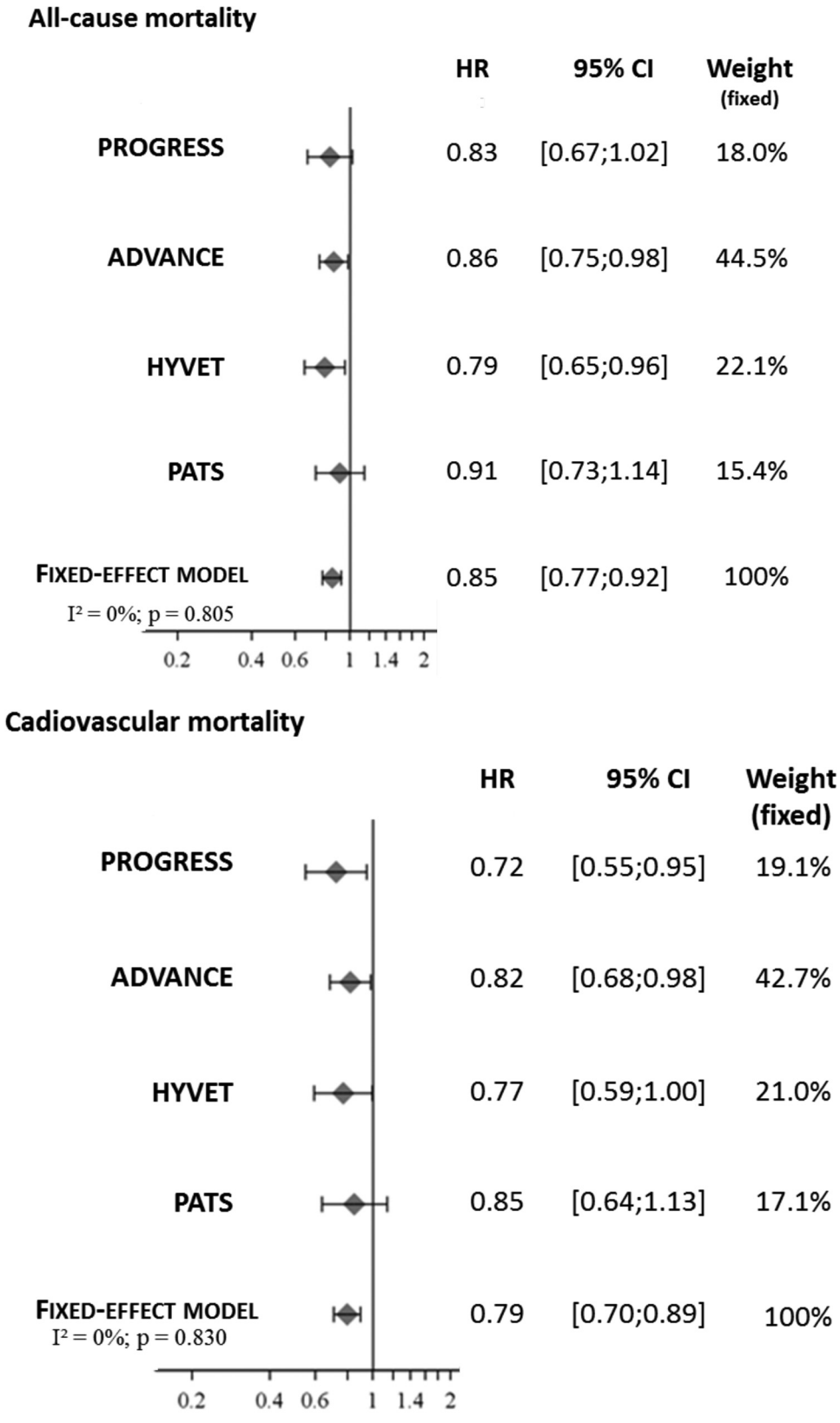

FIGURE 1 Forest plots for the endpoints of all-cause mortality and cardiovascular mortality resulting from treatment with combination of indapamide with or without perindopril. Hazard ratio (HR) with its 95% confidence interval overall and by study, using the fixed effect model.

TABLE 5. Hazard ratio for all-cause mortality and cardiovascular endpoints resulting from indapamide with or without perindopril-based treatment

Endpoints	No. of studies	Pooled analysis			HR (95% CI)	*P*	Heterogeneity (model)
		Total	Active	Placebo			
No. of patients		24 194	12 113	12 081			
Total mortality	4	1957	906 (7.5)	1 051 (8.7)	0.85 [0.77–0.92]	<0.001	None ($I^2 = 0\%$) Fixed
CV mortality	4	1085	485 (4.0)	600 (5.0)	0.79 [0.70–0.89]	<0.001	None ($I^2 = 0\%$) Fixed
Fatal stroke	4	448	176 (1. 5)	272 (2.3)	0.64 [0.53–0.77]	<0.001	None ($I^2 = 0\%$) Fixed
Stroke	4	1334	575 (4.8)	759 (6.3)	0.73 [0.57–0.94]	0.015	High ($I^2 = 80\%$) Random
MI	3	478	216 (1.8)	262 (2.2)	0.74 [0.49–1.12]	0.16	High ($I^2 = 68\%$) Random
Heart failure	3	612	274 (2.3)	338 (2.8)	0.64 [0.38–1.09]	0.10	High ($I^2 = 87\%$) Random
Major CV events	2	1598	711 (5.9)	887 (7.3)	0.75 [0.49–1.13]	0.17	High ($I^2 = 94\%$) Random
Major coronary events	2	728	332 (2.7)	396 (3.3)	0.78 [0.58–1.06]	0.11	High ($I^2 = 68\%$) Random

95% CI, 95% confident interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; No., number.

cardiovascular risk factor. They were relatively diverse in terms of ethnicity, age and cardiovascular profile, representing a mixed population of medium to high cardiovascular risk patients. In the actively treated patients, mainly receiving indapamide in combination with perindopril, statistically significant risk reductions were observed for the mortality endpoints, with trends towards benefit when nonfatal endpoints were considered (with a greater degree of heterogeneity, which made these point estimates less certain). The heterogeneity arose from several factors, including smaller sample size (as not all endpoints were reported in all studies), or the relative neutrality of ADVANCE for some endpoints (a trial in which patients received high levels of treatment for comorbid conditions, had a wide range of clinical conditions and risk levels, including patients with elevated and others with normal BP). The results of our analysis estimating the aggregate risk reduction afforded by the indapamide with or without perindopril-based regimen are in line with the well known effect of the thiazide-like diuretic class on major cardiovascular and mortality outcomes [15,18,20].

Although the positive benefits demonstrated by the meta-analysis of these four randomized trials might seem obvious to some readers, familiar with all four studies, it should be noted that they were published over a span of many years, ranging from 1995 to 2014. Furthermore, two trials deal with poststroke events [33–35], two reports concern a population with type 2 diabetes [36,42] and one deals with very elderly patients, over 80 years of age [37], so that many readers may have missed the main results of some of these trials.

Another interesting aspect of our study is that the rates of permanent treatment discontinuation for any reasons were similar between active and placebo groups, while rates of treatment discontinuation for safety reasons were approximatively twofold higher in the actively treated group (approximatively 6.4 vs. 3.8%, respectively), in line with previous observations [20,42]. The nonnegligible incidence of discontinuation in the placebo group is partly explained by the pattern of the studies, which authorized the maintenance of the previous antihypertensive treatments and the concomitant treatments for associated risk factors.

As pointed out by Atkins *et al.* [39] in their analysis of ADVANCE and PROGRESS pooled data across five BP strata, contrasting with the increase in discontinuation due to hypotension among patients with SBP less than 120 mmHg in the actively treated group (4.7 vs. 1.2% over 5.6 years), there was no clear difference between the two treatment groups in the other BP strata (0.7% absolute excess of discontinuation).

On the basis of the data from ADVANCE wherein both all-cause mortality and cardiovascular mortality in the patients who discontinued active treatment were lower than for those that discontinued placebo, the authors' suggestion was that the active medication continued to have a residual protective effect in the early months after cessation, and this benefit was greater than any hazards because of withdrawal syndromes [31]. The overall benefit observed in ADVANCE was even maintained in the long-term in ADVANCE-ON, where upon 6-year observational follow-up, the reduction in the risk of death in the BP-lowering intervention group was attenuated but still significant [43].

As highlighted by some guidelines, some meta-analyses investigated the potential difference between thiazide-type and thiazide-like diuretics, in favour of the latter, regarding both their BP-lowering effect [26,44,45] and their effect on cardiovascular prevention [17,18,27,45,46]. Interestingly, in people over 80 years old, total mortality decreased in HYVET, in which indapamide was used, contrasting with a meta-analysis, which included studies with other thiazide diuretics and that showed a nonsignificant 6% relative excess of death from all causes, with significant heterogeneity between HYVET and the other trials [47]. Such a beneficial effect of indapamide with or without perindopril on mortality outcomes was also observed in our analysis, pooling the four RCTs.

Two other meta-analyses highlighted the cardiovascular benefit of thiazide-like diuretics, in particular in terms of protective effect against cardiac events, heart failure and stroke [17] or coronary events and all-cause mortality [27]. Many publications [48–58] suggest that indapamide is an effective and well tolerated diuretic for hypertensive patients, in particular in improving micro-albuminuria (in diabetic individuals), reducing left ventricular mass index, inhibiting platelet aggregation and reducing oxidative stress. In combination with perindopril, indapamide may exert synergistic effects influenced by the sodium status of the organism [57]. Importantly, indapamide does not share with thiazide diuretics their adverse effects on lipid and

glucose metabolism, and so can be safely prescribed in diabetic patients [45].

Strength and limitations

The strength of our analysis resides in the extent of information available for the indapamide with or without perindopril-based regimen, including more than 24 000 patients, allowing a conclusion to be drawn on its net benefit, that is the benefit shown after balancing protective against adverse consequences, and in particular its benefit on mortality data. The study has limitations. Analyses were performed on aggregate and not individual patient data, and some unpublished data or previously published data were obtained from the investigators to reinforce the robustness of the results. Even though the analysis was performed on a limited number of trials, they were all of high quality. The four studies were relatively heterogeneous in terms of patient demographics and baseline risks; however, we argue that this heterogeneity more faithfully reflects clinical experience than the more carefully selected RCTs of some meta-analyses. Pooling together monotherapy and combination with perindopril reflects the pragmatic considerations of initiating treatment with either a mono or combined therapy according to the current guidelines. The fact that statistical evidence of low heterogeneity was observed in the analysis for mortality endpoints is therefore noteworthy. Unfortunately, treatment discontinuation data were only available for two studies. However, we believe they represent interesting data for physicians who manage hypertensive patients.

In conclusion, across relatively diverse medium to high cardiovascular risk patient populations, long-term indapamide with or without perindopril-based treatment provided a statistically significant risk reduction in all-cause mortality, cardiovascular death and fatal stroke, as well as total stroke, confirming its place in the management of high BP.

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Conflicts of interest

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