Title: Efficacy of a new single-pill combination of a thiazide-like diuretic and a calcium channel blocker (Indapamide SR/Amlodipine) in essential hypertension

Short title: Indapamide SR/Amlodipine in hypertension

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The University of Glasgow received funding in lieu of AFD's honorarium for coordinating the study.

RA received honoraria from Servier as coordinator of the out-of-office Blood Pressure assessments.

MdC and RB-V are employees of Servier.

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Abstract

Objectives: This international, 12-week, double-blind, randomised, controlled trial assessed the efficacy and safety of indapamide sustained release (SR)/amlodipine single-pill combination (SPC) in mild-to-moderate hypertensive patients.

Methods: Following a 4-week run-in period on amlodipine 5 mg, patients (SBP 150-180 mmHg and/or DBP< 110 mmHg) were randomized to indapamide 1.5 mg SR/amlodipine 5 mg (IndSR/Aml) SPC or amlodipine 5 mg/valsartan 80 mg (Aml/Val) SPC with conditional up-titration at week 6. Office BP was assessed at baseline, weeks 6 and 12; ambulatory and home blood pressure monitoring (ABPM / HBPM) at baseline and week 12.

Results: Baseline characteristics were similar in both groups (57 years, 51% men, BP 160/92 mmHg). 233 patients were randomized to IndSR/Aml and 232 to Aml/Val, of whom 48% and 57% were up-titrated, respectively. After 12 weeks, office SBP/DBP decreased similarly with both treatments (-21/-8 vs -20/-8 mmHg) leading to BP control in 50% and BP response in 70% of patients. Up-titration was effective (P<0.001) with both regimens, in favour of IndSR/Aml (SBP/DBP -12/-6 vs -7/-3 mmHg, respectively). ABPM (n=273) and HBPM (n=194) confirmed 24-hour efficacy of both regimens. In the subgroup of patients with sustained uncontrolled hypertension assessed by ABPM (n=216), office SBP/DBP decreased by -23/-13 vs -18/-10 mmHg, respectively (P=0.016/P=0.135, post-hoc analysis). Both treatments were generally well tolerated.

Conclusion: Both regimens produced effective BP reductions confirmed by ABPM/HBPM. Both treatments were well tolerated, in accordance with the individual agents' safety profile.

Trial registration number: EUDRA CT n° 2012-001690-84

Word count: 234 words (word limit: 250)

Keywords: ABPM, amlodipine, angiotensin receptor blocker, calcium channel blocker, HBPM, hypertension, indapamide SR, single-pill combination, thiazide-like diuretic, valsartan

Condensed abstract

Patients (n= 473) with mild-to-moderate uncontrolled essential hypertension treated with amlodipine were randomized to single-pill combination indapamide SR/amlodipine or amlodipine/valsartan regimens for 12 weeks, including up-titration at week 6 for those with uncontrolled blood pressure (BP). Both treatment regimens led to significant office BP reductions (BP control 50%, BP response 70%), with indapamide SR/amlodipine being more effective in decreasing systolic BP in case of sustained uncontrolled hypertension (post-hoc analysis). 24-hour ambulatory and home blood pressure monitoring results confirmed efficacy. Both treatment regimens were well tolerated in line with their known safety profile.

Word count: 92 words (word limit: 100)

Introduction

Hypertension (HT) is a major public health problem [1] with an estimated prevalence of 20-24% worldwide [2]. Despite the wide range of available antihypertensive medications, blood pressure (BP) control rates remain particularly low, irrespective of world region, with only one third of treated patients being controlled to a BP <140/90 mmHg [3,4]. As many patients having started treatment with a single agent will subsequently require ≥2 drugs from different pharmacological classes to reach their BP goals [4,5], the most recent 2018 European guidelines [6] recommend starting with a combination in most patients and preferably with a single-pill combination (SPC).

Simplification of HT treatment by using SPCs has received increasing support from most guidelines over the last few years [5–16]. SPCs can simplify the task of adjusting and titrating the doses of their components and improve adherence [17–19]. Moreover, patients on SPC experienced a lower 5-year rate of cardiovascular events than those on free combinations [20].

Diuretics and calcium channel blockers (CCB) are 2 major antihypertensive drug classes recommended for first line treatment, particularly for hypertensive patients with diabetes, the elderly, patients of African origin, patients with a history of stroke, isolated systolic hypertension or resistant hypertension [6,7,9,12,21,22]. Their combination is one of the recommended options with confirmed efficacy [5,7–9,12] in terms of BP reduction and clinical outcomes, but remains underused in clinical practice. A meta-analysis of four long-term randomized clinical trials assessing such a combination in a total of 30,791 patients [23], mostly driven by the VALUE and FEVER studies [24,25] showed significant risk reduction for myocardial infarction (RR, 0.83; CI, 0.73–0.95) and stroke (RR, 0.77; CI, 0.64–0.92) compared with other combinations, while total and cardiovascular mortality were both reduced by 11% (RR, 0.89; 95% CI, 0.75–1.06 and 0.89; CI, 0.71–1.10, respectively).

At the drug level, indapamide, a thiazide-like diuretic [26–29], and amlodipine [24,30,31], the most commonly used dihydropyridine CCB, have both demonstrated beneficial effects on cardiovascular and stroke outcomes in hypertensive patients. Indapamide SR/amlodipine is the first available SPC combining a thiazide diuretic with a dihydropyridine CCB, since 2013, and has been shown to be effective and well-tolerated in a real-world setting study [32]. Herein we report the results of a Phase 3 randomized clinical trial that assessed the blood pressure-lowering efficacy and tolerability of the 2 dosages of the SPC of indapamide SR / amlodipine with a step escalating dose strategy versus amlodipine/valsartan (dihydropyridine and angiotensin receptor blocker), a standard SPC commonly prescribed for hypertensive patients.

Methods

Patients

Eligible patients were men or women aged over 18 years with mild-to-moderate uncontrolled essential hypertension, defined as SBP at least 150 and less than 180 mmHg with DBP less than 110 mmHg (isolated systolic hypertension accepted). Patients were either not being treated or were not controlled by antihypertensive monotherapy and required a change of antihypertensive medication, without any exclusion criteria regarding the type of drug and duration of hypertension.

The main exclusion criteria were a body mass index (BMI) > 32 kg/m²; diabetes; significant cardiovascular, cerebrovascular, hepatic or renal disorders; secondary hypertension; electrolytes abnormalities (hyper or hyponatremia, hyper or hypokaliemia, hyperuricemia); and any contra-indications or hypersensitivity to treatment with indapamide and/or amlodipine.

Study design

Main study protocol

This was a randomized, double-blind, double dummy, multicenter, 12-week, parallel group, phase III trial conducted in 13 countries [Supplemental file 1: **Table S1**].

The study was conducted in compliance with the current revision of the Declaration of Helsinki in accordance with Good Clinical Practice (GCP) guidelines. The study protocol was approved by local study centers' institutional review boards or ethic committees. For all patients, the investigator proposed the participation in the Ambulatory Blood Pressure Monitoring and the Home Blood Pressure Monitoring protocols, considering few non selection criteria mainly related to anticipated difficulties to tolerate the device or to obtain valid out-of office measurements. All patients provided written informed consent before selection. The trial is registered at the European Union Clinical Trials Database (EUDRA CT n° 2012-001690-84).

All selected uncontrolled hypertensive patients entered a 4-week run-in period, stopped their previous medication if any and were given amlodipine 5 mg open-label as one capsule daily in the morning. Those with remaining high BP (SBP ≥ 150 and <180 mmHg and DBP <110 mmHg) at the end of this period were randomized to receive treatment of similar appearance for 12 weeks constituted by a SPC either of indapamide 1.5 mg SR /amlodipine 5 mg (IndSR/Aml) or amlodipine 5 mg/valsartan 80 mg (Aml/Val) with the use of a placebo miming the comparative drug. Three visits were performed: at baseline (visit 1), week 6 (visit 2) and week 12 (visit 3). Patients with uncontrolled BP (office SBP ≥140 or DBP ≥ 90 mmHg) were up-titrated to the next dose i.e., IndSR/Aml 1.5/10 mg or Aml/Val 5/160 mg at visit 2 (W6). Use of other antihypertensive drugs or of drugs affecting BP was prohibited during the trial.

The main criteria for efficacy were office BP changes at week 12, with supine SBP being the primary criterion. Secondary criteria included supine DBP, rates of BP control (SBP/DBP < 140/90 mmHg) or response to treatment (controlled BP or 20 mmHg decrease in SBP or 10 mmHg decrease in DBP).

Regarding safety assessment, patients were examined for orthostatic hypotension, vital signs and adverse events, recorded at all visits. Complete clinical laboratory examinations (biochemistry and haematology) and 12-lead electrocardiogram were performed at inclusion and at study end. Simplified laboratory tests (mainly sodium, potassium, uric acid, creatinine plasma measurements) were performed before the week-6 visit.

Office BP assessment

At each visit, office BP was measured at the same period of the day and recorded 3 times at 1 min intervals in supine position, after 10 min of rest, using a validated digital BP device with an appropriate cuff size and a thermal printer (OMRON® model 705CP-II, Omron Healthcare, Kyoto Japan). Office SBP and DBP were measured in a quiet room, at trough of study drug *(i.e.* 24 ± 3 hours after study drug intake). The mean of the last 2 values of the 3 measurements was considered for assessment. After the third measurement, patients were asked to stand up for an additional 1 min and 3-min BP measurements taken in a standing position.

Out-of office BP measurement

Out-of-office BP assessment was performed in 2 subgroups of patients on 24-h ABPM (ambulatory blood pressure monitoring) and HBPM (home blood pressure monitoring) parameters. ABPM and HBPM were performed using validated devices in agreement with current guidelines [33,34].

ABPM and HBPM were always set-up before drug intake. All patients were trained by the investigator to use the HBPM device (same model for all the patients), to fill in the diary and to follow the standard procedure.

ABPM over 24 hours was performed at baseline and week 12 using the Mobil-O-Graph® (Stolberg, Germany) 24h PWA device on the same arm, with appropriate cuff. The measures were taken every 20 minutes. For the validation of an ABPM recording, a minimum duration of 23:20 hours and a minimum of 46 BP readings during the 24-hour period were necessary. The earliest “Beginning of test” started at 7 a.m (the latest at 11 a.m), and ended the next day, just before the study drug intake. ABPM validation was done on-line by a study-specific software e-CoreLab®. Mean daytime (7:00 to 22:00), night-time (22:00-7:00) and 24-h blood pressure values were calculated for each treatment period.

The HBPM measurements were performed before each visit (baseline, week 6 and week 12), twice a day, on the same arm and at the same time every day, in the morning (between 6 a.m. and 10 a.m), before taking the study drug and in the evening (between 18:00 and 22:00, before dinner). A set of 3 seated BP measurements were automatically taken with a 1 minute interval 3 days before the visit and at the day of the office visit using an FOR A D40 (St. Gallen, Suisse)® device. Data were centralized, transferred to the e-CoreLab® and validated technically. Mean morning, evening and 24-h blood pressure values over the 3 complete days preceding the visit were calculated for each treatment period.

Statistical methods

Efficacy analyses were performed according to the ITT principle: all patients randomized to treatment who received at least one dose of assigned treatment and who had at least one baseline and one post-baseline office SBP value. DBP was

assessed in the whole population but also in the 2 subgroups of patients with systolic and diastolic hypertension and with isolated systolic hypertension. The same applied for the ABPM and HBPM sub-studies.

BP and heart rate (HR) changes were assessed using an analysis of covariance (ANCOVA) model adjusted for treatment, baseline and center (fixed effects), and control and response rates using Chi square tests for the comparison of the 2 treatment regimens. Compliance with treatment was assessed by pill counts, by calculating the ratio between the number of study drugs considered as taken (calculated by subtracting the number of pills returned to clinic from the number of pills dispensed) and their theoretical numbers required during the study for a given patient. Safety was described in all patients who had taken at least one dose of study drug.

The sample size of 224 patients per group was calculated to detect a difference of 3 mmHg in the change from baseline in office SBP between the 2 treatment groups with a 80% power and a 2-sided significance level of 5%, assuming an SD of 11 mm Hg for each treatment group and a dropout rate of 5% after randomization. Non inferiority of indapamide/amlodipine over amlodipine/valsartan was tested with a margin of 3 mmHg for SBP and 2 mmHg for DBP at the 1-sided significance level of 2.5% (post-hoc analysis). P value associated with General Linear Model was provided.
All statistical analyses were performed using SAS/PC Software version 9.2.

Results

Demography and baseline characteristics

A total of 473 patients were randomly allocated to the two combination regimens, equally distributed across the 2 groups and well matched for baseline characteristics.

The ITT population included 233 patients allocated to indapamide SR/amlodipine and 232 patients allocated to amlodipine/valsartan. The 12-week treatment period was completed by 94% of the patients (220 vs 223 patients, respectively). Out of the 30 (6%) patients who withdrew from the study, three patients withdrew due to adverse events in the indapamide SR/amlodipine group and one patient withdrew due to lack of efficacy in the amlodipine/valsartan group. Protocol deviation (n= 7 in each group) and non-medical reasons (7 and 5 patients in the IndSR/Aml and Aml/Val group, respectively) completed the reasons for withdrawal. No patients were lost to follow-up. The use of titration at week 6 benefited slightly more the amlodipine/valsartan group, with 59% of the patients receiving the next dose as compared to indapamide SR/amlodipine (50%). Pill count results were similar between the two groups: 99.0±3.3% vs 98.6±4.7% for IndSR/Aml and Aml/Val, respectively.

ABPM and HBPM efficacy subsets were similarly distributed across treatment regimens. ABPM comprised 273 patients (133 versus 140 patients in the IndSR/Aml and Aml/Val groups, respectively) of whom 216 (79%) had sustained uncontrolled hypertension (SUCH) correctly distributed across the 2 treatment groups (104 and 112 patients, respectively). SUCH is defined as an abnormal ABPM at baseline (mean 24h ASBP ≥ 130 mmHg and/or mean 24h ADBP ≥ 80 mmHg) excluding white coat uncontrolled hypertension (WUCH), defined by an elevated office BP but controlled ambulatory BP. HBPM comprised 194 patients distributed as 95 and 99 patients, respectively.

Baseline demographic characteristics (51% men, 57 years old in average) showed no relevant between-group differences (**Table 1**). BMI was on average 26.8±2.5 kg/m², with only 8 patients above 30 kg/m². 41% of the patients presented with an isolated systolic hypertension (DBP <90 mmHg) and were well distributed across the 2 treatment regimens. The majority of patients (71%) were on existing treatment for

hypertension at entry, mainly given as monotherapy (96%) represented by an agent acting on the renin-angiotensin system (50%), a calcium channel blocker (15%) or a diuretic (6%), well distributed across the 2 treatment regimens. Mean supine SBP/DBP at baseline was 160/92 mmHg after having received 5 mg of amlodipine for one month.

Over the study period, compliance to treatment was excellent (98.8 ± 4.1%), with similar results by dose in both treatment regimens.

Efficacy

Office blood pressure parameters

Overall, over 12 weeks, both treatment regimens significantly ($p<0.001$) decreased SBP and DBP by -21/-8 mmHg vs -20/-8 mmHg, in the indapamide SR/amlodipine and amlodipine/valsartan groups, respectively and showed equivalence between groups (**Table 2**). Pulse rate decreased slightly and similarly with both regimens, by -2.7 bpm and -0.7 bpm, respectively. In the subgroup of patients with isolated systolic hypertension, normal DBP at baseline remained preserved with both treatment regimens (by -2 mmHg, in both groups). At study end, 50% of the patients had their BP controlled (SBP<140/DBP<90 mmHg) and 70% responded to treatment, with both regimens.

Patients with moderate hypertension benefited more from treatment with an office SBP/DBP decrease of -25/-11 mmHg versus -23/-10 mmHg with indapamide SR/amlodipine (n=124) and amlodipine/valsartan (n=127), respectively.

When considering patients with sustained uncontrolled hypertension, the effect of indapamide SR/amlodipine on office SBP was found to be significantly superior (-4.7 mmHg difference, P=0.016) to amlodipine/valsartan; with office SBP/DBP decreases of

-23/-10 mmHg vs -18/-8 mmHg, from 160/94 mmHg and 161/92 mmHg, respectively (**supplemental file 2: Figure S2**).

Up-titration efficacy

With the indapamide SR/amlodipine regimen, fewer patients were up-titrated (113 (48%) versus 135 (58%) in the amlodipine/valsartan group). Uptitration was associated with further decreases in office BP with both treatment regimens (P<0.001 for each titration), favouring indapamide SR/amlodipine (-12/-6 mmHg versus -7/-3 mmHg for Aml/Val) (**Table 3**).

ABPM and HBPM sub-studies

ABPM was performed in 273 patients (133 in the IndSR/Aml group and 140 in the Aml/Val group), and confirmed the 24-hour efficacy of the 2 treatment regimens. Over 24 hours, ambulatory SBP/DBP (ASBP/ASDBP) decreased by -7/-5 mmHg and -7/-4 mmHg, respectively, reaching final ASBP/ADBP mean values of 128/80 mmHg and 129/80 mmHg, respectively (**Figure 1**). Ambulatory heart rate (AHR) remained stable with the 2 regimens and decreased by -1.7 and -1.1 bpm, respectively. No relevant differences were observed regarding the different time periods studied reaching final mean ASBP/ADBP values of 131/83 mmHg and 132/84 mmHg for daytime period and 123/74 mmHg and 123/75 mmHg for night-time period, respectively. Over these periods, AHR decreased by -1.6 and -1.1 bpm for daytime and -1.7 and -0.6 bpm for night-time, respectively. BP profiles over the 24-hour period at week 12 are shown in **Figure 2**.

Similar findings were observed with home blood pressure monitoring, assessed in 194 patients (95 in the IndSR/Aml group and 99 in the Aml/Val group). Home SBP/DBP decreased by -9/-5 mmHg in the indapamide SR/amlodipine group and by -8/-6 mmHg

in the amlodipine/valsartan group (**Figure 3**). Global, morning and evening periods provided similar profiles.

Safety

Treatment was generally well tolerated across the 2 groups, and no safety concerns were identified for any treatment dose. Overall, 3 patients (1.3%) in the indapamide SR/amlodipine group withdrew due to adverse events, all not serious and recovered (dizziness, asthenia and hypokalaemia). Overall, the rate of adverse events was 19.9% for the indapamide SR/amlodipine group (versus 11.9% for amlodipine/valsartan), mainly driven by the diuretic properties of indapamide: hypokalaemia (5.5% vs 0.8%, respectively), dizziness (2.1% vs 0%), hyperuricemia (1.3% vs 0%). Peripheral oedema, which is known to be amlodipine-dose dependent, occurred in few patients (1.3% vs 0.4%) and mainly with the 10mg dose of amlodipine. Orthostatic hypotension episodes were defined as BP decrease of 20mmHg for systolic and 10mmHg for diastolic pressure, respectively. These episodes were infrequent, only 3 in each group. Two patients in each group reported a serious adverse event: renal cancer and hypokalaemia for indapamide SR/amlodipine, and colon adenoma and myocardial ischemia for amlodipine/valsartan. Of note, 4 patients erroneously started treatment with double dose of indapamide SR/amlodipine 1.5/5 mg for up to 10 days without any symptoms.

As expected with thiazides, there were few relevant changes in laboratory plasma values (**Table 4**). Mean changes were -0.2 ±0.5 and -0.0±0.4 mmol/L for potassium, -0.1±2.6 and -0.4±2.3 mmol/L for sodium, -0.3±9.9 and 0.7±10.9 µmol/L for creatinine and 40.4±182.4 and -8.1±170.6 µmol/L for uric acid, in the indapamide SR/amlodipine and amlodipine/valsartan groups, respectively.

Discussion

Efficacy on BP at office and out-of office measurements

Our study showed that both dual regimens with indapamide SR/amlodipine or amlodipine/valsartan (respectively belonging to the thiazide-like diuretic/CCB or angiotensin receptor blocker(ARB)/CCB classes) were effective in lowering BP and were generally well tolerated in a population whose baseline characteristics were well distributed across the 2 treatment arms including pre-treatment drug classes.

Interestingly, our study used the 3 main methods for accurately assessing BP-lowering efficacy, i.e. office (100% of the cohort) and out-of-office BP measurements in a large proportion using both ABPM (79% of the cohort) and/or HBPM (66% of the cohort). In that context, these last two measurements are a valuable supplement to office values [6,35,36] to overcome issues such as white-coat hypertension [5,6,10,37] and have been shown to be more predictive of cardiovascular risk than office BP [38–40].

Efficacy was observed with each of the 3 methods in the overall cohort, with similar profile in the non-Caucasians who represented 20% of the population (data not shown). Regarding the sub-groups of either isolated systolic hypertension (41%) or systolic and diastolic hypertension (59%), the patients were well distributed across the 2 treatment groups, and their changes in office DBP decreased similarly in both treatment groups (-2 mmHg for ISH and -12 mmHg for SDH).

After controlling the comparability of the patients' baseline characteristics between the whole population and those who underwent ABPM and HBPM, both of these methods corroborate and confirm the efficacy of the 2 treatments. In addition ABPM allowed the identification of a significant proportion of patients (21%) having white coat uncontrolled HT i.e. considered as not controlled at the office but controlled at ABPM after one

month of amlodipine monotherapy. With exclusion of these patients in post-hoc analyses we observed a difference between the two treatment regimens in favour of indapamide/amlodipine (while baseline values were found to be similar) in the sub-group of sustained uncontrolled hypertension patients, which seems to be at higher cardiovascular risk [7,41–43]. This difference cannot be accounted for by a difference in treatment compliance, as both regimens were formulated as SPCs and pill count results were similar between the two groups.

Method and design in line with the 2013 and 2018 European guidelines

In line with usual practice and the 2013 ESH/ESC guidelines, office BP was measured in the presence of a healthcare professional, at trough (i.e., 24 hour after dosing) with a validated automatic device (Omron in supine position) with a BP target of <140/90 mmHg. This remains the preferred method according to the 2018 European ESC/ESH guidelines [6].

Regarding treatment options, the design of our study was drafted to be in line with the 2013 ESH/ESC guidelines and current practice, which at the time of the protocol recommended to start treatment with monotherapy for most patients, followed by two-drug therapy as the next step for patients with uncontrolled BP. Using a scheme with an active run-in period, we could verify the persistence of uncontrolled hypertension despite monotherapy with amlodipine 5 mg and to provide the same chance for both groups at inclusion. The combination of Indapamide/Amlodipine or Amlodipine/Valsartan was for both regimens the next logical step for these uncontrolled hypertensive patients (SBP/DBP: 150-180/<110 mmHg). The 12-week period provided sufficient study duration and allowed accurate evaluation of the BP-lowering efficacy with a conditional up-titration scheme at mid-course.

Safety

Safety results for both regimens were in line with known safety profile of the individual agents and both regimens were generally well tolerated. Safety was mostly driven by the well-known thiazide properties of indapamide. Peripheral oedema, which is known to be related to CCB and which was reported to occur in 6% of patients over 12-week treatment [44], was uncommon in our study. It is recognized that ACEI or ARB combined with CCB reduce the risk [45], but we also observed a low occurrence with IndSR/Aml in our study, confirming previous results observed in the NESTOR study [46].

In light of the strong recommendation of the latest 2018 ESC/ESH guidelines [6] to initiate treatment in most hypertensive patients with a combined therapy – preferably as SPC - indapamide SR/amlodipine represents an effective alternative to agents that inhibit the RAAS in patients with low-renin hypertension [47]. Black and elderly patient populations, who have a high incidence of low-renin hypertension, have also been shown to be the population that best respond to diuretics and CCBs [48]. Evidence from trials using amlodipine, indapamide or regimens based on either of these drugs have shown improvement in morbidity and mortality outcomes and target organ protection, as reviewed by Safar and Blacher [47].

Limitations

Our study has some limitations. First, according to the study design assessing the 2 dosage strengths available for indapamide SR/amlodipine (1.5/5 and 1.5/10mg) SPC, only 2 usual dosages of amlodipine/valsartan were tested.

Second, considering the inclusion and exclusion criteria, the results reported herein are valid for the selected population, and were not evaluated in other populations at risk, for example in patients with diabetes. However, even though not evaluated in this study, data in diabetic patients including elderly patients have been previously reported

in the NESTOR-CCB analyses that showed the BP benefit of the combination over an ACE inhibitor and CCB combination [46,49].

Similarly, the study did not focus on low-renin hypertension patients, such as the black or the elderly, who would probably benefit more from the indapamide/amlodipine combination, as recently confirmed by the CREOLE study [50], specifically performed to assess the most efficient combination treatment classes including a CCB + diuretic, in the black sub-saharian population.

Perspectives

The use of SPC is highly recommended by most guidelines and emphasized by the recent 2018 ESC/ESH guidelines as we have evidence that it improves the rate of BP control in hypertensive patients. The indapamide SR/amlodipine combination is of particular interest for patients with low-renin hypertension – considered as relatively common, and is believed to affect up to 30% of patients with essential hypertension [51], especially in the black population, given that to our knowledge there is no other SPC of a thiazide diuretic and CCB marketed yet.

Conclusion

In patients with mild-to-moderate, essential hypertension, indapamide SR/amlodipine SPC was found to be at least equivalent to amlodipine/valsartan with regard to office BP reduction. Each dose was associated with significant decreases in office BP. At study end, 50% of patients had achieved BP control and 70% a response to treatment. Efficacy was confirmed by ABPM and HBPM measurements. The persisting 24-hour effect on BP is known to have a beneficial effect on cardiovascular risk reduction. No safety concern occurred in the study as the safety profile was mostly driven by the thiazide properties of indapamide. This is the first marketed SPC that includes a

thiazide diuretic and a calcium channel blocker and thus provides a new therapeutic opportunity for the treatment of hypertension.

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Conflicts of interest

The University of Glasgow received funding in lieu of AFD's honorarium for coordinating the study. RA received honoraria from Servier as coordinator of the out-of-office blood pressure assessments. MdC and RB-V are employees of Servier.

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Data sharing statement: Anonymized patient-level, study-level clinical trial data (including clinical study report) and study protocol, underlying the results reported in

this article will be shared in agreement with the Servier Data Sharing Policy available at https://clinicaltrials.servier.com/data-request-portal/.

Access to data will be granted to researchers identified in the research proposal directed to: https://clinicaltrials.servier.com/data-request-portal/, to achieve the aims described in this proposal, and provided its approval by a dedicated Committee and signature of data sharing agreement by requestor.

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TABLE AND FIGURE LEGENDS

Table 1: Baseline demographic characteristics in the randomized set

Table 2: Office supine blood pressure parameters and heart rate: change from baseline in the whole population

Table 3: Changes in office blood pressure (mean ± standard error) according to dose (up-titration efficacy) in the whole cohort

Table 4: Changes in plasma metabolic and renal parameters – Mean changes over the period (Mean ± SD)

Figure 1: 12-week changes in ambulatory blood pressure monitoring parameters (whole cohort): Change from baseline in the Ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP) and ambulatory heart rate (AHR).

Figure 2: 24-hour BP profile at week 12 with both treatment regimens

Figure 3: 12-week changes in Home blood pressure parameters (whole cohort). Change from baseline in Home systolic blood pressure (HSBP), Home diastolic blood pressure (HDBP) and Home heart rate (HHR).

Supplemental Files

Supplemental File 1: Table S1: Study characteristics

Supplemental File 2: Figure S2: 12-week change in office supine blood pressure (SBP and DBP) in patients with sustained uncontrolled hypertension

Table 1: Baseline demographic characteristics in the randomized set

Baseline characteristic (m±SD)	IndSR/Aml (n=237)	Aml/Val (n=236)	Global (n=473)
Age (years)	57 ± 11	57 ± 12	57 ± 11
Men, n (%)	121 (51%)	120 (51%)	241 (51%)
Caucasian, n (%)	189 (80%)	185 (78%)	374 (79%)
Mean Office Supine SBP ± SD (mmHg)	160 ± 7	160 ± 7	160 ± 7
Mean Office Supine DBP ± SD (mmHg)	92 ± 10	91 ± 10	92 ± 10
Mean Heart Rate HR± SD (bpm)	76 ± 12	75 ± 12	75 ± 12
Duration of hypertension (months), median	29	36	35
Hypertension severity:			
Mild (%)	47.3	44.6	46.0
Moderate (%)	52.7	55.4	54.0
Previously treated , n (%) with :	171 (72%)	163 (69%)	374 (71%)
Blockers of the Renin-Angiotensin System	125 (53%)	111 (47%)	236 (50%)
• ACE inhibitors	91 (38%)	79 (34%)	170 (36%)
• ARBs	34 (14%)	33 (14%)	67 (14%)
Calcium Channel Blockers	37 (16%)	35 (15%)	72 (15%)
Diuretics	14 (6%)	15 (6%)	29 (6%)
Hypercholesterolemia (%)	24.5	25.4	25.0
Smoker (%)	12.7	15.3	14.0

ACE: angiotensin-converting enzyme ; Aml/Val : Amlodipine/Valsartan ; ARBs: angiotensin receptor blockers ; bpm: beats per minute; DBP: diastolic blood pressure ; HR: heart rate; IndSR/Aml: indapamide SR/Amlodipine ; SBP: systolic blood pressure; SD: standard deviation

Table 2: Office supine blood pressure parameters and heart rate: change from baseline in the whole population

Office supine blood pressure – overall population (m±SD)	**Indapamide SR/Amlodipine N=233**	**Amlodipine/Valsartan N=232**	Between group difference E [95%, CI], P value (non inferiority)
SBP at baseline - Mean value (mmHg)	160 ± 7	160 ± 7	
Change from baseline (mmHg)	-21 ± 15***	-20 ± 16***	-1.1, [-3.7; 1.6], p=0.001
DBP at baseline - Mean value (mmHg)	92 ± 10	91 ± 10	
Change from baseline (mmHg)	-8 ± 10***	-8 ± 11***	0.2 [-1.4; 1.8], p=0.014
Heart rate at baseline – Mean value (bpm)	76±12	74±12	
Change from baseline (bpm)	-2.7 ± 11	-0.7 ± 11.9	-0.6 [-2.4; 1.1]

Change over 12-week. E, estimate of the between-group difference in adjusted mean changes from baseline using a general linear model with treatment, baseline and country as covariates, with associated 95% confidence intervals (CIs) and P non inferiority value with a limit margin of 3 mmHg for SBP and 2 mmHg for DBP.

*** P within group <0.001

Aml/Val : Amlodipine/Valsartan ; bpm: beats per minute; DBP: diastolic blood pressure; IndSR/Aml: indapamide SR/Amlodipine ; SBP: systolic blood pressure; SD: standard deviation

Table 3: Changes in office blood pressure (mean ± standard error) according to dose (up-titration efficacy) in the whole cohort

	Period	Treatment dose	n	Office SBP	Office DBP
Step 1	W0-W6	IndSR/Aml 1.5/5 mg	233	-17±1***	-6±1***
		Aml/Val 5/80 mg	231	-16±1***	-7±1***
Step 2	W6-W12	IndSR/Aml 1.5/10 mg	113	-12±1***	-6±1***
		Aml/Val 5/160 mg	135	-7±1***	-3±1****

*****, P<0.001**

Aml/Val : Amlodipine/Valsartan; DBP: diastolic blood pressure ; IndSR/Aml: indapamide SR/Amlodipine ; SBP: systolic blood pressure

Table 4: Changes in plasma metabolic and renal parameters – Mean changes over the period (Mean ± SD)

Parameter (unit)	Change from baseline	
	Indapamide SR/Amlodipine	**Amlodipine/Valsartan**
Sodium (mmol/L)	-0.1±2.6	-0.4±2.3
Potassium (mmol/L)	-0.2±0.5	-0.0±0.4
Creatinine (umol/L)	-0.3±9.9	0.7±10.9
Glucose (mmol/L)	0.2±1.5	0.1±1.6
Triglycerides (mmol/L)	-0.04±1.07	0.02±1.03
Cholesterol (mmol/L)	-0.04±1.08	-0.14±1.06
HDL Cholesterol (mmol/L)	-0.13±2.05	-0.53±3.17
LDL Cholesterol (mmol/L)	0.02±2.56	-0.17±1.71
Uric acid (µmol/L)	40.4±182.4	-8.1±170.6

HDL: high-density lipoprotein; LDL: low-density lipoprotein

Figure 1. 12-week changes in ambulatory blood pressure monitoring parameters (whole cohort). Change from baseline in the ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP) and ambulatory heart rate (AHR).

ASBP and ADBP values are in mmHg; AHR values are in bpm.

Aml/Val : Amlodipine/Valsartan; IndSR/Aml: indapamide SR/Amlodipine

Figure 2. 24-hour profile at week 12 with both treatment regimens

Aml/Val : Amlodipine/Valsartan; IndSR/Aml: indapamide SR/Amlodipine

Figure 3. 12-week changes in Home blood pressure parameters (whole cohort). Change from baseline in Home systolic blood pressure (HSBP), Home diastolic blood pressure (HDBP) and Home heart rate (HHR)

HSBP and HDBP values are in mmHg; HHR values are in bpm.

Aml/Val : Amlodipine/Valsartan; IndSR/Aml: indapamide SR/Amlodipine

Supplemental Files

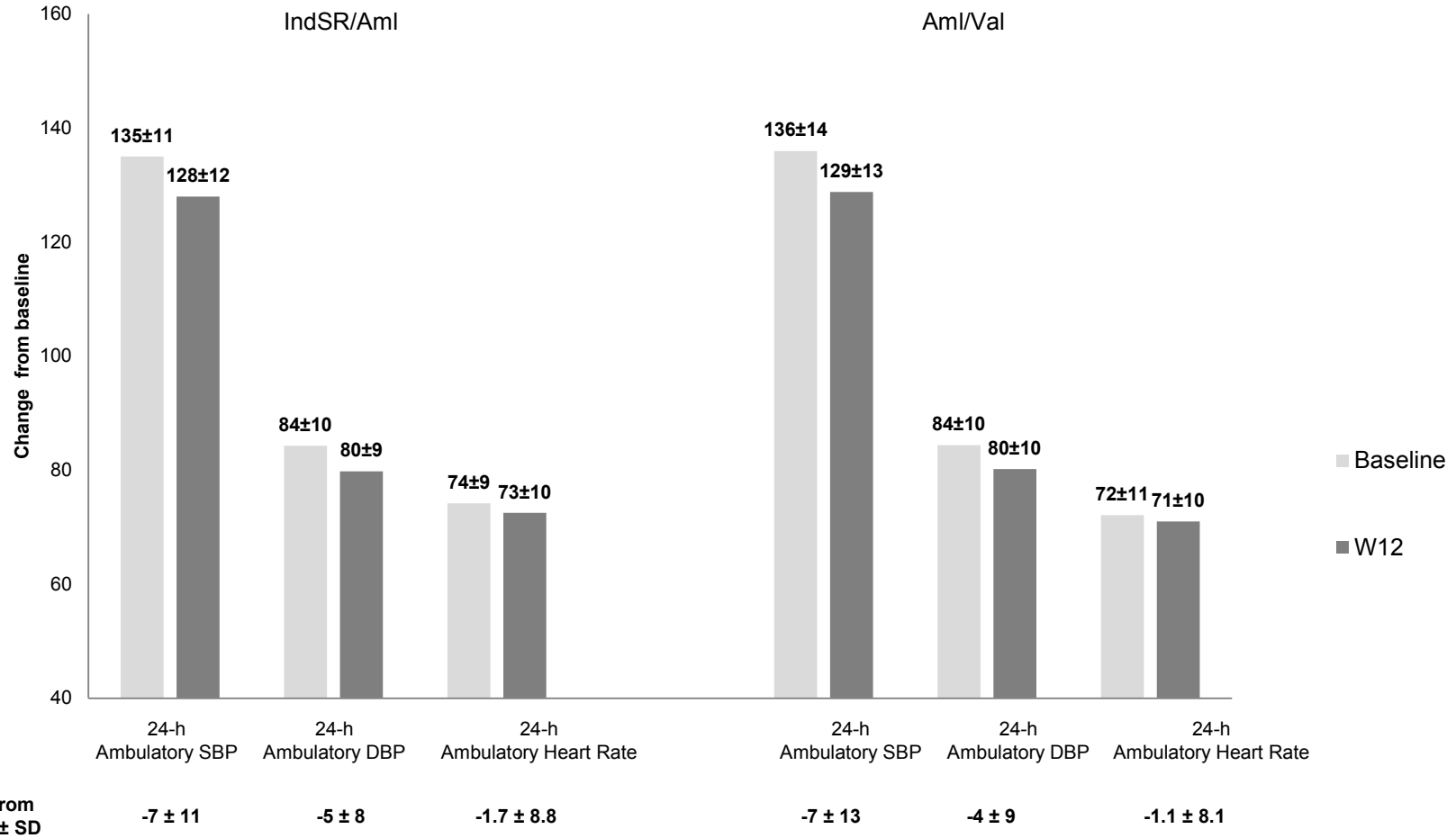
Supplemental File 1: Table S1. Study characteristics

Countries involved in the study : Argentina, Bulgaria, Hungary, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, South Africa, Thailand, Ukraine, Vietnam.
The investigators were hypertension specialists or general practitioners.
Patients and investigators were blinded to the treatment allocation.
Fixed Treatment randomization was balanced (ratio 1 to 1) and stratified by centre
Treatment –regimens used the double dummy and were strictly of the same appearance to respect study blinding.
Therapeutic units were supplied by Les Laboratoires Servier Industrie.
Centralisation of the ABPM/HBPM data was performed by a web-based system (e-CoreLab®, Paris, France) including an automatic test validation

Supplemental File 2: Figure S2. 12-week change in office supine blood pressure (SBP and DBP) in patients with sustained uncontrolled hypertension

IndSR/Aml: indapamide SR/amlodipine (n=104) ; Aml/Val: amlodipine/valsartan (n=112)
Difference between group: mean, 95%CI adjusted on baseline values and country
*** P within group <0.001

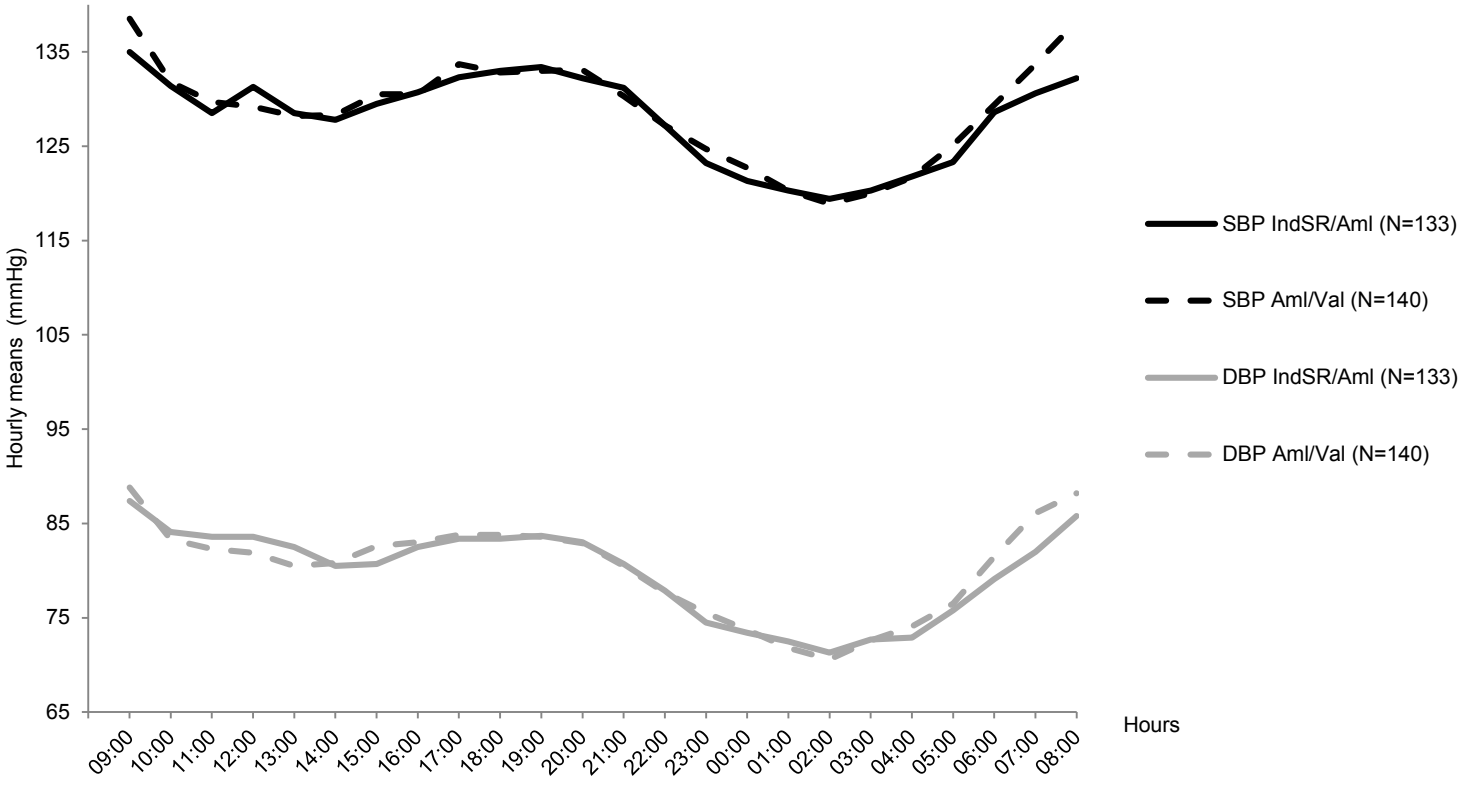
New Figure 1



Change from baseline ± SD	-7 ± 11	-5 ± 8	-1.7 ± 8.8	-7 ± 13	-4 ± 9	-1.1 ± 8.1

Between group comparisons E [95% CI]:		
	IndSR/Aml N=133	Aml/Val N=140
24-h ASBP	-0.3 [-2.8; 2.3]	
24-h ADBP	-0.3 [-2.1; 1.4]	
24-h AHR	0.2 [-1.7; 2.0]	

New Figure 2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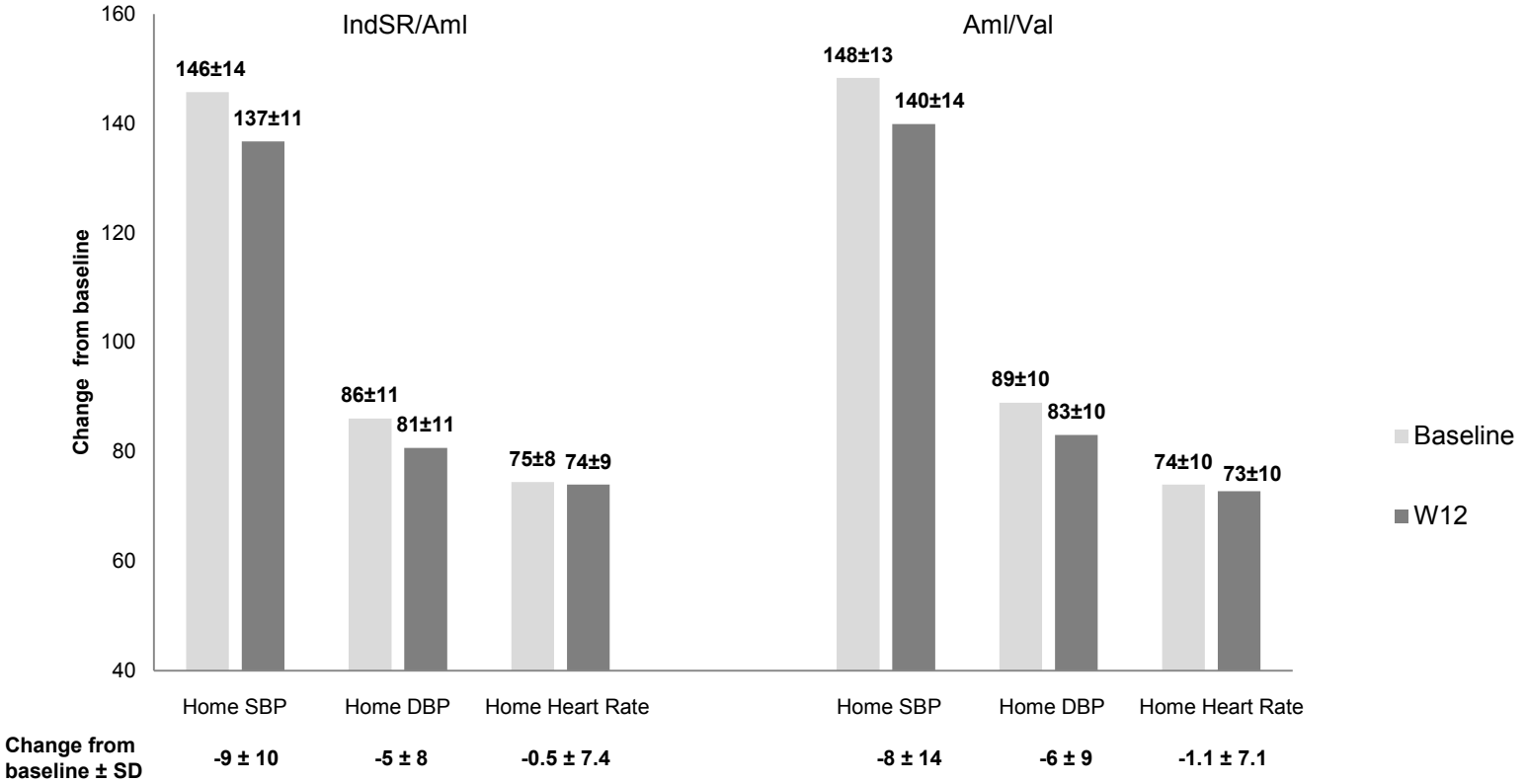
DBP IndSR/Aml (N=133)
DBP Aml/Val (N=140)

New Figure 3



	Between group comparisons E [95% CI]	
	IndSR/Aml N=95	Aml/Val N=99
HSBP	-1.9 [-4.9; 1.1]	
HDBP	-0.5 [-2.8; 1.7]	
HHR	0.8 [-1.1; 2.7]	

New Figure S2