Original Article

Evaluation of the antihypertensive effect of nocturnal administration of acetylsalicylic acid: a cross-over randomized clinical trial

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Objective: Several studies have shown that evening intake of aspirin has antihypertensive effect in healthy adults, which has not been proven in patients with cardiovascular disease, who mostly take aspirin in the morning. We have evaluated the antihypertensive effect of bedtime administration of aspirin in patients with cardiovascular disease already treated for hypertension.

Methods: This is a multicenter randomized triple-blind placebo-controlled crossover trial, with hypertensive patients treated with aspirin for secondary prevention. There was a baseline-randomized assignment to 2-month periods of bedtime aspirin (100 mg) first and morning-time aspirin later, or inversely, both periods separated by an open label 2–4 weeks period of morning-time aspirin. At the start and end of each treatment period, a 24-h ambulatory blood pressure monitoring was performed. The main outcome measure was mean 24-h blood pressure. The analyses were performed according to the intention-to-treat principle.

Results: Overall, 225 patients were randomized. No significant differences were observed in ambulatory blood pressure by time of intake of usual low doses of aspirin. The mean SBP/DBP was 123.2/69.9 (95% CI 121.58–124.9/68.86–76.86) with bedtime administration and 122.4/68.8 (95% CI 120.76–124.01/67.85–69.83) with daytime administration ($P = 0.3$ and $P = 0.23$ for SBP and DBP, respectively).

Conclusion: Administering aspirin at bedtime rather than in the morning does not modify the 24-h ambulatory blood pressure in hypertensive patients in secondary cardiovascular prevention.
The trial was registered with ClinicalTrials.gov (number NCT01741922).

Keywords: aspirin, cross-over trial, hypertension, primary care

Abbreviations: AMPS, ambulatory blood pressure monitoring; BP, blood pressure; CRF, case report form; HR, heart rate; NO, nitrogen monoxide; OR, odds ratio; PP, pulse pressure

INTRODUCTION

The importance of controlling blood pressure (BP), one of the main risk factors for cardiovascular disease, is universally known and accepted [1]. Nevertheless, despite the numerous antihypertension drugs available, we currently fail to achieve completely satisfactory control of BP and we are still looking for new approaches [2,3].

Several studies, mostly in healthy adults, untreated patients with mild hypertension, and pregnant women, have indicated that the evening intake of aspirin at low doses has an antihypertensive effect [4–7]. What is more, it was found that evening intake of aspirin changed the diurnal pattern of BP, patients shifting from nondipper to dipper patterns [8]. A later study found significantly lower plasma renin activity, and plasma cortisol and urine catecholamine concentrations in the 24 h following evening intake of low doses of aspirin, no such changes being observed with daytime intake [9]. These effects have been attributed to the inhibition of the renin–angiotensin system and an increase in the release of nitric oxide (NO) after evening intake of aspirin [9–11].

The aforementioned studies have indicated a need to investigate the antihypertensive effect of evening aspirin intake. The studies to date, however, have been conducted in healthy individuals and untreated hypertensive patients who had not been regularly taking aspirin. Hence, it is necessary to determine whether the effect observed is reproduced in patients under continuous treatment with aspirin for the secondary prevention of cardiovascular events and who are also being treated with

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antihypertensive effect drugs and other drugs for comorbid conditions [12].

According to the recent review of Bem *et al.*, three very interesting studies have been published including this type of patient [13–16]. None of these studies, however, used placebo to control for the psychosocial and behavioural effects. These circumstances might, for example, trigger changes in behaviour or in the intake of other drugs that affect BP. All of these factors would then be acting at the same time as the aforementioned biological effects associated with evening intake of aspirin, which is what we are seeking to assess. To isolate these effects, it is desirable to create the same treatment context for daytime and evening aspirin intake, doubling the number of tablets taken but with one set containing an inert substance [17–20]. Additionally, in all three studies, there was a risk of some kind of bias in the selection of participants. The first two studies were based on relatively small sample sizes and the doses of aspirin were different from those usually recommended for secondary prevention [14,15]. The third study imposed an upper age limit of 75 years, included only 16% of the eligible population and 52% of participants did not follow the protocol correctly [16].

All three studies concluded that BP did not decrease with evening intake of aspirin compared with levels observed with morning aspirin intake. Despite this, given the great benefit that being able to decrease BP without adding medications would bring to patients, these findings need to be confirmed in randomized, placebo-controlled, clinical trials. In this way, we can assess whether there is really an antihypertensive effect of evening compared with morning intake of aspirin among patients with hypertension who are already taking this drug for the secondary prevention of cardiovascular disease [21].

METHODS

Study design and participants

We conducted a multicentre, randomized, triple-blind, placebo-controlled, crossover study (the TAHPS trial) in patients with hypertension and a history of cardiovascular events under treatment with low-dose aspirin taken during daytime. The theoretical framework, design, and methods have been described in a previous publication [22]. The research was conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and all local regulations. The study protocol was approved by the Clinical Research Ethics Committee of Euskadi (Ref:115/2011), the Spanish Agency for Medicines and Health Products (Eudra CT: 2011-004760-29) and BioCruces research committee.

The study was carried out in a total of 20 primary care centres: six in Bizkaia and six in Gipuzkoa, all managed by the Basque Health Service (Osakidetza), and a further eight in Barcelona, managed by the Catalan Health Service. Thirty-five doctors and 34 nurses collaborated in the study.

All the patients included were over 18 years old, had hypertension treated with low doses of aspirin (75–125 mg) for secondary prevention of cardiovascular events and had a more than 6-month history of vascular disease (ischaemic heart disease, cerebrovascular accident, or peripheral artery disease). Further, they all had no changes in treatment for their hypertensive condition in the 3 months prior to inclusion in the study. Patients who took their aspirin at bedtime prior to the study completed a 1-month open-label period in which they took the drug in the morning before inclusion.

We excluded pregnant or breastfeeding women; shift workers; heavy drinkers (men and women who consumed >280 and 170 g of alcohol/week, respectively), long-term users of nonsteroidal anti-inflammatory drugs, anticoagulants, antiplatelet agents, or aspirin at doses other than those mentioned above; and individuals who had unstable BP despite treatment for hypertension, with severe heart failure (NYHA class III or IV), with glomerular filtration less than 45 ml/min, with any serious or terminal illness, or with any physical or mental illness that might hinder his or her collaboration. All participants gave written informed consent.

Randomization and masking

Using the health information systems of OSABIDE in the Basque Health Service (Osakidetza) and SISAP in the Catalan Health Service, we identified patients who met the selection criteria, each patient was registered in the case report form (CRF), thus automatically generating a unique study code for the patient.

Patients were randomized using a computer in the laboratory where the medication was packed. This laboratory produced two types of packs with individual numbers: one for participants assigned to take first aspirin in the morning (0800–1000 h) and placebo at bedtime (2000–2200 h; group B), and the other for those assigned to placebo in the morning (0800–1000 h) and aspirin at bedtime (2000–2200 h; group A). When a patient was included in the study, their doctor gave them a medication pack with a corresponding code, which was recorded on the CRF. In this way, doctors did not know to which group their patients had been assigned.

During the entire study, the doctors, nurses, study monitors, and data analysts did not know the time the active ingredient was taken by any of the patients. The colour, size, texture, and packaging of the tablets containing placebo and aspirin were identical.

Procedures

Once the central information technology services (of OSABIDE or SISAP) had identified patients who met the selection criteria and were on lists of doctors participating in the study, all participating doctors were provided with a complete coded list of all patients on their list who met these criteria. These doctors forwarded the amended list (still coded) to the Primary Care Research Unit of Bizkaia. The research unit then randomized this coded list and the doctors used this new version of the list to contact their patients in a random order.

The study constitutes two periods of 60 days randomized double-blind treatment separated by 15–30 days of open-label aspirin in the morning. All patients underwent 24-h ambulatory BP monitoring (ABPM) at the start of the study, at the end of the first period, before starting the second period (after the open label crossover period), and at the end of the second period (Fig. 1). Laboratorium Sanitatis manufactured both the drug and the placebo.

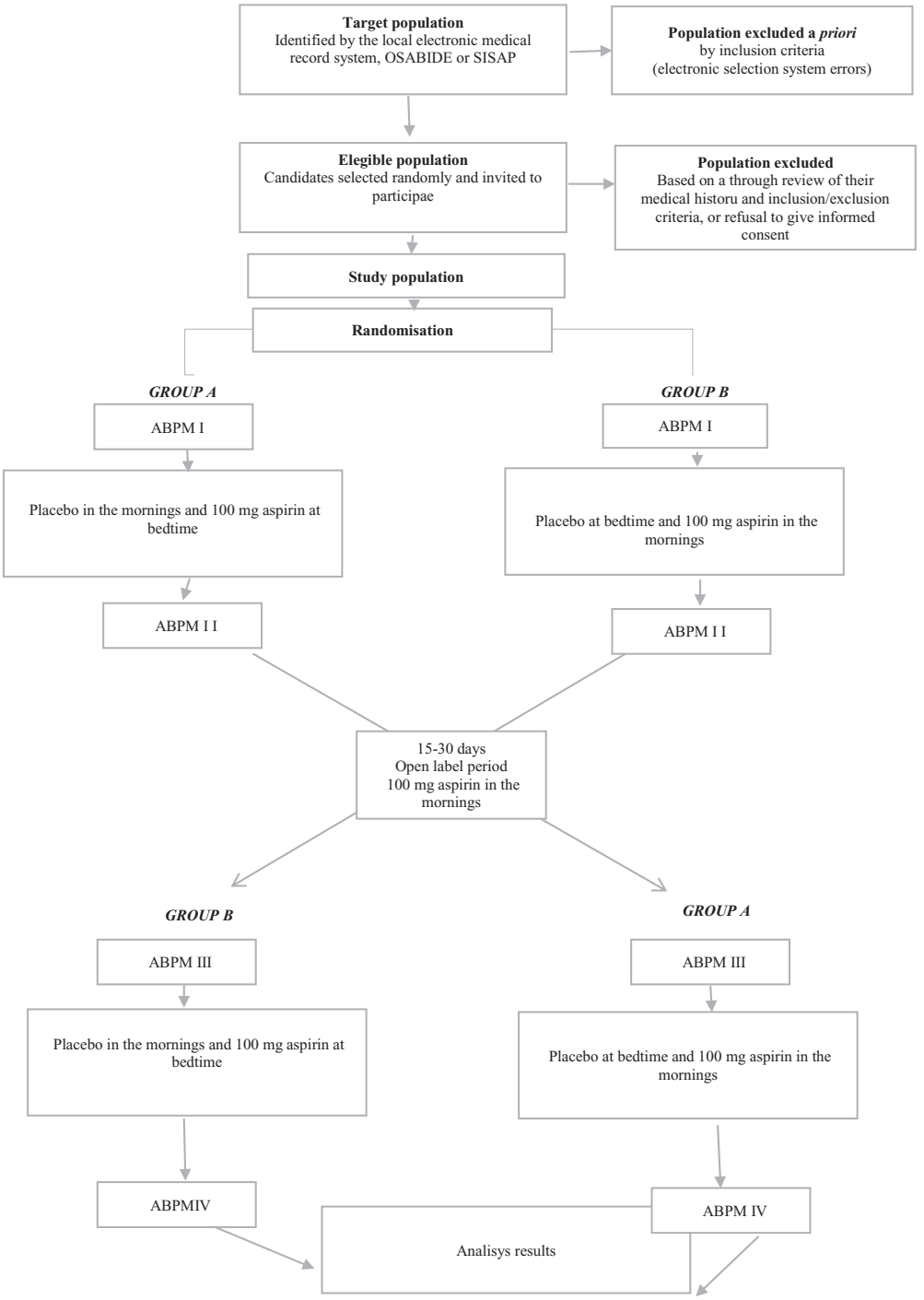

FIGURE 1 Flow of patients through the study. ABPM, ambulatory blood pressure monitoring.

Once a month during the 5 months of the study, all patients were invited to an appointment with a nurse in which treatment adherence was assessed by interviewing the patient and by tablet counting, and possible adverse effects were recorded. We considered that patients had adhered to the treatment if they had taken 80–110% of the tablets. At the start and end of the study, the following were measured in all patients: blood count, lipid profile, kidney and liver function, and microalbuminuria. All data were recorded in the CRF.

Outcomes

The primary outcome measure was the 24-h BP, and the secondary outcome measures included the 24-h heart rate (HR) and 24-h pulse pressure (PP). All of these were measured over 24-h periods with a clinically validated

ABPM device (WatchBP03). The research nurses or doctors fitted this ABPM, having first measured the patient's BP with a validated OMRON M6 BP monitor twice, or three times if the difference between the first two measurements was more than 5 mmHg. The SBP and DBP and HR were measured every 20 min between 0700 and 2300 h and every 30 min between 2300 and 0700 h. ABPM readings were considered invalid if more than 30% of the data were missing or if there were no data for a period of more than 2 h. They were also considered invalid if the patient had an irregular sleep–wake rhythm, with resting times more than 12 h or less than 6 h per night, during the monitoring period [17]. We defined the daytime BP as the mean of the measurements collected between 0900 and 2100 h and the night-time BP as the mean of the measurements taken between midnight and 0600 h, as this is the timetable that most closely matches the habits of most of our patients.

In addition, we calculated the SBP and DBP night/day ratios and used these values to classify patients: greater than 0.9, nondipper and 0.9 or less, dipper. As another secondary outcome, we assessed whether patients changed between dipper and nondipper patterns when the time of aspirin administration was changed.

Statistical analysis

Intention-to-treat analyses were carried out comparing outcomes at the end of the period of bedtime intake with those observed after the daytime intake, adjusting for the baseline values at the start of each period, using mixed effects repeated measures analysis of covariance models. Patients who participated in at least one of the periods of treatment were included in the analysis. These models included the time of aspirin intake (bedtime/daytime), the period of measurement, and the baseline values of the outcome variable in each period as explanatory fixed effects. The patient was included as a random effect (intercept), to take into account the correlation between two measurements in the same individual. We assessed the potential carry-over effect of the treatment by including an interaction term between the time of aspirin intake and the period. Missing values for baseline were imputed using the mean. No other value imputation was performed, as mixed effects models have shown to be highly robust in dealing with missing data [23].

Additionally, we extended these models simultaneously adjusting for the following potential confounding or modifying variables: changes in medication, age, sex, unhealthy habits (being smoker vs. nonsmoker), risk factors (being a nondipper vs. dipper), comorbidities (diagnosis of hyperlipidemia, diabetes, stroke, peripheral vascular disease, coronary heart disease), and time of study enrolment. For the analysis of dichotomous variables such as 'being a dipper,' we used logistic mixed effect models adjusting for dipper status at the start of each period.

We performed predefined subgroup analysis and per-protocol analyses to test the hypotheses that the bedtime intake was more effective in older people, male participants, individuals with certain concomitant pharmacological treatments, dippers, those with comorbidities, and those who adhered to the study protocol. We included interaction terms between these variables and bedtime intake to test the aforementioned hypotheses. The significance level was set at 0.05 for the main analysis (one-tailed hypothesis test), but it was corrected for multiple comparisons by the Bonferroni method yielding a value of 0.001 for the subgroup analyses.

A post hoc power calculation based on formulas developed by Senn [24] and adjusting to the final sample size and actual data variability shows that the study has a power greater than 95% to detect as significant ($P < 0.05$) a predefined minimal relevant difference in SBP between comparison groups of at least 2.5 mmHg. Accordingly, our beta error rate is lower than 5% when concluding between-group differences are nonsignificant.

Analyses were performed with SAS, version 9.4 (Cary, North Carolina, USA). This trial is registered with ClinicalTrials.gov, number NCT01741922.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, reporting of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between November 2012 and April 2013, 546 participants were screened at 24 health centres (Fig. 2). Of these, 321 were not included (221 for not meeting selection criteria) and 225 patients were randomly assigned to a group. As it was a blinded placebo-controlled trial, patients were unable to change the treatment to which they were assigned; 82% of participants met the treatment adherence criteria, and all patients were analysed as allocated for both safety and efficacy analyses. At baseline, both groups had similar values of outcome variables: mean 24-h values of SBP and DBP of 125.6 and 70.7 mmHg, respectively, and the percentages of SBP and DBP dippers were 48 and 64%, respectively. The averages of BP measurements taken at the screening visit by doctors and nurses were 137.1 mmHg for SBP and 77.2 mmHg for DBP with a correlation with the 24-h baseline readings of 0.51 and 0.59, respectively. Clinical and sociodemographic variables were equally balanced between the groups (Table 1).

The entire study was completed by 85.3% of patients. Only the variable 'working outside home' was associated with dropping out of the study [odds ratio (OR) 1.2, 95% CI 0.9–1.3). In 159 patients, we obtained valid ABPM readings at the end of both periods. The rates of dropout and invalid ABPM readings were balanced across the groups. Four patients were excluded from the analysis as they had no valid ABMP readings.

The 24-h BP means over the course of the study are shown in Fig. 3. A nonsignificant period effect was observed, with BP values tending to decrease during the first period of the study in both groups of patients, regardless of whether aspirin was taken at bedtime or in the morning ($P = 0.06$ and $P = 0.29$ for SBP and DBP, respectively). Patients' SBP was not lower with bedtime intake of aspirin than with morning intake of the drug; in fact, the mean BP was actually higher, with a nonsignificant

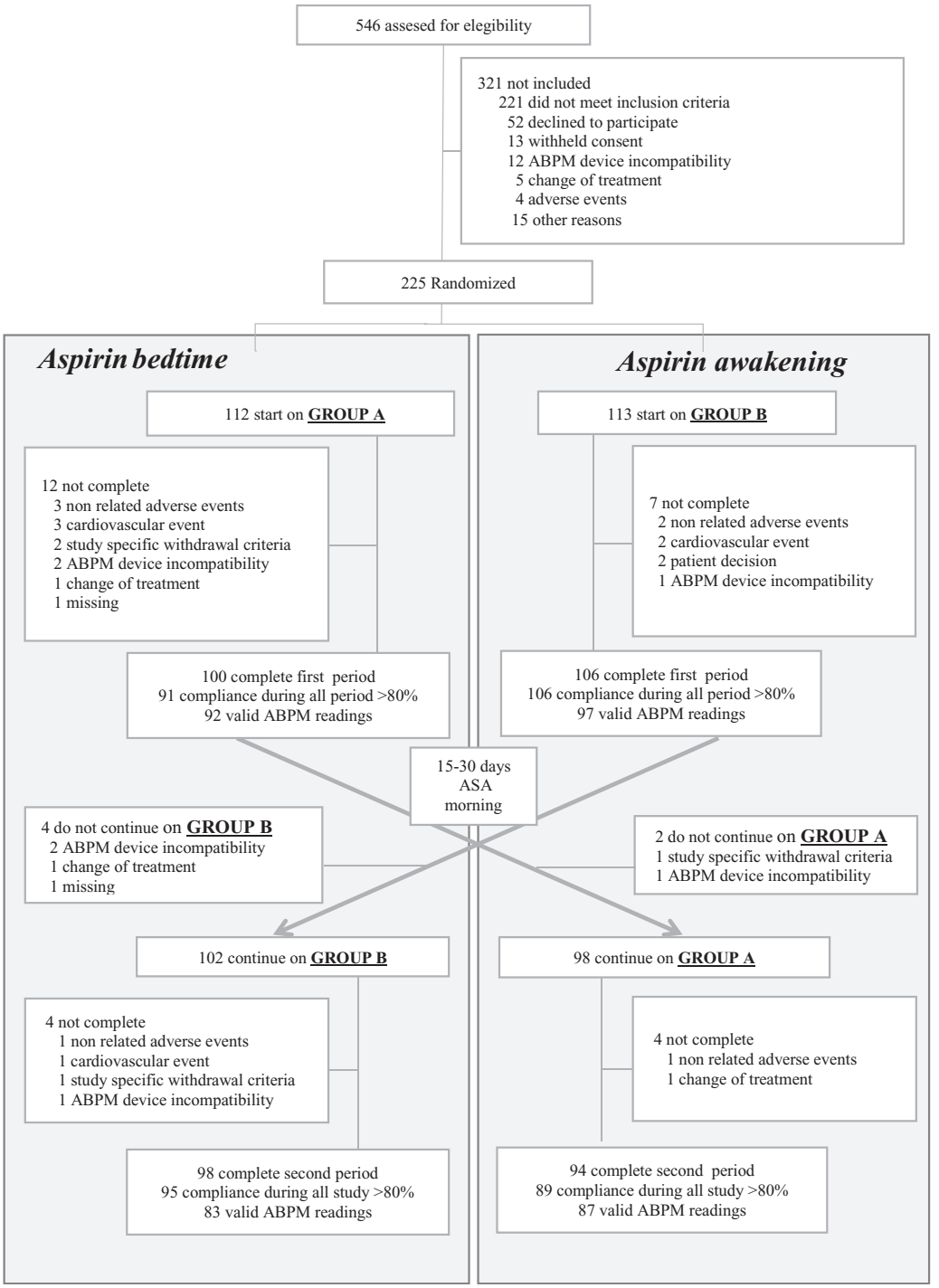

FIGURE 2 Trial profile. ABPM, ambulatory blood pressure monitoring.

estimated difference of 0.75 mmHg ($P = 0.3$). Similarly, DBP was not lower with bedtime intake (0.52 mmHg, $P = 0.23$).

We did not find any significant differences for the rest of the outcomes analysed with the linear mixed models, even after adjusting for potential confounding or modifying variables (Table 2). There were no significant carry-over effects in any analysis testing the interaction between period and the time of aspirin intake ($P > 0.4$). The probability of being a dipper did not increase significantly after bedtime aspirin intake (OR = 1.17, 95% CI = 0.74–1.87 based on SBP; OR = 1.39, 95% CI = 0.88–2.2, based on DBP). The night-to-day ratio decreased not significantly after bedtime administration both for SBP and DBP (Table 2).

TABLE 1. Baseline characteristics

Characteristic	Group A ($n = 112$) mean (SD)	Group B ($n = 113$) mean (SD)
Outcomes basal measures		
SBP (mmHg)	126.1 (11.6)	125.1 (11.7)
DBP (mmHg)	71.3 (7.3)	70.1 (6.6)
HR (mmHg)	65.6 (9.4)	65.7 (9.6)
PP (mmHg)	54.7 (9.7)	55 (9.5)
SBP dipper, *n* (%)	52 (49.1)	51 (47.2)
DBP dipper, *n* (%)	69 (65.1)	69 (63.9)
Patient characterisitcs		
Age,	67.8 (9.4)	68.7 (9)
Female, *n* (%)	32 (28.6)	35 (31)
BMI	28.8 (3.8)	29.5 (4.1)
Smoker, *n* (%)	11 (10)	11 (9.8)
Ethnicity, *n* (%)		
Caucasic	101 (90.2)	102 (90.3)
Latin-american	10 (8.9)	11 (9.7)
Work situation, *n* (%)	0 (0)	0 (0)
Work outside home	19 (17)	12 (10.6)
Homemaker	15 (13.4)	13 (11.5)
Retired	72 (64.3)	74 (65.5)
Unemployed	3 (2.6)	7 (6.2)
Educational level, *n* (%)		
None	4 (3.6)	5 (4.4)
Elementary school	65 (58)	57 (50.4)
Middle or highschool	27 (24.1)	35 (31)
University studies	14 (12.5)	16 (14.2)
Comorbidities and medication		
Comorbidities, *n* (%)		
Congestive heart failure	2 (1.8)	3 (2.7)
COPD	10 (8.9)	10 (8.9)
Diabetes	44 (39.3)	36 (31.9)
Hyperlipidemia	74 (66.1)	73 (64.6)
Coronary heart disease	72 (64.3)	73 (64.6)
Peripheral vascular disease	18 (16.1)	23 (20.4)
Stroke	29 (25.9)	26 (23)
Current medications, *n* (%)		
Lipid lowering drugs	91 (82.7)	87 (77.7)
Angiotensin II inhibitors	41 (37.3)	45 (40.2)
ACE-inhibitors	44 (40)	44 (39.3)
Diuretics	48 (43.6)	45 (40.2)
Calcium antagonists	32 (29.1)	26 (23.2)
Beta blockers	36 (32.7)	47 (42)
Omeprazole	52 (47.3)	52 (46.4)
Haematology and biochemistry		
Hemoglobin, g/dl	14.5 (1.4)	14.4 (1.4)
Platelets, $\times 10^9$/l	209.2 (49.8)	220.8 (49)
Leukocytes, $\times 10^9$/l	7.5 (2.9)	7.2 (2)
Glucose (mg/dl)	118.2 (38.5)	113.9 (30.3)
Creatinine (mg/dl)	0.9 (0.2)	0.9 (0.2)
Cholesterol (mg/dl)	175.4 (35.7)	171.2 (33.4)
Triglycerides (mg/dl)	126.1 (60.5)	119.3 (57)

ACE, angiotensin-converting enzyme; ARC, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; HR, heart rate; PP, pulse pressure; SD, standard deviation.

Five serious adverse events occurred (hospitalization for stroke, thoracic pain, angina, pneumonia, and hip fracture), but patients recovered in all cases. A total of 210 nonserious events were reported, the most prevalent being headache, dizziness, and lower back pain. None of the adverse events were related to study procedures.

Adherence to the study protocol had a significant effect on the outcome (*P* values for interaction of 0.02 and 0.021 for SBP and DBP, respectively), there being no effect in those who adhered to the treatment. Further, the effect of bedtime intake of aspirin was not modified in any other subgroup analysed (older people, male participants, users of certain medications, smokers, dippers, individuals with certain comorbidities, or groups by time of enrolment; minimum *P* value for interaction is 0.3).

DISCUSSION

In this study, we have assessed the behaviour of BP as a function of the timing of aspirin intake in 225 patients under usual treatment low-dose aspirin for secondary prevention in a randomized, triple-blind, crossover clinical trial. We have not observed changes in BP, either in the mean 24-h BP, or daytime or night-time BP, when patients took aspirin at bedtime rather than in the morning. Additionally, there has been no change in night-to-day ratio of BP values or dipper/nondipper status of patients, as a function of the timing of aspirin intake.

Considering that any potential antihypertensive effect of low-dose aspirin would be related to its effect on the vascular endothelium [6,10,11], it is logical to suppose that this effect might vary in the presence of different comorbidities. Hence, we explored the effects of this medication separately in patients with diabetes, obesity, and hyperlipidaemia, but found no significant differences between them. It has been postulated that aspirin acts by facilitating the release of NO by the vascular endothelium and inhibiting the night-time peak in angiotensin II, and therefore, we would expect the effect of aspirin to be weaker in patients taking angiotensin inhibitors. Nevertheless, analysing patients on angiotensin-converting enzyme inhibitors, calcium antagonists, betablockers, and diuretics, we found no significant differences between these subgroups.

On the other hand, we observed a decrease in BP in all subgroups, regardless of the timing of aspirin intake, between the first (baseline) and the second ABPM tests, the BP remaining lower at the following ABPM tests, but with no further decreases. We attribute this to the fact that, during the study period, patients were interviewed once a month by a nurse and were closely monitored, with checks of their adherence not only to the study drug but also to other drugs they had been prescribed. Knowing that, generally, half of hypertensive patients do not strictly adhere to their treatment, it could be that the close monitoring improved adherence during the study period [25,26]. Another potential explanation of this decrease in BP is that in the second ABPM test, patients were more familiar with the monitor.

Several studies of the effect of evening intake of aspirin have been published recently, with different conclusions, as reflected in the systematic review of Bem *et al.* [13].

In various nonblinded randomized clinical trials, Hermida *et al.* observed a decrease in BP and patients changing from nondippers to dippers when aspirin was taken at night. In all these trials, patients were healthy or had mild hypotension that was not being treated with other drugs and had not previously been treated with aspirin [4,5,7]. Hence, these conclusions cannot be extrapolated to patients in secondary prevention, which is the very group for which aspirin treatment is generally indicated [27]. In contrast to Hermida *et al.* [4–8], we did not find differences

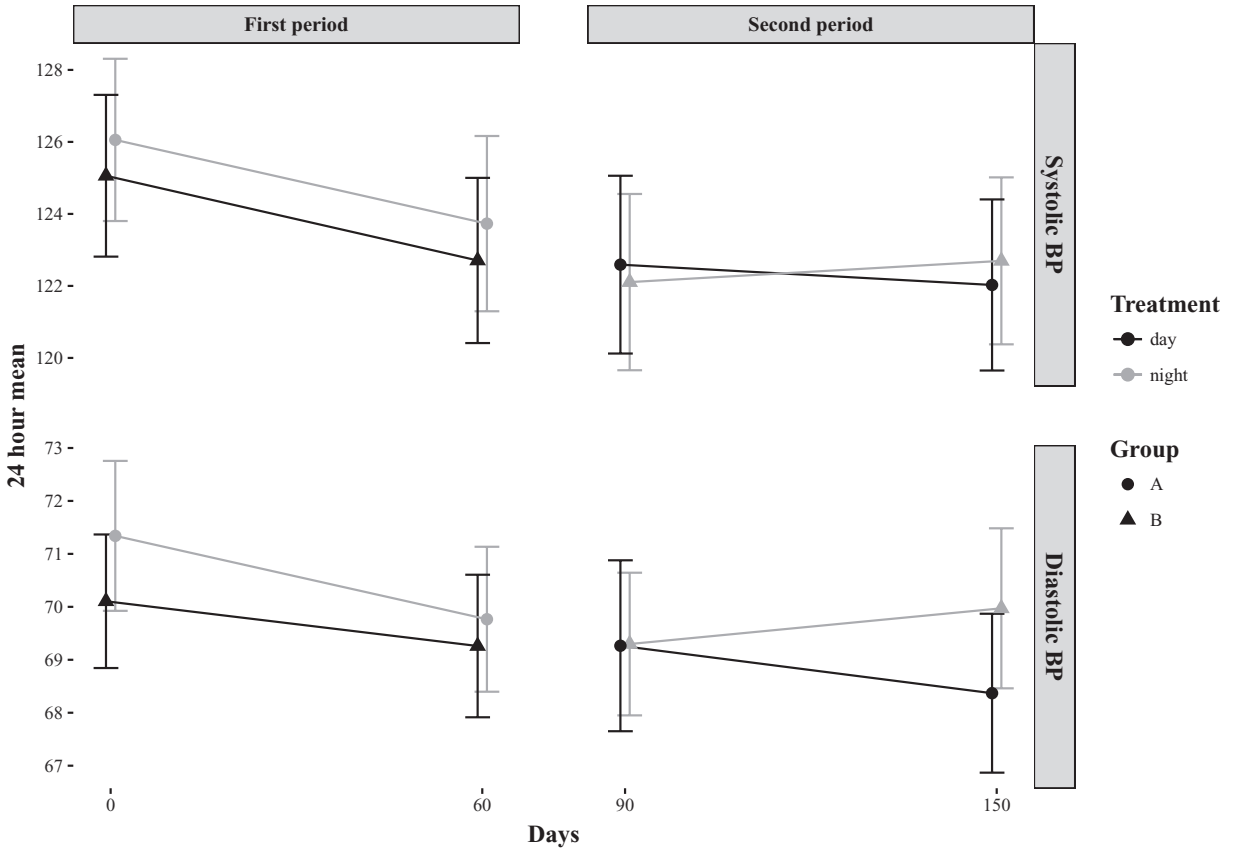

FIGURE 3 24-h blood pressure means. BP, blood pressure.

in BP or in the dipper behavior of patients when they took aspirin at night. This discrepancy may be because of the dissimilarities of the populations included in the studies: as our patients had been previously treated with aspirin and with other antihypertensive drugs, it is reasonable that there were interactions between the mechanisms of action of the different drugs, especially taking into account that antihypertensive mechanism of aspirin 100 mg ingested at night

TABLE 2. Primary and secondary outcomes

Outcome measure	Mean (SD), bedtime administration ($n = 214$)	Mean (SD), daytime administration ($n = 211$)	Baseline adjusted attributable difference[a] (95% CI)	Multivariate adjusted attributable difference[b] (95% CI)
Primary outcomes				
SBP				
24 h	123.2 (11)	122.4 (11)	0.67 (−0.78 to 2.13)	0.6 (−0.87 to 2.06)
Day	125.9 (11.2)	124.5 (11.7)	1.24 (−0.29 to 2.78)	1.14 (−0.42 to 2.71)
Night	115.5 (13.4)	115.4 (13.1)	0.21 (−1.80 to 2.22)	0.27 (−1.76 to 2.3)
DBP				
24 h	69.9 (6.6)	68.8 (6.7)	0.47 (−0.38 to 1.32)	0.35 (−0.5 to 1.18)
Day	72.5 (7.1)	71.2 (7.3)	0.7 (−0.21 to 1.61)	0.6 (−0.32 to 1.51)
Night	63.3 (7.7)	62.8 (7.8)	0.22 (−1.03 to 1.47)	0.13 (−1.11 to 1.39)
Secondary outcomes				
HR				
24 h	65.6 (10.1)	65.5 (9.4)	0.4 (−0.67 to 1.47)	0.19 (−0.82 to 1.19)
Day	68.4 (11.3)	68 (10.3)	0.8 (−0.39 to 1.99)	0.61 (−0.5 to 1.71)
Night	60.4 (9.5)	60.8 (8.9)	−0.2 (−1.53 to 1.13)	−0.3 (−1.57 to 1.05)
PP				
24 h	53.4 (8.9)	53.5 (9.3)	0.27 (−0.79 to 1.32)	0.2 (−0.87 to 1.27)
Day	53.5 (9)	53.3 (9.3)	0.58 (−0.57 to 1.73)	0.48 (−0.67 to 1.64)
Night	52.2 (10.1)	52.7 (10.4)	0.1 (−1.26 to 1.46)	0.18 (−1.19 to 1.55)
Night/day ratio				
SBP	0.92 (0.08)	0.931 (0.09)	−0.009 (−0.024 to 0.006)	−0.008 (−0.023 to 0.007)
DBP	0.877 (0.1)	0.884 (0.1)	−0.006 (−0.023 to 0.01)	−0.006 (−0.023 to 0.011)

HR, heart rate; PP, pulse pressure.
[a]Adjusted by period of measurement, and baseline outcome value.
[b]Adjusted by period, baseline values, age, sex, being smoker, risk factors, comorbidities, and time of study enrolment.

has been postulated to be related to the inhibition of angiotensin secretion. However, we must recognize that we did not find significant differences when we analyzed by subgroups of patients treated with angiotensin inhibitors, calcium channel blockers, beta blockers or diuretics.

In addition to the pharmacological treatment, the patients in our study differed from the previous ones in that they had vascular disease. This entails endothelial affectation, which could modify the response to the aspirin 100 mg.

Other research has focused on patients under treatment with antihypertensive drugs and in secondary prevention, namely, the studies of Suomela and Dimitrov, respectively [14,15]. They did not find changes in BP after evening intake of aspirin. These studies were, however, based on small samples and used nonstandard doses of aspirin (50–250 mg, whereas doses of 75–125 mg are recommended for secondary prevention) [27], and therefore, the results are difficult to generalize.

Bonten *et al.* analysed 290 patients between 18 and 75 years of age on aspirin for secondary prevention. This was a blinded-endpoint but open-label, randomized, crossover trial [16]. The authors concluded that there were no changes in BP after evening intake of aspirin. Notably, in this study, only 16% of eligible patients were included and that only half (52%) of these completed the protocol, and hence, the representativeness is questionable. Additionally, though it was a crossover study, placebo was not used, and patients knew they were participating in a study assessing evening intake of aspirin. Given this, changes in behaviour, habits, and attitudes of patients during the study period cannot be ruled out, and such changes might have had an effect on a parameter as sensitive as BP [17,18].

We have conducted a randomized, triple-blind, crossover clinical trial, and to strengthen the evidence obtained, it was also placebo-controlled. The use of placebo should have avoided potential changes, even involuntary ones, in the behaviour of patients when they took aspirin at bedtime or in the morning, and notably in this case raised no ethical concerns, as patients always received their usual aspirin dose. Additionally, there was an open-label period between the two treatment periods, during which patients took their aspirin in the morning [20,28].

There was no age limit for inclusion in our study, considering that many patients on aspirin for secondary prevention are elderly, and if we restricted the age of patients included, we would not be able to extrapolate our results to a large proportion of the population using this drug for secondary prevention. Further, unlike previous studies, we performed ABPM at baseline.

In our study, 41% of eligible patients agreed to participate and, of these, 85% completed the trial, and for 71%, we had complete ABPM data for both treatment periods. We believe that these relatively high rates of acceptance and completion, despite the tedious nature of the study (involving four ABPM recordings) can be explained by the close relationship of patients with their primary care doctors and nurses. All the follow-up visits and fitting and removal of the ABPM devices were carried out in patients' own health centres by the clinicians usually responsible for their care, closely mimicking daily practice. In previous studies, these tasks were carried out in a research centre, and therefore, involved a clear change in patient routines that might have affected BP values on the day of monitoring.

In conclusion, we can say that in hypertensive patients treated with aspirin as a secondary prevention, the time they take aspirin does not have influence on BP with a methodologically rigorous study, and hence, our findings have implications for routine clinical practice in that patients should not be recommended to change their pattern of aspirin intake for this purpose. Nevertheless, various studies have been published in which, unlike morning aspirin intake, aspirin taken in the evening was observed to decrease the morning peak in platelet aggregation, plasma renin activity and cortisol levels in blood, and 24-h catecholamine levels in urine [9,16]. Hence, although there are no changes in BP values, we are not able to state that evening intake of aspirin does not modify patients' vascular morbidity and mortality; to clarify this issue, further studies are required.

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Legal and ethical considerations: This clinical trial will comply with the following regulations: the 2008 version of the Declaration of Helsinki, the Spanish Royal Decree 223/2004 of 6th February and the recommendations of the Council of Europe (Good Clinical Practices for Clinical Trials and Medicinal Products in the European Community, 17 January 1997). The protocol of the clinical trial has been agreed on by the primary care research committee, approved by the Clinical Research Ethics Committee of Euskadi, which is the reference committee, and authorized by the Spanish Agency for Medicaments and Health Products.

Only the researchers involved in the study will have access to patient codes. In relation to this, we will comply with the Spanish Act 14/2007 of Biomedical Research and Royal Decree 1720/2007 of 21st December that approves the regulations on the Development of the Organic Act 15/1999 of 13th December on Personal Data Protection.

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Conflicts of interest

There are no conflicts of interest.

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