



Concomitant Treatment of Hypertensive Patients with Bisoprolol and Perindopril in Routine Clinical Practice: A Post Hoc Analysis of the CONFIDENCE II, PROTECT I, and PROTECT III Observational Studies

Murielle Abeel · Anil Gupta · Christian Constance

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ABSTRACT

Introduction: The combination of angiotensin-converting enzyme inhibitors and beta-blockers is recommended in a wide range of patients with hypertension, including those with stable coronary artery disease and/or elevated heart rate. This post hoc analysis of three observational studies provides effectiveness and safety data on treatment with perindopril on top of bisoprolol-based therapy, in routine clinical practice.

Methods: Data were analyzed from three open-label, prospective, multicenter, observational studies of Canadian patients with mild-to-moderate hypertension, which shared the same inclusion and exclusion criteria, treatment duration, and primary outcome. This post hoc analysis focused on the subpopulation of patients treated with perindopril on top of bisoprolol-based therapy. All patients were followed for 16 weeks and underwent baseline, week 4, and week 16 visits. Primary outcomes

were mean changes in blood pressure (BP) and proportion of patients achieving BP control (< 140/90 mmHg) in the full analysis set (FAS).

Results: A total of 845 patients (mean age 68.3 ± 11.3 years, mean baseline BP 151.5/86.0 mmHg) were analyzed in the FAS. After 16 weeks, mean SBP/DBP decreased by $-20.4/-9.8$ mmHg with statistically significant reductions observed at all visits in all three studies allowing 78% of patients to achieve the BP treatment goal. No statistically significant changes in heart rate were observed and no serious adverse events reported. The most frequent doses of bisoprolol and perindopril were 5 + 4 mg (34.9%), followed by 5 + 8 mg (16.9%), and 2.5 + 4 mg (12.5%).

Conclusion: The addition of perindopril on top of bisoprolol-based therapy in patients with mild-to-moderate hypertension was associated with significant reductions in BP compared with baseline and with achievement of BP targets in the majority of patients. The results suggest this strategy is safe and effective for use in routine clinical practice.

M. Abeel (✉)
Institut de Recherches Internationales Servier (IRIS),
Paris, France
e-mail: murielle.abeel@servier.com

A. Gupta
Trillium Health Partners, Mississauga, ON, Canada

C. Constance
Department of Medicine, University of Montreal,
Quebec, Canada

Key Summary Points

Why carry out this study?

Although there is considerable rationale for combining angiotensin-converting enzyme inhibitors (ACEI) with beta-blockers (BB), to date the evidence base regarding the effectiveness and safety of a combination of a BB with an ACEI in the treatment of patients with hypertension is small. Perindopril and bisoprolol target different pathways in the pathogenesis and progression of hypertension and both provide 24-h efficacy with once-a-day dosing making them good options for use in combination.

This retrospective post hoc analysis combined data from three large observational studies with the same design to evaluate the effectiveness and safety of treatment with perindopril on top of bisoprolol-based therapy in a large population of patients, in routine clinical practice.

What was learned from the study?

The addition of perindopril to bisoprolol-based therapy was associated with statistically significant reductions in blood pressure compared with baseline after 16 weeks of treatment.

At least three out of four patients with hypertension achieved blood pressure treatment goals at the end of the study and treatment was well tolerated.

Addition of perindopril on top of bisoprolol-based therapy is a safe and effective option for use in routine clinical practice.

INTRODUCTION

The causes of elevated blood pressure (BP) are multifactorial, making it unlikely that a single antihypertensive agent with one mechanism of action will be able to normalize levels [1]. Clinical guidelines for the management of hypertension now strongly underline the importance of optimizing treatment by initiating therapy with combination treatment in most patients, and tailoring treatment to individual patients on the basis of their hypertension profile and level of cardiovascular risk [2, 3]. In addition to achieving greater reductions in BP compared with uptitration of the dose of a single drug [4], the use of combination therapy regimens as first-line treatment offers other advantages including a faster reduction in BP and a greater possibility of achieving target, improved tolerability due to use of lower dosages of individual components, and improved patient adherence [5].

The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guideline recommendations for initial dual treatment combinations include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) with either a calcium channel blocker (CCB) or diuretic [3]. In patients with hypertension and chronic coronary syndromes, angina, or chronic heart failure with reduced ejection fraction, beta-blockers, except if contraindicated, should be included in the therapeutic strategy. They should also form part of the strategy at any stage of treatment when they are specifically indicated, e.g., post-myocardial infarction and for heart rate (HR) control [3]. The combination of beta-blockers with ACE inhibitors plays a major therapeutic and preventive role in the management of coronary artery disease (CAD) and heart failure [6, 7], and many patients receive treatment with both agents in routine clinical practice [8]. Among ACE inhibitors, perindopril is supported by substantial efficacy and safety data from large, randomized outcome studies [9–11]. Among beta-blockers, bisoprolol has shown a significant mortality benefit among patients with heart failure [12].

Table 1 Summary of the studies

Study	CONFIDENCE II [15]	PROTECT I [17]	PROTECT III [16]
Title	Effectiveness of hOme blood pressure monitoring and education material For the control of mIld to moDerate hypertEnsioN with Coversyl in a Canadian real-life routine mEdical practice II	Effectiveness of PeRindOpril in the management of hyperTension: idEntification of patient and physiCian determinants of response to Treatment (PROTECT study)	Effectiveness of a support program designed to sensitize and assist patients with mild to moderate hypertension treated with perindopril to decrease their salt consumption
No. of patients	13,886	15,665	12,697
Study period	2008–2010	2009–2011	2011–2013
Inclusion criteria	Patients with mild to moderate hypertension, previously treated (not with perindopril) or not treated, defined as: $140 \leq \text{SBP} \leq 179 \text{ mmHg}$ and $90 \leq \text{DBP} \leq 109 \text{ mmHg}$ (Patients with diabetes: $130 \leq \text{SBP} \leq 179 \text{ mmHg}$ and $80 \leq \text{DBP} \leq 109 \text{ mmHg}$) If previously treated with ACE inhibitors or ARB and not controlled, switch to perindopril		
Non-inclusion criteria	Diagnosed with unstable CAD History of MI occurring less than 1 month prior to study entry Uncontrolled, treated hypertension: $\text{SBP} > 179 \text{ mmHg}$ and/or $\text{DBP} > 109 \text{ mmHg}$ while on treatment		
Treatment	Perindopril 4 mg for 1 month, up to 8 mg if not controlled BP and safety assessment at inclusion (visit 1), after 1 month (visit 2), and after 4 months (visit 3)		

Evidence for the benefits of the combination of perindopril with a beta-blocker has been provided by the results from EUROPA trial [10, 13] and by a retrospective pooled analysis of patients from three large perindopril outcome trials (EUROPA, ADVANCE, and PROGRESS) [14], but data on the specific combination of perindopril with bisoprolol are scarce.

This post hoc analysis was performed in a subpopulation of patients selected from a large database from three observational studies that examined the efficacy and tolerability of perindopril in patients with hypertension receiving treatment with other antihypertensive agents, including beta-blockers, in a real-world setting. In the present analysis, we focused on the subpopulation of patients

treated with perindopril on top of bisoprolol-based therapy.

METHODS

Study Design

This post hoc analysis was performed using data from three previously published [15–17], open-label, prospective, multicenter, observational studies: CONFIDENCE II, PROTECT I, and PROTECT III, conducted across Canada. All shared the same inclusion and exclusion criteria, treatment duration, and primary outcome (Table 1). This post hoc analysis of the individual and combined studies focused on the

subpopulation of patients treated with perindopril on top of bisoprolol-based therapy.

In these studies, the decision to treat patients with perindopril was independent of study participation and was decided by the treating physicians prior to enrollment. After the physician's decision to prescribe perindopril, a voluntary informed consent form was obtained from the patient to initiate participation into the study.

Compliance with Ethics Guidelines

This was a post hoc analysis of previously conducted studies. The individual studies were conducted according to the Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects. Before the start of the studies, the protocol, informed consent form, and all other appropriate study documents were submitted to an independent central research ethics committee for review and approval. Studies were approved by the Canadian Shield Ethics Review Board.

Patient Population

All three studies shared the same inclusion and exclusion criteria, namely patients with untreated or uncontrolled mild-to-moderate hypertension defined according to the Canadian Hypertension Education Program (CHEP) guidelines in force at the time of inclusion ($140 \leq \text{SBP} \leq 179 \text{ mmHg}$ and/or $90 \leq \text{DBP} \leq 109 \text{ mmHg}$, or $130 \leq \text{SBP} \leq 179 \text{ mmHg}$ and/or $80 \leq \text{DBP} \leq 109 \text{ mmHg}$ in the presence of diabetes mellitus, renal disease, or proteinuria) [18–20], aged at least 18 years of age, without unstable CAD or recent (less than 1 month before participation) myocardial infarction. All patients were followed for 16 weeks and underwent three visits: baseline (visit 1), week 4 (visit 2), and week 16 (visit 3). Patients treated previously with an ACE inhibitor or an ARB and not controlled could be switched to perindopril at the time of study entry according to the judgement of the treating physician. For these patients, the initial dose of perindopril was that considered appropriate by the treating physician and, if BP control was not achieved at 4 weeks, perindopril was uptitrated to 8 mg/day,

for the following 12 weeks. The specific populations of patients over 70 years of age and patients with renal impairment received a dose of 2 mg of perindopril *tert*-butylamine (perindopril *tert*-butylamine 4 mg and 8 mg corresponds to 5 mg and 10 mg of perindopril arginine, respectively). Perindopril either directly replaced all previous ACE inhibitors or ARBs or was added to antihypertensive treatment with CCBs, diuretics, or β -adrenoceptor antagonists (beta-blockers).

All patients included in this analysis received treatment with bisoprolol. The most frequent bisoprolol dose at baseline was 5 mg/day, followed by 2.5 mg and 10 mg.

Outcome Measures

The primary outcomes for these post hoc analyses were mean changes in BP from baseline following treatment with perindopril 4 and 8 mg/day on top of bisoprolol-based therapy as well as the proportion of patients achieving BP control ($< 140/90 \text{ mmHg}$, or $< 140/85 \text{ mmHg}$ in patients with diabetes according to the thresholds recommended in European ESH/ESC guidelines [21]) in the intent-to-treat populations. Adverse events were monitored throughout the studies.

BP was measured at each visit after the patient had been seated for at least 5 min, according to a standardized BP measurement protocol, which was provided to all study sites. The average of two BP measurements, taken 5 min apart, was used to assess BP control.

Safety was assessed by reports of emergent adverse events (EAEs), and emergent serious adverse events (ESAEs) at visits 2 (4 weeks) and 3 (16 weeks).

Statistical Methods

Descriptive statistics, including the mean and standard deviation (SD) for continuous variables, and frequency distributions for categorical variables, were produced for patient demographics and baseline characteristics on the full analysis set (FAS), comprising all patients receiving concomitant perindopril and bisoprolol at baseline who had at least one follow-up BP measurement while on free

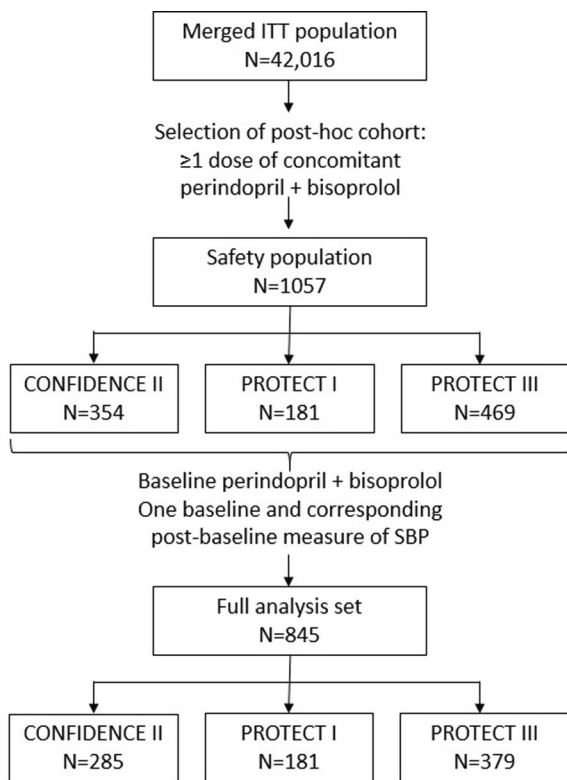


Fig. 1 Patient flow chart

combination treatment. Efficacy analyses were performed on the FAS. Absolute changes in SBP and DBP to visit 3 were conducted applying the last observation carried forward (LOCF) method, with missing SBP or DBP data at visit 3 imputed from visit 2 values. Safety analyses were performed on the safety set, which included all patients receiving concomitant perindopril and bisoprolol at least once during follow-up.

RESULTS

Baseline Characteristics

The merged population included 42,248 patients: 13,886 from the CONFIDENCE II study [15], 15,665 from the PROTECT I study [17], and 12,697 from the PROTECT III study [16]. Among them, 4357 patients received at least one dose of concomitant perindopril and beta-blocker, of whom 1057 patients received

bisoprolol as beta-blocker, 845 (with at least one baseline and one corresponding post-baseline measurement of SBP) were included in the FAS (Fig. 1), and 713 (84.4%) received perindopril and bisoprolol for the 16-week study duration. During the trials, 132 patients (15.6%) withdrew: 121 were lost to follow-up, 9 due to adverse events, and 2 due to other reasons.

The main demographic and baseline characteristics of patients are presented in Table 2. The studied population (mean age 68.3 ± 11.3 years) had a high proportion of patients over 60 years old (79%) and had a mean body mass index of 29.4 ± 5.7 kg/m². Mean baseline BP was 151.5/86.0 mmHg overall versus 155.1/88.0 mmHg, 147.2/83.7 mmHg, and 150.8/85.6 mmHg observed in the CONFIDENCE II, PROTECT I, and PROTECT III studies, respectively.

Treatment Dose

Across all three studies, the most frequent starting dose of perindopril at baseline was 4 mg/day (60.7%), followed by 2 mg/day (17.4%) and 8 mg/day (14.1%), and for bisoprolol it was 5 mg/day (56%), followed by 2.5 mg (19.3%) and 10 mg (18.4%).

When bisoprolol and perindopril were co-administered, the most frequent doses received throughout these studies were 5 mg + 4 mg ($n = 74$; 30.2%), and 5 mg + 8 mg ($n = 58$; 23.7%). Other dosages were 2.5 mg + 4 mg (11.4%), 10 mg + 10 mg (9.4%), 10 mg + 5 mg (8.2%), and 2.5 mg + 2 mg (2%). Other concomitant antihypertensive treatments [CCBs (36.7%) and diuretics (29.8%)] remained unchanged during the study (Table 2).

Effect of Treatment on Blood Pressure Parameters

In the subpopulation of patients receiving perindopril on top of bisoprolol-based therapy (merged data from three studies), a significant SBP decrease from baseline was observed at visit 2 (-14.7 ± 12.3 mmHg, $P < 0.001$); the decrease in DBP of -6.7 ± 8.2 mmHg did not reach statistical significance ($P = 0.059$). The BP change at visit 3 (LOCF) versus baseline ($-19.5 \pm 12.9/-9.2 \pm 8.9$, $P < 0.001$) was

Table 2 Baseline demographic and patient characteristics by study and for the merged full analysis set

	CONFIDENCE II [15] (<i>N</i> = 285)	PROTECT I [17] (<i>N</i> = 181)	PROTECT III [16] (<i>N</i> = 379)	Merged FAS (<i>N</i> = 845)
Men/women, <i>n</i> (%)	139 (49.1)/144 (50.9)	107 (59.4)/73 (40.6)	207 (55.2)/168 (44.8)	453 (54.1)/385 (45.9)
Mean age ± SD (years)	68.0 ± 10.8	65.6 ± 11.0	69.8 ± 11.5	68.3 ± 11.3
Age range (years)	27.5–92.5	38.7–91.6	31.0–95.0	27.5–95.0
Age category (% patients)				
≤ 39 years	1.1	0.6	0.8	0.8
40–59 years	19.3	27.1	17.7	20.2
60–79 years	63.2	61.9	57.8	60.5
> 79 years	16.5	10.5	23.7	18.5
BMI, mean ± SD	29.3 ± 5.6	28.7 ± 4.8	29.9 ± 6.1	29.4 ± 5.7
SBP, mean ± SD	155.1 ± 12.3	147.2 ± 9.9	150.8 ± 8.3	151.5 ± 10.6
DBP, mean ± SD	88.0 ± 9.8	83.7 ± 8.2	85.6 ± 8.7	86.0 ± 9.1
Concomitant antihypertensive treatment, <i>n</i> (%)				
CCB	130 (45.6)	46 (25.4)	134 (35.4)	310 (36.7)
Diuretics	119 (41.8)	67 (37.0)	66 (17.4)	252 (29.8)

similar to the reduction observed at visit 3 (Table 3). Figures 2a, b illustrate the mean change in SBP and DBP for each study and in the merged FAS.

After 16 weeks of treatment, when data from the three study cohorts were combined, over three quarters of patients (78.0%) achieved the target BP. The corresponding proportions with BP control in the individual studies were 60.4% of patients in CONFIDENCE II, 88.0% in PROTECT I, and 86.3% in PROTECT III. The proportion of patients achieving target BP goals by visit are shown in Fig. 3.

Over the course of the studies there were no statistically significant changes in heart rate.

Safety Analysis

In the merged safety population, of the 1057 patients who received concomitant treatment

with perindopril and bisoprolol, 7.1% reported at least one emergent adverse event: mostly cough (3.5%), headache (0.9%), dizziness (0.8%), and hypotension (0.4%) (Table 4). No serious adverse events were reported in any of the patients.

In the individual studies, at least one emergent adverse event was reported in 9%, 9%, and 4.7% of patients in CONFIDENCE II, PROTECT I, and PROTECT III, respectively.

A total of 1.1% of patients discontinued treatment because of an adverse event: six patients in CONFIDENCE II, two in PROTECT I, and one in PROTECT II. Reasons for withdrawals were cough in four patients, hypotension in one patient, constipation in one patient, headache in one patient, and dysphagia in one patient; for one patient in PROTECT I the reason was unknown.

Table 3 Mean absolute changes in SBP and DBP from baseline in the individual studies and in the full analysis set

Mean change \pm SD (mmHg)	CONFIDENCE II [15] (n = 285)	PROTECT I [17] (n = 181)	PROTECT III [16] (n = 379)	FAS (n = 845)	P value*
Systolic blood pressure (mmHg)					
n	282	181	368	831	
Visit 2– baseline	– 13.6 \pm 14.4	– 12.8 \pm 12.7	– 16.4 \pm 10.1	– 14.7 \pm 12.3	< 0.001
n	235	167	299	701	
Visit 3 – baseline	– 18.8 \pm 15.1	– 16.4 \pm 11.8	– 23.9 \pm 10.4	– 20.4 \pm 12.9	< 0.001
N	284	181	379	844	
LOCF – baseline	– 17.8 \pm 14.9	– 16.8 \pm 12.0	– 22.1 \pm 11.1	– 19.5 \pm 12.9	< 0.001
Diastolic blood pressure (mmHg)					
N	282	181	368	831	
Visit 2 – baseline	– 6.8 \pm 9.9	– 5.9 \pm 6.9	– 6.9 \pm 7.3	– 6.7 \pm 8.2	0.059
N	235	167	299	701	
Visit 3 – baseline	– 9.0 \pm 9.9	– 6.7 \pm 7.9	– 12.1 \pm 7.4	– 9.8 \pm 8.7	< 0.001
N	284	181	379	844	
LOCF – baseline	– 8.7 \pm 10.1	– 7.0 \pm 8.0	– 10.6 \pm 8.2	– 9.2 \pm 8.9	< 0.001

FAS full analysis set, LOCF last observation carried forward. Visit 2, 4 weeks. Visit 3, 16 weeks

*P value for FAS compared with baseline

DISCUSSION

This retrospective post hoc analysis in a merged patient population from three large observational studies showed that the addition of perindopril to background bisoprolol therapy was associated with statistically significant reductions in BP compared with baseline. The SBP/DBP decrease from baseline after 4 weeks of treatment was $-14.7 \pm 12.3/-6.7 \pm 8.2$ mmHg ($P < 0.001$), with an additional decrease after 16 weeks of treatment ($-20.4 \pm 12.9/-9.8 \pm 8.7$ mmHg, $P < 0.001$). Over three quarters (78%) of patients in the FAS achieved BP treatment goals at study end.

As expected, analysis of heart rate over the course of the studies revealed no statistically significant changes compared with baseline, as all patients were already receiving bisoprolol at study entry and perindopril has no effect on heart rate. The addition of perindopril to bisoprolol was well tolerated, demonstrating a

safety profile similar to that of perindopril and bisoprolol administered as single agents. No unexpected adverse events were observed and there were no serious adverse events.

Beta-blockers and ACE inhibitors represent major therapeutic classes in the management of hypertension, stable CAD, and chronic heart failure, and their position in the therapeutic strategy for these conditions is clearly defined in the respective clinical practice guidelines [3, 21, 22]. In the ESC/ESH guidelines for the management of arterial hypertension, combination treatment is recommended as initial therapy for most patients with hypertension [3]. First-line treatment should comprise a RAS blocker (either an ACE inhibitor or ARB) with a CCB or diuretic, with the option to add a beta-blocker to any of the other major drug classes when there are specific clinical situations, e.g., angina, post-myocardial infarction, heart failure, or heart rate control. In the ESC guidelines on the management of stable CAD [21, 23],

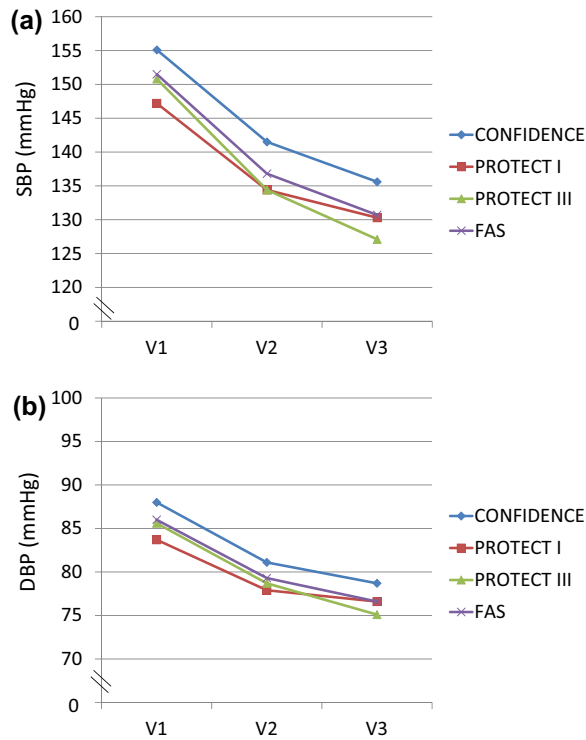


Fig. 2 **a** Mean SBP and **b** DBP reductions from baseline to visit 3 (16 weeks) in patients receiving concomitant bisoprolol and perindopril

beta-blockers are indicated as first-line treatment to control heart rate and symptoms, whereas ACE inhibitors are recommended to prevent cardiovascular events, especially in the presence of other conditions (e.g., heart failure, hypertension, or diabetes). Finally, the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure state that ACE inhibitors and beta-blockers are treatments recommended in potentially all patients with systolic heart failure [22]. According to the guideline recommendations, the spectrum of patients for whom a beta-blocker combination may be appropriate is therefore quite large.

The benefits of adding perindopril to beta-blocker therapy were first demonstrated in the EUROPA trial, which randomized 12,218 patients with coronary heart disease to perindopril or placebo for a mean follow-up duration of 4.2 years [10]. Perindopril treatment was associated with a significant 20% relative risk reduction (95% CI 9–29, $P = 0.0003$) in the primary endpoint (cardiovascular mortality, non-fatal myocardial infarction, and resuscitated cardiac arrest). The beneficial effect of perindopril on the primary endpoint was also

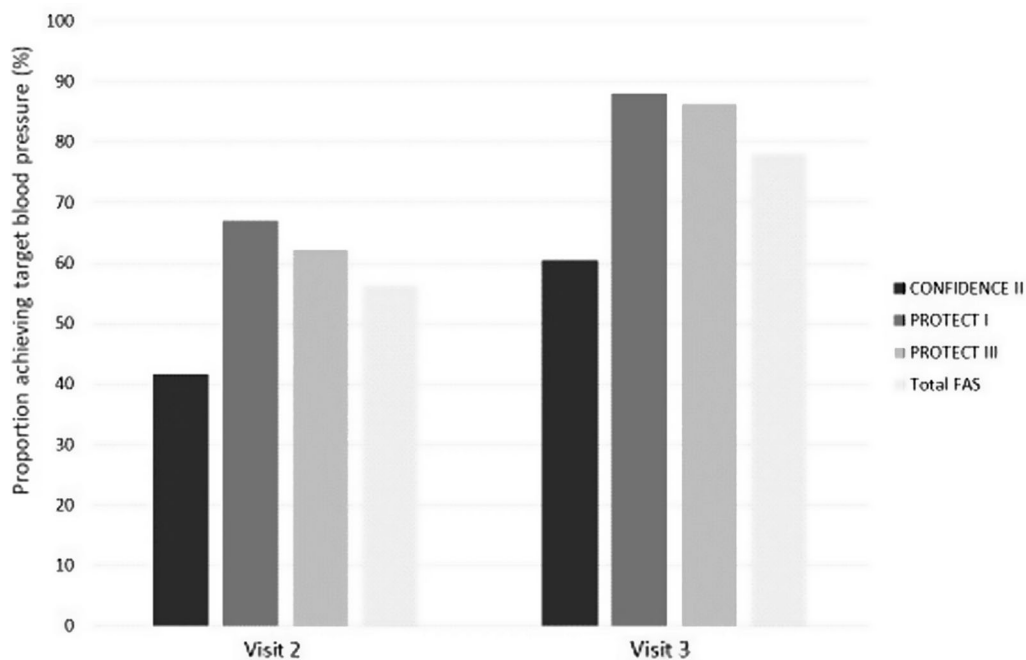


Fig. 3 Proportion of patients achieving target blood pressure (< 140/90 mmHg for patients without diabetes, or < 140/85 mmHg for patients with diabetes) at visit 2 (4 weeks) and visit 3 (16 weeks)

Table 4 Emergent adverse events (EAEs) by study and for merged safety population

	CONFIDENCE II [15] (<i>N</i> = 354)	PROTECT I [17] (<i>N</i> = 234)	PROTECT III [16] (<i>N</i> = 469)	Merged safety (<i>N</i> = 1057)
Total no. of EAEs reported	48	24	29	101
No. patients reporting ≥ 1 EAE, <i>n</i> (%)	32 (9.0)	21 (9.0)	22 (4.7)	75 (7.1)
No. patients reporting most common EAE, <i>n</i> (%)				
Cough	22 (6.2)	8 (3.4)	7 (1.5)	37 (3.5)
Headache	3 (0.8)	4 (1.7)	2 (0.4)	9 (0.9)
Dizziness	2 (0.6)	2 (0.9)	4 (0.9)	8 (0.8)
Hypotension	2 (0.6)	–	2 (0.4)	4 (0.4)
Hyperhidrosis	–	2 (0.9)	–	2 (0.2)
Palpitations	–	–	2 (0.4)	2 (0.2)

significant in the pre-defined subgroup of patients with beta-blocker therapy at baseline (62% of the trial population), relative risk reduction 26.4% (95% CI 14.3–36.8, $P < 0.001$).

A further subanalysis of EUROPA, conducted in patients receiving both perindopril and beta-blockers at randomization and at the time of the event, confirmed a significant reduction in the relative risk for the primary endpoint (-24% , $P = 0.002$) and secondary endpoints, including myocardial infarction (-28% , $P = 0.001$) and hospitalization for heart failure (-45% , $P = 0.025$), for patients on beta-blocker/perindopril treatment compared with beta-blocker/placebo [13].

Other large-scale trials have also provided evidence on cardiovascular outcomes following the addition of perindopril to background beta-blocker therapy. These have been conducted among patients with previous stroke or ischemic attack (PROGRESS, 17% receiving beta-blocker [9]) and type 2 diabetes (ADVANCE, 25% receiving beta-blocker [11]). A subsequent retrospective pooled analysis of PROGRESS, EUROPA, and ADVANCE reported a decreased risk of the primary composite endpoint of cardiovascular mortality, non-fatal MI, and stroke (-20% , 95% CI 0.71–0.90), as well as

the secondary endpoints of non-fatal MI (-23% , 95% CI 0.65–0.91) and all-cause mortality (-22% , 95% CI 0.68–0.88) for patients on perindopril and background beta-blocker therapy compared with beta-blocker/placebo [14].

Within the beta-blocker class, individual agents have a number of pharmacological differences, such as beta-adrenergic selectivity, lipid solubility, and dual receptor activity, which make each agent unique. Among the cardioselective beta-blockers, bisoprolol has the greatest affinity for the cardiac β_1 -adrenoceptor and is less likely to cause constriction of airways or peripheral vasculature [24]. Bisoprolol is also highly absorbed after oral administration, has a half-life in plasma of 10–12 h that gives a 24-h effect dosing once daily, and is eliminated by both hepatic and renal routes [25]. The last of these means that it does not require dose adjustments for patients with either renal or liver dysfunction, and is also less likely to interact with other medicines. Among the beta-blockers, bisoprolol was the first to demonstrate improved survival in a cardiovascular outcome trial, with a 34% relative risk reduction in all-cause mortality in patients with heart failure with reduced ejection fraction and NYHA class III–IV symptoms when added to standard

therapy including ACE inhibitors and diuretics [12].

Compared with other ACE inhibitors, perindopril has higher lipophilicity, stronger tissue ACE-inhibiting properties, and the highest selectivity for bradykinin versus angiotensin I binding sites, leading to enhancement of nitric oxide and inhibition of endothelial cell apoptosis [26, 27]. Perindopril has a 24-h duration of action and trough effects are about 87–100% of peak effects [28].

There is therefore considerable rationale for combining perindopril with beta-blockers, and in particular, bisoprolol. However, to date, the evidence base regarding the effectiveness and safety of a combination of a BB with ACEI in the treatment of patients with hypertension based on clinical trials is very small. A search of the literature for data on perindopril/bisoprolol combinations identified a few relevant studies. An exploratory study in patients with hypertension, which examined BP lowering and inflammatory markers after 4 weeks of treatment with perindopril, bisoprolol, or a perindopril/bisoprolol combination, found that perindopril reduced mean 24-h SBP/DBP by $-15.9/-8$ mmHg, while the bisoprolol and perindopril combination caused a more pronounced decrease of $-24.9/-16.2$ mmHg [29]. A small-scale study, which compared an ACE inhibitor/atenolol with an ACE inhibitor/bisoprolol combination, reported greater BP lowering and achievement of target with the bisoprolol combination [30].

As combination therapy is now recommended in most patients, it is important to evaluate the effectiveness and safety of combination treatments in a wide spectrum of patients with different disease severity and duration that will be encountered in clinical practice.

In a Canadian observational study in patients with hypertension and additional cardiovascular risk factors [31], the addition of perindopril to the subgroup of patients who were on beta-blocker therapy at baseline resulted in a reduction in mean SBP/DBP of $-22.1/-9.7$ mmHg after 10 weeks of treatment. Furthermore, a large retrospective database analysis found that among patients

uncontrolled on beta-blocker therapy, the addition of an ACE inhibitor resulted in an additional reduction in SBP of -16 mmHg and in DBP of -4.9 mmHg [32].

Our post hoc analysis provides data on a population of 845 patients receiving perindopril on top of background bisoprolol therapy, showing a SBP/DBP decrease of $-20.4 \pm 12.9/-9.8 \pm 8.7$ mmHg, $P < 0.001$ after 16 weeks of treatment. The most important BP decrease was observed in PROTECT III, and it is worth noting that in this study patients followed a support program to decrease their salt consumption, which is known to have an impact on BP decrease, and which is a lifestyle modification recommended by guidelines.

Effective and well-established treatments are available for the management of hypertension and hypertension-mediated organ disease, so efforts are now increasingly focused on improving treatment implementation and tailoring treatment to patient needs. The availability of two-drug single-pill combinations (SPC) is currently mainly limited to a RAS blocker with either a CCB or diuretic, and the ESC/ESH guidelines emphasize that it would be desirable to see the development of an expanded range of SPCs in different drug formulations, tailored to different clinical requirements.

The first SPC of bisoprolol and perindopril became available in 2016 in the form of bisoprolol/perindopril (Cosyrel[®]), which facilitates meeting guideline recommendations to use a single-pill-based treatment strategy whenever possible [3].

Real-world data on the benefits of using a bisoprolol/perindopril SPC in patients with hypertension and stable CAD (previously treated with bisoprolol with or without concomitant perindopril) were obtained from two recent open-label, prospective, observational studies [33, 34]. Patients were treated with SPC for 1 month ($n = 2394$) and 3 months ($n = 1892$), respectively. The results of both studies support the addition of a bisoprolol/perindopril SPC to standard antihypertensive therapy to simultaneously reduce BP and heart rate in patients with hypertension and stable CAD, and to allow more patients to achieve BP treatment goals. The beneficial effects of the SPC on these risk

factors were accompanied by improvements in angina symptoms and quality of life. Furthermore, the treatment was well tolerated in a broad patient population representative of those seen in everyday clinical practice. In the present analysis, we also observed a high prevalence of patients with CAD (61%), suggesting that the finding might be relevant to this patient population. Unfortunately, we did not collect data on other comorbidities that would allow us to conclude on the benefits of this combination in specific patient profiles.

Recent European hypertension guidelines included resting HR > 80 bpm among CV risk factors [3], and BB are the main drug class acting on HR. This combination has indeed a strong rationale in patients with chronic marked sympathetic nervous system overactivity and RAAS overstimulation, especially those with elevated HR.

The results of this post hoc analysis are limited by the observational nature of the individual studies included; more specifically, the lack of a comparator arm and randomization. In addition, patients were on a range of antihypertensive medications at baseline including CCBs and diuretics, which could be continued for the duration of the trial. Similar to the retrospective pooled analysis of the ADVANCE, EUROPA, and PROGRESS pivotal clinical trials [14], the current analysis was strengthened by only including studies with similar designs. A major limitation of the current post hoc analysis was related to the cutoff used for the achievement of target BP in patients with diabetes. This was updated to reflect the 2013 ESC/ESH recommendation current at the time of the analysis (140/85 mmHg) [21], but as the 2012 CHEP guideline thresholds were implemented in the individual studies, this led to protocol-defined uncontrolled hypertension in patients with diabetes being established at BPs \geq 130/80 mmHg. As a result, 234 patients with diabetes were considered to have controlled hypertension at baseline (visit 1) due to the post hoc adoption of the 2013 ESC/ESH targets. Although included in the individual and merged safety and FAS populations, these patients were excluded from the target BP

analyses in order to provide a more accurate representation of BP control.

CONCLUSIONS

The results of this retrospective post hoc analysis of three large observational studies show that addition of perindopril on top of bisoprolol-based therapy is commonly prescribed in routine clinical practice for patients with mild-to-moderate hypertension. Treatment effectiveness was confirmed by significant reductions in BP compared with baseline and achievement of BP targets by 78% of patients. The addition of perindopril to background bisoprolol was well tolerated, making it a safe and effective therapy option for patients in routine clinical practice.

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Compliance with Ethics Guidelines. This was a post hoc analysis of previously conducted studies. The individual studies were conducted according to the Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects. After the physician's decision to prescribe perindopril, a voluntary informed consent form was obtained from the patient to initiate participation into the study. Before the start of the studies, the protocol, informed consent form, and all other appropriate study documents were submitted to an independent central research ethics committee for review and approval. Studies were approved by the Canadian Shield Ethics Review Board. After the physician's decision to prescribe perindopril, a voluntary informed consent form was obtained from the patient to initiate participation into the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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