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Perindopril
In Congestive Heart Failure

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Contents

Abstract

▲ Perindopril is a long-acting ACE inhibitor, acting through its only active metabolite perindoprilat. It inhibits the renin-angiotensin system by preventing both the conversion of angiotensin I to angiotensin II and the degradation of bradykinin, thereby reducing the vasoconstriction and left ventricular remodelling characteristic of heart failure.

▲ Perindopril 4mg significantly improved a range of haemodynamic parameters in single-dose and long-term (8 weeks and 3 months) studies involving patients with congestive heart failure (CHF), with little or no effect on blood pressure or heart rate.

▲ In randomised, double-blind, placebo-controlled clinical trials conducted over 3 months and a large noncomparative study (up to 30 months), perindopril 4mg once daily significantly increased exercise tolerance and reduced symptoms of heart failure in patients with mild to moderate CHF.

▲ Perindopril 4mg once daily is generally well tolerated in patients with mild to moderate CHF. In a large noncomparative study the most commonly reported adverse clinical event was cough, which led to 2.8% of patients discontinuing treatment.

▲ In short-term comparative trials there was a significantly lower incidence of first-dose hypotension following the recommended starting dose of perindopril 2mg than after the equivalent starting doses of captopril, enalapril and lisinopril.

Features and properties of perindopril	
Indications	
Congestive heart failure; focus of this profile	
Hypertension	
Mechanism of action	
ACE inhibitor	Vasodilation, and improved myocardial function and haemodynamics
Dosage and administration	
Usual dose in clinical trials	Starting dose 2mg, titrated to 4mg
Route	Oral
Frequency of administration	Once daily in the morning
Pharmacokinetic profile of perindoprilat (after single-dose perindopril 4mg in patients with CHF)	
Peak plasma concentration	5 μg/L
Time to peak plasma concentration	8.2h
Area under the curve	126 μg • h/L
Terminal elimination half-life	42h
Adverse events	
Most frequent	Cough

Perindopril is a well established ACE inhibitor, widely evaluated and extensively used in the treatment of hypertension.[1-3] It has also been evaluated at a lower dosage as treatment for congestive heart failure (CHF), which is the focus of this profile. Perindopril is approved for the treatment of CHF in numerous countries worldwide (not in the US).

CHF is a major cardiovascular disease associated with left ventricular dysfunction of multiple aetiologies, but predominantly due to ischaemic heart disease.[4] Patients present with symptoms of fatigue, dyspnoea and fluid retention as a result of deteriorating cardiac structure and function.[5,6] CHF is a leading cause of morbidity and mortality, estimated to affect up to 2% of the population in most Western countries, including Europe.[7,8] Of patients diagnosed with CHF, 50% die within 4 years, and of those with severe CHF, 50% die within 1 year.[9] The prevalence of CHF rises with age, with up to 10% of the population over 70 years of age affected.[10] CHF is therefore a major public health problem for developed countries with an aging population.

ACE inhibitors have shown a number of beneficial class effects in patients with CHF,[9-11] such as improved survival and symptoms and reduced hospitalisation.[9] ACE inhibitor therapy is associated with blockade of the renin-angiotensin system, leading to reduced levels of circulating neurohormones and consequently vasodilation, and improved myocardial function and haemodynamics.[5] ACE inhibitors are recommended as first-line treatment for patients with CHF in the absence of fluid retention, and are used together with diuretics in patients with fluid retention.[5,9,12]

1. Pharmacodynamic Properties

The pharmacodynamic properties of perindopril and perindoprilat, its active metabolite, are well established and have previously been reviewed in detail.[1,2] This section provides a brief overview of only those properties relevant to CHF.

Effects on the Renin-Angiotensin-Aldosterone System

Most of the symptomatic and cardioprotective effects of perindopril can be attributed to its blockade of the renin-angiotensin II system.[1] The compensatory response of this system to the failing heart is initially beneficial and appropriate but in time leads to worsening of the condition.[13,14]

• In patients with CHF [New York Heart Association (NYHA) class II to IV], perindopril 4mg once daily significantly reduced plasma ACE activity[15-17] and plasma angiotensin II levels,[17] and produced a transient increase in plasma renin activity[15,16] which returned to pretreatment levels during 3 months' treatment.[16] One study was randomised, compared perindopril with placebo, and involved 24 patients for 8 weeks.[17] The other two were noncomparative studies, one recording the effect of a single dose of perindopril 4mg ($n = 10$),[15] the other investigating both the short-term (days 1 and 2) and longer term (3 months) effects of perindopril treatment ($n = 15$).[16] The decreases in plasma aldosterone levels observed in the above studies were not significant.[15-17]

• Prolonged plasma ACE inhibition was shown in ten patients with severe CHF receiving a single dose of perindopril 4mg.[15] Maximum inhibition (72%) was exhibited at 12 hours ($p < 0.01$ *vs* baseline), 56.3% at 24 hours ($p < 0.01$), with some activity (31.5% inhibition) still evident at 48 hours ($p < 0.05$). The slow dissociation of the perindoprilat-ACE complex facilitates administration of a single daily dose of perindopril.[1]

• Reduced plasma and vascular ACE activity (to 70 and 65%, respectively, of control levels) in both the endothelium and adventitia, increased AT_1 receptor expression (by 80% from baseline) and increased nitric oxide synthetase expression (as assessed by quantitative autoradiography and immunocytochemistry) were observed in seven patients with ischaemic heart disease treated with perindopril 4mg once daily for up to 5 weeks (mean 18 days) before coronary artery bypass surgery.[18]

Effects on Bradykinin

Bradykinin, possibly through its association with the release of vasodilators (nitrous oxide and prostaglandins) from the vascular endothelium,[19,20] is thought to have beneficial effects on vascular tone and the left ventricular remodelling characteristic of heart failure.[21-23] Bradykinin may also be responsible for some of the adverse events, like cough, associated with long-term treatment with ACE inhibitors.[24]

• A significant increase (up to 4 to 10 times basal level; $p < 0.05$) in the level of the nonapeptide bradykinin 1-9 accompanied the acute haemodynamic changes observed in canine CHF models treated with perindoprilat (the active metabolite of perindopril) 0.03, 0.3 or 1 mg/kg.[25]

Haemodynamic Effects

Cardiac Function

• In short-term[15,16] and long-term studies[16] in patients with CHF (NYHA class III or IV), perindopril increased cardiac index (CI) and decreased pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), mean arterial pressure (MAP) and right atrial pressure (RAP), effectively decreasing the preload and afterload and improving the performance of the failing heart. Haemodynamic parameters were significantly improved during the first 2 days and after 3 months' treatment with perindopril 4mg once daily (first dose 2mg) in a study involving 15 patients with severe CHF (NYHA class III or IV), 11 of whom required concomitant maintenance treatment.[16] For the 11 patients who completed 3 months' treatment with perindopril 4mg once daily,[16] CI at peak effect increased from baseline by 44% to 2.67 L/min/m^2 ($p < 0.01$). MAP was decreased by 18% from baseline to 84.5mm Hg ($p < 0.01$), PCWP by 45% ($p < 0.05$) to 10.8mm Hg, and SVR by 36% ($p < 0.01$ *vs* baseline) to 1627 dyn • sec/cm^{-5}. Haemodynamic changes following single- and multiple-dose perindopril administration were correlated to[13] serum ACE activity and plasma concentration of perindoprilat.[16]

• Following a single dose of perindopril 2mg (the recommended starting dose for CHF), there was no significant change in heart rate in two double-blind, placebo-controlled trials in patients with CHF, monitored over 5[26] and 24 hours.[27] In addition, in a large nonblind study in 725 patients[28] the maximum and minimum heart rate in the perindopril group (2mg once daily) did not differ significantly from that in the captopril recipients (6.25mg three times daily) during the monitoring period. Heart rate at 36 hours, however, was slightly less in patients receiving perindopril than in the captopril group (75.2 *vs* 77.5 beats/min; $p = 0.039$).

• Consistent with most short-term studies,[26,27] no significant change in heart rate was seen following treatment with perindopril 4mg once daily in two long-term (3 months[29] and 8 weeks[17]) placebo-controlled trials involving 125[29] and 24[17] patients with CHF and in a noncomparative 3-month study in 15 patients.[16] However, in a multicentre, noncomparative study of perindopril in patients with mainly NYHA class II or III CHF,[30] heart rate at 6 and 12 months showed a slight reduction from baseline [3 beats/min, $p < 0.01$ ($n = 192$) and 5 beats/min, $p < 0.001$ ($n = 100$)].

Blood Pressure

In patients with CHF without hypertension, short-term studies of perindopril 2mg,[26,27,31] the recommended starting dose for CHF, and long-term studies of perindopril 4mg[17,32] (maintenance dose), showed little or no change in blood pressure.

• Compared with placebo there was no significant change in blood pressure after 8 weeks' and 3 months' treatment[17,32] with perindopril 4mg once daily in patients with CHF. Baseline systolic blood pressures were 137 to 145mm Hg[17] and 130 to 136mm Hg.[32]

• Mean SBP and DBP decreased slightly (from baseline 137/83mm Hg) over the study period in a noncomparative trial[30] investigating perindopril 4mg once daily for CHF. Blood pressure at 6 months ($n = 208$), 12 months ($n = 102$) and 30 months ($n = 30$) was 132/80mm Hg, ($p < 0.01$),

130/80mm Hg, ($p < 0.001$) and 131/77mm Hg, ($p < 0.05$), respectively.

First-Dose Hypotension

• In large (n = 240 and 298)[33,34] and small (n <100)[26,27,31,35,36] clinical trials, patients with CHF experienced a significantly smaller reduction in blood pressure after the recommended starting dose of perindopril 2mg than after the equivalent starting dose of captopril 6.25mg[26,27,33,35,36] or enalapril 2.5mg.[26,27,31,34,36]

• In three randomised, double-blind, placebo-controlled trials, two involving 48[27,31] and one including 80 patients[26] with CHF, blood pressure was monitored for 5 to 48 hours following one[26,27] or two doses[31] of perindopril 2mg or the equivalent number of doses of the comparators captopril 6.25mg, enalapril 2.5mg, lisinopril 2.5mg or placebo. Blood pressure in the perindopril group did not decrease significantly from baseline at any time during the studies. The blood pressure profile after perindopril was similar to that with placebo, whereas captopril, enalapril and lisinopril produced mean maximum blood pressure falls significantly greater than those with placebo.[26,27,31,36] The time to maximum MAP reduction following the first dose of perindopril ranged from 1.5 to 8 hours,[26,27,31,36] compared with 1.5 to 4 hours with captopril[26,27,36] and 4 to 10 hours with enalapril.[26,27,31,36]

• The blood pressure response to perindopril 2mg once daily and captopril 6.25mg three times daily was monitored for 36 hours in a large nonblind, randomised study involving 725 patients hospitalised for an episode of heart failure or an acute coronary event.[28] The drop in blood pressure 4 hours after the first dose was significantly greater in the captopril group than in the perindopril group ($p < 0.0001$) resulting in a higher rate of withdrawal from the study among patients receiving captopril (see section 4). At 36 hours, there was no significant difference in reductions from baseline between the two groups. Despite randomisation, baseline characteristics revealed a significantly greater number of patients with left ventricular failure in the captopril group than in the perindopril group (198 *vs* 165; $p < 0.045$).

• First-dose hypotension (FDH), defined as a >20mm Hg drop in MAP, was observed in significantly ($p < 0.001$) fewer individuals receiving perindopril 2mg than in those receiving enalapril 2.5mg[34] or captopril 6.25mg (see figure 1). Compared with patients receiving perindopril, captopril recipients also experienced lower MAP minimum levels (78.0 *vs* 84.5mm Hg, $p < 0.0001$) and greater maximum falls in blood pressure (17.6 *vs* 12.8mm Hg, $p < 0.0001$).[33]

Regional Blood Flows

• In ten patients with severe heart failure (NYHA class III and IV), a single dose of perindopril 4mg significantly increased below-normal brachial and renal blood flows, whereas subnormal hepatic blood flow was unchanged.[15] In the forearm, brachial blood flow (measured by the pulsed Doppler technique) was increased by 130 and 100% at 6 and

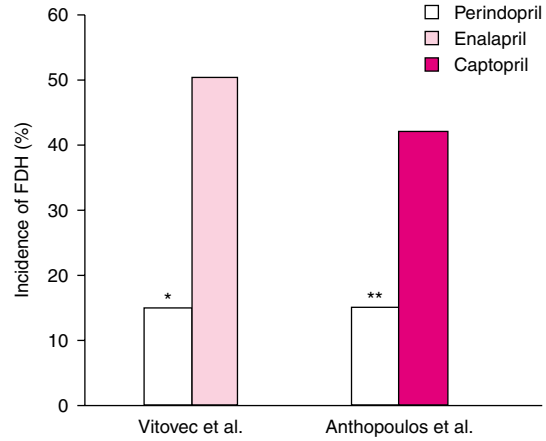

Fig. 1. Incidence of first-dose hypotension (FDH) in patients receiving perindopril, enalapril or captopril. Patients with New York Heart Association class II to IV congestive heart failure received a single dose of perindopril 2mg (n = 147) or enalapril 2.5mg (n = 151),[34] or perindopril 2mg (n = 116) or captopril 6.25mg (n = 124)[33] in two randomised studies where blood pressure was monitored for 10[34] and 8 hours.[33] FDH is defined as a mean arterial pressure fall >20mm Hg. * $p < 0.001$ versus enalapril; ** $p < 0.0001$ versus captopril.

24 hours (both $p < 0.01$ *vs* baseline). Compared with baseline, the renal blood flow increased by 34% ($p < 0.05$) and 24% at 6 and 24 hours, respectively.

Endothelial Dysfunction

In animal studies, CHF (from left coronary artery ligation) induces endothelial dysfunction in peripheral vessels, manifested by reduced vasodilator responses of isolated segments of rat mesenteric and femoral vessels.[37-39] This dysfunction, together with the activation of the renin-angiotensin system, may contribute to the increased vascular tone characteristic of CHF.[20,23]

- Perindopril administered in rat models of CHF for 1 month[39] and 12 months[38] improved the attenuated acetylcholine-induced vasodilator response of isolated mesenteric arterial segments.

- In 15 patients with mild to moderate CHF treated with perindopril 4mg once daily for 3 months, reversal of impaired endothelial-dependent vasodilation of peripheral vessels was observed.[40] Radial artery diameter measured with an ultrasonic echo-tracking device, and forearm blood flow determined using the Doppler technique, were increased.

- A study of 13 patients with mild to moderate CHF[22] treated for 3 months with perindopril 4mg (dose stated in review article[23]) showed that only those patients who improved clinically (8 from 13) had improved markers for peripheral vessel endothelial function (acetylcholine-induced increased forearm blood flow and soluble adhesion molecule levels). This suggests that milder forms of CHF might not exhibit the same degree of peripheral vessel endothelial dysfunction as more severe forms of the disease.

Other Effects

- Renal function, as determined by changes in plasma creatinine, was unaffected by perindopril administration. Mean plasma creatinine levels in patients with CHF treated with perindopril 4mg once daily were not significantly changed compared with those in placebo recipients in two studies (8 weeks, n = 24[17] and 3 months, n = 125 [29]) and compared with baseline in a long-term study (up to 30 months, n = 320).[30] Among 19 patients with raised plasma creatinine levels at baseline, 18 experienced either no change or a return to normal plasma creatinine levels during one study.[30] Changes in individual plasma creatinine levels are discussed in section 4.

- Mean plasma potassium levels remained within the normal range despite a slight increase (3.8 to 4.2 mmol/L, $p < 0.001$ *vs* placebo) occurring when patients with CHF were treated with perindopril 4mg daily for 8 weeks.[17] In a long-term study (n = 320)[30] involving a similar population, the slight increase from baseline in plasma potassium levels observed at 6 months (from 4.15 to 4.27 mmol/L, $p < 0.01$, n = 208) and 12 months (4.10 to 4.24 mmol/L, $p < 0.01$, n = 100) was not sustained and the change at 30 months (n = 27) was not significant (see section 4); potassium levels remained within normal limits.

- In animal models of CHF, perindopril reduced cardiac hypertrophy after 4 weeks[39] and 12 months,[38] evidenced by reduced heart weights and a decreased cardiac weight/bodyweight ratio.

- Perindopril 4mg daily improved respiratory muscle function in 12 patients with CHF in a 6-month study[41] that monitored a range of parameters including maximum inspiratory and expiratory pressures (PI_{max} and PE_{max}). The increases from baseline for the predicted normal values of PI_{max} and PE_{max} were 57 to 78% and 62 to 73%, respectively, ($p < 0.05$).

2. Pharmacokinetic Properties

The pharmacokinetic properties of perindopril are well established and have been reviewed previously.[1] This section focuses on data from patients with CHF and includes data for other population groups where necessary.

The pharmacokinetics of perindopril and its active metabolite perindoprilat have been studied in patients with severe CHF (NYHA class III or IV) following a single oral dose of 4mg (n = 10) in two

studies,[42,43] and after short-term (2 days) and long-term treatment (4mg daily for 3 months) in another study in 15 patients.[16] All values presented here are means.

• Perindopril was rapidly absorbed after a single dose of 4mg, reaching a peak plasma concentration (C_{max}) of 113 μg/L at 1.9 hours (t_{max}) with the area under the curve for 0 to 72 hours (AUC_{72h}) measuring 544 μg • h/L.[42] In patients who received perindopril 4 mg/day starting on day 2 (after an initial dose of 2mg on day 1), there was no significant difference between results on day 2 and those at 3 months (C_{max} 104.5 *vs* 83.6 μg/L; t_{max} both 1 hour; AUC_{24h} 474.0 *vs* 338.4 μg • h/L).[16]

• In the single-dose studies of the metabolite, perindoprilat C_{max} was 16 μg/L[42] and 5.0 μg/L,[43] t_{max} was 2.9 hours[42] and 8.2 hours,[43] AUC_{72h} was 109 μg • h/L in one study[42] and in the other study AUC (time period not stated) was 126 μg • h/L.[43] Values for perindoprilat on day 2 showed no significant differences from those at 3 months (C_{max} 7.4 *vs* 9.6 μg/L; t_{max} both 6 hours; AUC_{24h} 104.6 *vs* 138.7 μg • h/L).[16]

• Animal studies have shown that perindopril is rapidly and widely distributed, mainly to tissues with high ACE activity, without any accumulation in the kidneys, lungs or liver.[1] The mean apparent volume of distribution for perindopril and perindoprilat was 0.22 and 0.16 L/kg, respectively, after an oral dose in healthy volunteers.[1,2]

• Only 17 to 19% of perindopril is metabolised to perindoprilat, the remainder being biotransformed to inactive compounds.[1] In healthy volunteers, perindopril is eliminated principally in the urine, with 75% of a radiolabelled dose recovered over 96 hours, the remaining 25% appearing in the faeces.[1] The mean residual time for perindopril after a single 4mg dose in patients with CHF was 6.9 hours, and for perindoprilat was 6.1 hours.[42] The terminal elimination half-life for perindopril was 4.6 hours[42] and for perindoprilat was 42 hours.[43]

• In 16 patients with renal failure compared with 10 healthy volunteers, the absorption of perindoprilat but not perindopril was greatly increased and perindoprilat ACE inhibition was prolonged.[43] The elimination and renal clearance of perindoprilat were substantially reduced, with the trough perindoprilat concentration increasing 4- to 24-fold with increasing severity of renal impairment.[43] Perindoprilat administered to elderly patients showed greater bioavailability and lower renal clearance than that seen in younger individuals.[1,43]

• Hepatic insufficency has shown no significant effect on the pharmacokinetics of perindopril and dosage adjustments in patients with impaired liver function appear to be unnecessary.[1]

3. Therapeutic Trials

The efficacy of perindopril in patients with mild or moderate (NYHA class II or III) CHF of various aetiologies has been evaluated over 3 months in two randomised, double-blind, placebo-controlled, multicentre trials.[29,32] Efficacy was the secondary endpoint in a noncomparative study conducted over 6 to 30 months.[30]

Comparative Trials

• In the two double-blind trials,[29,32] 125 (perindopril n = 61, placebo n = 64)[29] and 103 (perindopril n = 50, placebo n = 53)[32] ambulatory patients received perindopril or placebo in addition to baseline therapy; all patients received diuretics and approximately half received digoxin. Treatment groups were well matched for baseline characteristics except for a significant difference in CHF severity between placebo and perindopril recipients in one trial[32] (for NYHA class II/III, perindopril = 22/28 and placebo = 37/16, $p < 0.008$). A starting dose of perindopril 2mg was increased in most patients to 4mg after 2 weeks, unless the SBP was <100mg Hg. Six of 46 individuals in one treatment group,[32] and an unstated number in the other,[29] remained on perindopril 2mg throughout the studies. The major efficacy endpoints were exercise tolerance, NYHA functional class, overall heart failure symptom severity score and cardiothoracic ratio.[29]

• Patients with CHF belonging to NYHA class II or III, most of whom were receiving perindopril 4mg, showed a significant improvement in exercise capacity, NYHA classification, and symptom severity score compared with those receiving placebo.[29,32]

• In the two studies, the mean increase in duration of exercise testing from baseline to 3 months was 5.6-fold ($p < 0.001$; n = 125, intention-to-treat analysis)[29] and 2.7-fold ($p = 0.007$; n = 92, per-protocol analysis[32]) greater with perindopril than with placebo (see figure 2). Exercise tolerance was determined by recording the change from baseline in exercise test duration using a bicycle ergometer or treadmill.[29,32]

• On an intention-to-treat basis, the NYHA functional class rating improved in 51% of perindopril-treated individuals compared with 25% in the placebo group ($p = 0.009$) in one study.[29] Of the original 50 patients in the perindopril-treated group in the second trial, 25 (50%) improved by at least one class in the NYHA functional class rating compared with 10 (19%) of the 53 placebo recipients ($p = 0.002$); more perindopril than placebo recipients had severe disease at baseline (NYHA II/III perindopril 22/28 and placebo 37/16, $p = 0.008$).[32]

• The overall heart failure symptom severity score is the sum of scores for symptom severity in nine categories covering specific disease characteristics, with the maximum of 17 points indicating the greatest severity of heart failure. The perindopril treatment group in both studies[29,32] showed a significant improvement in the severity score ($p < 0.001$[29] and $p < 0.01$[32]) compared with placebo groups.

• Cardiothoracic ratio was determined by standard radiological procedures. At 3 months in the perindopril-treated patients in both comparative trials[29,32] there was a reduction in the cardiothoracic ratio; however this reduction was statistically significant in only one of the studies ($p = 0.042$ *vs* placebo).[32]

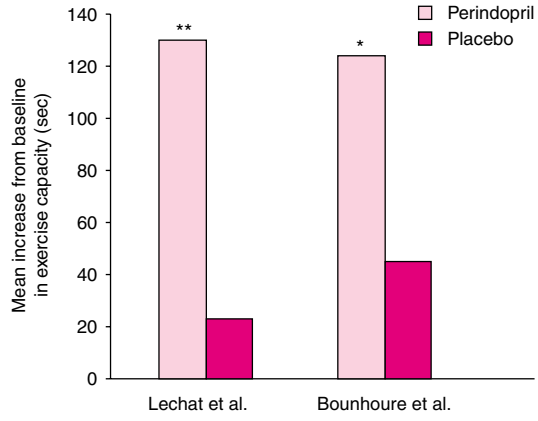

Fig. 2. Efficacy of perindopril in patients with congestive heart failure (CHF). Patients with New York Heart Association class II or III CHF received perindopril 4mg or placebo once daily for 3 months in two randomised, double-blind studies (Lechat et al.[29] n = 125; intention-to-treat analysis; Bounhoure et al.[32] n = 92; per-protocol analysis); * $p = 0.007$, ** $p < 0.001$ versus placebo.

Long-Term Study

• A noncomparative study involving 320 patients with CHF (NYHA class II or III), 208 of whom were treated for 6 months, 105 for 12 months and 30 for 30 months, was designed primarily to assess the tolerability of perindopril, with efficacy as a secondary outcome.[30] Patients were stabilised on diuretic treatment (with or without digoxin) and received perindopril 2mg daily for the first 2 weeks, titrated to 4mg daily unless the SBP was <100mm Hg. Exercise tolerance, NYHA class and overall symptom severity score were significantly improved compared with baseline. The gain in mean exercise test time from baseline (assessed using a treadmill or ergometric bicycle) at 6, 12 and 30 months was 143, 180 and 101 seconds, respectively (n = 208, 105 and 30; $p < 0.01$, $p < 0.01$ and $p < 0.05$). Mean symptom severity score decreased at 6, 12 and 30 months by 2.7, 2.9 and 2.0 points, respectively, from baseline values 5, 5.1 and 3.9 (n = 208, 105 and 30; $p < 0.01$, $p < 0.001$ and $p < 0.01$). At 6, 12 and 30 months, NYHA class rating improved by at least one class in 55.6, 63.7 and

63.3% of patients, respectively (statistical data not reported).

4. Tolerability

General

• Perindopril was generally well tolerated in single-dose studies[26,28,31,33,34,44] and multiple-dose studies conducted over 8 weeks to 30 months.[29,30,32] Few adverse events occurred and serious events were rare.

• In the largest and longest study available investigating the tolerability of perindopril in 320 patients with CHF,[30] 208 participants were treated with perindopril 4mg once daily for at least 6 months and 105 for at at least 12 months. At least one symptom was reported by 30.3% of patients, the most common being cough (characteristic of ACE inhibitors) which was spontaneously reported by 6.3% of patients leading to 2.8% discontinuing treatment. Dizziness or orthostatic discomfort was reported by 6% of patients and one third withdrew as a result. Angioneurotic oedema was responsible for one patient withdrawing from the trial.

• Perindopril was well tolerated in patients with CHF participating in two double-blind, placebo-controlled trials including 125[29] and 103[32] individuals treated with perindopril 4mg daily for 3 months. The most common spontaneously reported symptoms (causality not determined) were gastrointestinal (various) 14%[32] and 6%,[29] fatigue 7%,[29] and asthenia 6%.[32] Cough was reported by 3%[29] and 2%[32] of patients.There were two withdrawals from the perindopril treatment group compared with five from the placebo group in the first study (statistical analysis not reported).[29] No patients discontinued perindopril treatment because of adverse events in the other comparative study.[32]

First-Dose Hypotension

• A reduction in MAP (>20mm Hg) and/or blood pressure <90/60mm Hg after the first oral dose has been reported less frequently with perindopril than with other ACE inhibitors in patients with CHF[26,28,33,34,45] (see section 1).

• In a single-dose study comparing perindopril 2mg with captopril 6.25mg (n = 240),[33] there was one instance (<1%) of symptomatic FDH in the perindopril group versus 10 (8%) with captopril ($p < 0.029$). There were no instances of symptomatic FDH in patients receiving perindopril in two other single-dose studies, one comparing perindopril 2mg with enalapril 2.5mg (n = 298)[34] and the other comparing perindopril 2mg with captopril 6.25mg, enalapril 2.5mg and lisinopril 2.5mg (n = 80).[26]

• In a large nonblind, randomised trial[28] involving 725 patients hospitalised for an episode of heart failure or an acute coronary event, the blood pressure response in the initial 36 hours following perindopril (2mg once daily) was compared with that after captopril (6.25mg three times daily). More than twice as many patients receiving captopril as those receiving perindopril (4.5 *vs* 1.7%; $p < 0.04$) withdrew from treatment because of orthostatic hypotension (SBP <90mm Hg) within the first 36 hours.[28]

• In a subgroup analysis of 66 elderly patients (aged ≥70 years) with CHF, hypotensive episodes following the first dose occurred in fewer patients taking perindopril 2mg than in those taking captopril 6.25mg (2.7 *vs* 17.2%, $p = 0.042$).[45]

Laboratory Parameters

• During a long-term study that assessed the tolerability of perindopril in patients with CHF (n = 320),[30] plasma creatinine levels that were normal on inclusion were increased in 24 patients (137 to 237 μmol/L). Elevated levels in 16 of these patients were transient; however, one patient withdrew at 3 months because of a sustained increase in plasma creatinine levels (107 to 180 μmol/L) which remained elevated one month after treatment withdrawal (see section 1).

• In the above study,[30] transient hyperkalaemia (K^+ 5.4 to 5.9 mmol/L) was observed in 1.25% of

patients, none of whom needed to withdraw from treament (see section 1).

• In a 3-month, placebo-controlled study (n = 125), an increase in plasma creatinine levels of >50 μmol/L from baseline was observed in 2.4% of patients receiving perindopril, though no patients withdrew from treatment.[29]

• In a multicentre, noncomparative study conducted over 6 to 30 months, patients with NYHA class II (n = 64) or III (n = 24) CHF and impaired renal function, 70 of whom were treated for at least 6 months, received perindopril 4 mg once daily.[46] The slight decrease in plasma creatinine levels at 1, 3 and 6 months was not significant, and there was no change from baseline at 12 and 30 months. Plasma potassium remained unchanged at all timepoints in this study.

5. Dosage and Administration

According to European prescribing information,[47] the recommended starting dose for patients with mild to moderate CHF is perindopril 2mg, titrated in one step to the normal maintenance dose of 4mg, provided SBP does not drop below 100mm Hg. The dose should be taken once daily in the morning before food.

European guidelines for the treatment of CHF recommend that the dose of ACE inhibitors should not be based on symptomatic improvement but be titrated to the maximum, where possible, to reduce long-term morbidity and mortality.[9] The 4mg maintenance dose of perindopril is reached through a one-step dose-titration. A small retrospective observational study of treatment of CHF in general practice has shown that a higher proportion of perindopril recipients achieved the target dose than patients receiving enalapril, captopril or lisinopril (statistical significance not reported).[48] Among 22 perindopril recipients, 19 (86%) achieved the target 4mg dose, compared with 0 to 50% of patients who achieved the target doses of comparators.

As with other ACE inhibitors, treatment in high-risk patients (the elderly and those with severe CHF, low to normal blood pressure or impaired renal function) should be initiated under close supervision, with careful monitoring of blood pressure and renal function following any dose adjustment.

6. Perindopril: Current Status in Congestive Heart Failure

Perindopril is a long-acting ACE inhibitor currently approved for the treatment of CHF in numerous countries worldwide (not in the US). In controlled clinical trials, perindopril 4mg once daily has shown efficacy (increased exercise capacity and reduced symptoms) in treating patients with mild to moderate CHF of various aetiologies. Perindopril was generally well tolerated in these trials and a 2mg starting dose was associated with less frequent FDH than equivalent starting doses of some other ACE inhibitors. The effect of perindopril on mortality and morbidity in elderly patients with CHF with preserved left ventricular systolic function is being investigated in the multicentre, double-blind, placebo-controlled PEP-CHF (Perindopril in Elderly Patients with CHF) trial[49] involving approximately 1000 patients over 70 years of age.

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