

Cost-effectiveness of zofenopril in patients with left ventricular systolic dysfunction after acute myocardial infarction: a post hoc analysis of SMILE-4

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Background: In SMILE-4 (the Survival of Myocardial Infarction Long-term Evaluation 4 study), zofenopril + acetylsalicylic acid (ASA) was superior to ramipril + ASA in reducing the occurrence of major cardiovascular events in patients with left ventricular dysfunction following acute myocardial infarction. The present post hoc analysis was performed to compare the cost-effectiveness of zofenopril and ramipril.

Methods: In total, 771 patients with left ventricular dysfunction and acute myocardial infarction were randomized in a double-blind manner to receive zofenopril 60 mg/day (n = 389) or ramipril 10 mg/day (n = 382) + ASA 100 mg/day and were followed up for one year. The primary study endpoint was the one-year combined occurrence of death or hospitalization for cardiovascular causes. The economic analysis was based on evaluation of cost of medications and hospitalizations and was applied to the intention-to-treat population (n = 716). Cost data were drawn from the National Health Service databases of the European countries participating in the study. The incremental cost-effectiveness ratio was used to quantify the cost per event prevented with zofenopril versus ramipril.

Results: Zofenopril significantly ($P = 0.028$) reduced the risk of the primary study endpoint by 30% as compared with ramipril (95% confidence interval, 4%–49%). The number needed to treat to prevent a major cardiovascular event with zofenopril was 13 less than with ramipril. The cost of drug therapies was higher with zofenopril (328.78 Euros per patient per year, n = 365) than with ramipril (165.12 Euros per patient per year, n = 351). The cost related to the occurrence of major cardiovascular events requiring hospitalization averaged 4983.64 Euros for zofenopril and 4850.01 Euros for ramipril. The incremental cost-effectiveness ratio for zofenopril versus ramipril was 2125.45 Euros per event prevented (worst and best case scenario in the sensitivity analysis was 3590.09 and 3243.96 Euros, respectively).

Conclusion: Zofenopril is a viable and cost-effective treatment for managing patients with left ventricular dysfunction after acute myocardial infarction.

Keywords: acute myocardial infarction, left ventricular dysfunction, angiotensin-converting enzyme inhibitors, zofenopril, ramipril, acetylsalicylic acid, cost-effectiveness

Introduction

The results of major clinical trials clearly demonstrate that angiotensin-converting enzyme (ACE) inhibitors effectively prevent morbidity and mortality of patients after acute myocardial infarction (AMI), particularly if associated with left ventricular dysfunction (LVD).^{1–5} Thus, practice guidelines now recommend that all AMI patients receive treatment with an ACE inhibitor in combination with a beta-blocker,

a lipid-lowering agent, and acetylsalicylic acid (ASA), unless a contraindication exists.^{6–9}

In addition, several large-scale, randomized, prospective studies have evaluated the cost-effectiveness of ACE inhibitors in the treatment of AMI and heart failure. The results of such economic analyses unanimously indicate that ACE inhibitors are cost-effective when used to treat patients after AMI,^{10–13} and argue for the widest possible use of ACE inhibitors in this setting.^{14–17}

Zofenopril is a sulfhydryl-containing lipophilic ACE inhibitor with ancillary and cardioprotective properties.^{18–21} Following extensive evidence of its efficacy and safety derived from the randomized controlled studies of the SMILE (Survival of Myocardial Infarction Long-term Evaluation) program, zofenopril is currently indicated for treatment initiated within the first 24 hours in patients with AMI with or without signs and symptoms of heart failure, who are hemodynamically stable and have not received thrombolytic therapy.^{22,23} Recently, the SMILE-4 study demonstrated that the efficacy of zofenopril associated with ASA is superior to that of ramipril + ASA in patients with LVD following AMI, in terms of prevention of major cardiovascular outcomes.²⁴

Although the clinical efficacy of zofenopril is clear from the SMILE studies, the question remains as to whether the added benefit of zofenopril is worth the added cost. For this reason, we undertook a post hoc cost-effectiveness analysis to compare the cost-effectiveness of zofenopril and ramipril in patients with LVD after an AMI.

Materials and methods

Clinical trial

The SMILE-4 trial was a large multicenter, randomized, prospective study, the methodology and results of which are reported in detail elsewhere.²⁴ Briefly, male and nonpregnant female patients aged 18–85 years with a confirmed diagnosis of ST or non-ST segment elevation myocardial infarction in the 24 hours preceding enrollment (not treated with primary percutaneous transluminal coronary angioplasty, treated or not with thrombolysis and recommended pharmacologic treatment) and with clinical and/or echocardiographic evidence of LVD (Killip class > 1, plus a third heart sound, pulmonary congestion on chest x-ray, and/or a left ventricular ejection fraction < 45%) were enrolled in 79 hospitals in eight European countries.

Eligible patients entered a four-day, open-label phase during which zofenopril was administered to all patients according to an uptitration scheme. On days 1 and 2, patients received zofenopril 7.5 mg twice daily + an evening dose

of ASA 100 mg. On days 3 and 4, the zofenopril dose was doubled (to 15 mg twice daily) while the dose of ASA remained unchanged. On day 5, patients were randomized 1:1 in a double-blind manner to receive zofenopril 30 mg twice daily + ASA 100 mg once daily or ramipril 5 mg twice daily + ASA 100 mg once daily for 12 months. The study medications were administered in combination with standard recommended treatments for AMI, excluding ACE inhibitors, angiotensin receptor blockers, and antiplatelet drugs other than ASA, clopidogrel, or ticlopidine. Concomitant chronic anticoagulant treatment was allowed in the acute phase of myocardial infarction and in case of a specific indication, or in patients who reached a study endpoint. Patients were seen at enrollment, at randomization (5 days after enrollment) and after months 1, 6, and 12. Blood pressure and heart rate were measured, an echocardiogram was performed, blood samples were drawn (centralized estimation of N-terminal pro-brain natriuretic peptide), and occurrence of concomitant diseases, adverse events, use of concomitant medications, and compliance with the study drugs were checked at each study visit. A physical examination, a 12-lead electrocardiogram, and laboratory tests (hematology, clinical chemistry, and urinalysis) were performed at entry, at randomization, and at study end.

Cost analysis

The initial aim of the cost analysis was to investigate whether use of zofenopril might be cost-neutral or cost-saving. Only drug and hospitalization or event costs were included in this analysis. The perspective adopted for the study was that of a third-party payer, ie, the individual national health services of the countries participating in the study. A reference cost was obtained by averaging costs for each country and presenting them in 2012 Euros.

Medications

The unit costs of the study drugs (zofenopril, ramipril, and ASA) were derived from the national pharmaceutical formulary for each country, using the reimbursement price for the generic drug as reference. The cost of zofenopril was estimated at 0.80 Euros per day using the 28-tablet pack, that of ramipril 0.34 Euros per day using the 14-tablet pack, and that of ASA 0.10 Euro per day using the 30-tablet pack.

Events

The unit costs for post-AMI events were calculated considering a Diagnosis-Related Group code. Information on costs for each type of event and for each individual

country was collected and averaged to obtain a reference cost.²⁵ Because the reference payment list did not refer to a decline in left ventricular ejection fraction > 15%, this cost was conservatively estimated as one-third of the cost of a hospitalization for symptomatic heart failure. The assumption underlying this choice was that a patient with such clinical worsening will experience at least one admission for symptomatic heart failure in the next three years, with no other major cardiovascular events.

Statistical analysis

The economic evaluation of SMILE-4 was based on estimation of the costs of drugs and events, and on cost-effectiveness analysis. The clinical benefits were also calculated from endpoints used in the trial, and converted to the “number needed to treat”, an expression of the number of patients who must be treated with one drug to prevent one adverse event. The calculation was done as follows:

$$1/(\text{Relative frequency of major cardiovascular events with zofenopril} - \text{Relative frequency of major cardiovascular events with ramipril}).^{26}$$

The analysis was carried out in the intention-to-treat population, as for the clinical outcomes in the original study,²⁴ ie, in patients treated with at least one dose of study medication and documenting at least once, the measure of the primary efficacy assessment, even in the event of protocol violation or premature withdrawal from the study.

The economic effects were established by undertaking an incremental cost-effectiveness analysis. The results of the analysis were expressed by means of an incremental cost-effectiveness ratio (ICER), and calculated as incremental drug costs divided by incremental effects. The difference in the rate of occurrence of major cardiovascular events between the two study groups (first occurrence of cardiovascular death or hospitalization for cardiovascular causes, including congestive heart failure, acute myocardial infarction, angina, revascularization, or a decline in left ventricular ejection fraction > 15%) was used as the incremental effect. This was the original primary study endpoint for the main study.²⁴

The ICER was calculated by the following equation:

Incremental cost-effectiveness ratio

$$= (\text{Cost of zofenopril treatment for 1 year} - \text{Cost of ramipril treatment for 1 year}) / (\text{Relative frequency of major cardiovascular events with zofenopril over one year} - \text{Relative frequency of major cardiovascular events with ramipril over one year}).^{27-29}$$

The cost-effectiveness study was done according to a base-case analysis supplemented with a sensitivity analysis.^{27,30} In the base-case analysis, exclusively average values of the model input parameters were used. In the sensitivity analysis, we assessed the impact of increasing the price of zofenopril by 20% and decreasing the price of ramipril by 20% on the cost-effectiveness of the intervention according to a deterministic one-way analytical approach. Uncertainty in the point estimate of the ICER was also investigated by varying the event size while costs remained the same or by combining changes in unit costs and event size, in order to obtain a worst/best case scenario analysis.

Results

Clinical efficacy

The present study analyzed the 716 patients included in the intention-to-treat analysis of the main SMILE-4 study (365 treated with zofenopril 60 mg and 351 with ramipril 10 mg). No significant differences in baseline patient demographic and clinical characteristics were observed between the treatment groups (Table 1), with the only exception being the proportion of patients with arterial hypertension ($P = 0.033$), previous percutaneous transluminal coronary angioplasty ($P = 0.044$), and impaired left ventricular ejection fraction ($P = 0.009$). Further details are reported in the main study publication.²⁴

During the 12 months of double-blind, randomized treatment, major cardiovascular events occurred in 105 of the 365 patients treated with zofenopril (29%) and in 128 of the 351 patients treated with ramipril (37%), with a 30% significantly ($P = 0.028$) lower risk of achieving the combined endpoint (95% confidence interval, 4%–49%) in zofenopril-treated patients²⁴ (Table 2). This figure resulted in a number needed to treat of 13, indicating that one major cardiovascular event could be prevented with zofenopril by treating 13 fewer patients than with ramipril.

Cost effectiveness

The average cost of drug treatment per patient per year was 328.78 Euros for zofenopril + ASA and 165.12 Euros for ramipril + ASA. The cost related to occurrence of major cardiovascular events averaged 4983.64 Euros for zofenopril and 4850.01 Euros for ramipril (Table 3). When the two study groups were pooled together, the average estimated cost per event was 4910.23 Euros. Treatment with zofenopril yielded an ICER of 2125.45 Euros for any additional event prevented compared with ramipril.

Table 1 Baseline demographic and clinical characteristics of the intention-to-treat population in SMILE-4²⁴ (n = 716)

Characteristics	Zofenopril (n = 365)	Ramipril (n = 351)
Age (years, mean ± SD)	61 ± 11	61 ± 11
Males (n, %)	268 (73)	276 (79)
BMI (kg/m ² , mean ± SD)	28 ± 4	28 ± 4
Diabetes mellitus (n, %)	68 (19)	63 (19)
Treated hypercholesterolemia (n, %)	68 (19)	72 (21)
Treated arterial hypertension (n, %)	237 (65)	200 (57)
Relevant concomitant treatments (n, %)		
ACE inhibitors	13 (4)	3 (1)
Angiotensin II antagonists	4 (1)	1 (1)
Beta-blockers	199 (55)	177 (50)
Alpha-blockers	24 (7)	28 (8)
Calcium antagonists	8 (2)	13 (4)
Diuretics	73 (20)	74 (21)
Digoxin	–	3 (1)
Nitrates	128 (35)	117 (33)
Antiarrhythmic drugs	14 (4)	9 (3)
Statins	217 (59)	200 (57)
Other lipid-lowering drugs	15 (4)	17 (5)
Other cardiovascular drugs	47 (13)	32 (9)
Atrial fibrillation (n, %)	7 (2)	2 (1)
Peripheral arterial occlusive disease (n, %)	17 (5)	18 (5)
Previous myocardial infarction (n, %)	72 (20)	61 (18)
Angina pectoris (n, %)	140 (39)	123 (35)
Prior PTCA (n, %)	26 (7)	13 (4)
Prior CABG (n, %)	6 (2)	6 (2)
Congestive heart failure (n, %)	24 (7)	25 (7)
PTCA performed at entry (n, %)	115 (31)	109 (31)
Thrombolytic therapy performed at entry (n, %)	141 (39)	134 (38)
LVEF ≤ 40% (n, %)	151 (41)	111 (32)
SBP (mmHg, mean ± SD)	139 ± 24	140 ± 24
DBP (mmHg, mean ± SD)	83 ± 14	83 ± 13
HR (beats per minute, mean ± SD)	81 ± 17	79 ± 16

Abbreviations: ACE, angiotensin-converting enzyme; SD, standard deviation; BMI, body mass index; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Sensitivity analysis

The overall result was not modified by applying sensitivity analysis. A first analysis varying the price of zofenopril and ramipril returned an ICER of 3408.26 Euros. When the lower limit of the 95% confidence interval for the event rate was used, the ICER was 2238.82 Euros, whereas the corresponding figure was 2022.96 Euros when the upper limit was selected. The worst case scenario, determined by combination of the modified drug costs and the lower limit for event rate, gave an ICER of 3590.09 Euros, while the best case scenario returned an ICER of 3243.96 Euros.

Discussion

Economic analysis of drug treatment is increasingly incorporated routinely into many clinical trials, because

Table 2 Absolute and relative frequency (%) for the various components of the SMILE-4 primary study endpoint (hospitalization for cardiovascular causes or cardiovascular mortality) in the intention-to-treat population of SMILE-4²⁴ (n = 716)

	Zofenopril (n = 365)	Ramipril (n = 351)
Hospitalization for cardiovascular causes (n, %)		
Congestive heart failure	4 (1.1)	7 (2.0)
Acute myocardial infarction	13 (3.6)	16 (4.6)
Angina pectoris	20 (5.5)	22 (6.3)
Decline in left ventricular ejection fraction > 15%	15 (4.1)	28 (8.0)
Revascularization	25 (6.8)	32 (9.1)
Other causes	11 (3.0)	12 (3.4)
Total	88 (24.1)	117 (33.3)
Unadjusted OR (95% CI)	0.64 (0.46–0.88)	
P value	0.006	
Adjusted OR (95% CI)	0.65 (0.46–0.91)	
P value	0.012	
Cardiovascular death (n, %)		
Congestive heart failure	4 (1.1)	2 (0.6)
Acute myocardial infarction	6 (1.6)	1 (0.3)
Sudden death	6 (1.6)	6 (1.7)
Cardiac rupture	1 (0.3)	1 (0.3)
Stroke	0 (0.0)	1 (0.3)
Total	17 (4.7)	11 (3.1)
Unadjusted OR (95% CI)	1.51 (0.70–3.27)	
P value	0.293	
Adjusted OR (95% CI)	1.18 (0.51–2.70)	
P value	0.704	
Overall major cardiovascular events (n, %)	105 (28.8)	128 (36.5)
Unadjusted OR (95% CI)	0.70 (0.51–0.96)	
P value	0.028	
Adjusted OR (95% CI)	0.68 (0.49–0.95)	
P value	0.024	

Notes: Unadjusted and adjusted odds ratio and corresponding confidence intervals with P values are also reported. OR adjustment by age, gender, glomerular filtration rate, left ventricular ejection fraction, Killip class, revascularization, diabetes, metabolic syndrome, hypercholesterolemia, low high-density lipoprotein, ST versus non-ST elevation myocardial infarction, N-terminal pro-brain natriuretic peptide, and heart rate.

Abbreviations: CI, confidence interval; OR, odds ratio.

this type of information, in conjunction with the usual safety and efficacy data, is becoming more important to pharmaceutical companies, regulatory authorities, third-party payers, and end-users. The present study examined vis-à-vis the cost-effectiveness of two ACE inhibitors used widely in post-AMI patients with LVD, ie, zofenopril and ramipril. According to our findings, treatment with zofenopril costs between 2023 Euros (best case sensitivity analysis) and 3590 Euros (worst case analysis) to generate any additional event prevented compared with ramipril. This cost-effectiveness threshold is within the range of health care programs currently funded in developed countries which usually consider a threshold < 20,000–40,000 USD (about 15,000–30,000 Euros) as being compatible with a

Table 3 Unit and overall costs for treating each single event in SMILE-4

Outcome	Cost per event per patient (Euros)	Zofenopril (n = 365)		Ramipril (n = 351)	
		Events (n)	Total cost (Euros)	Events (n)	Total cost (Euros)
Congestive heart failure	3425.51	4	13,702.04	7	23,978.57
Acute myocardial infarction	4019.04	13	52,247.52	16	64,304.64
Angina pectoris	2642.24	20	52,844.80	22	58,129.28
Decline in LVEF > 15%	1141.84	15	17,127.55	28	31,971.43
Revascularization	10,993.14	25	274,828.38	32	351,780.32
Other causes	3650.20	11	40,152.20	12	43,802.40
Death	4257.64	17	72,379.88	11	46,834.04
Overall cost			523,282.37		620,800.68
Average cost per patient			4983.64		4850.01

Note: Number of occurrences for each outcome is also indicated.

Abbreviation: LVEF, left ventricular ejection fraction.

highly cost-effective treatment in the management of heart disease.^{10,31,32}

As summarized in Table 4, the cost-effectiveness ratio calculated for zofenopril also appears favorable compared with many other strategies for the management of AMI or stable angina, including drug treatment, thrombolysis, percutaneous coronary intervention, or coronary artery

Table 4 Cost-effectiveness of various interventions versus standard care in the management of acute myocardial infarction

Strategy	Cost effectiveness (Euros/YLS or QALYS)
Drugs	
Medical treatment alone in patients with multivessel CAD and normal EF ³³	7000
β-blocker in high risk post-AMI patients ¹⁰	2800
β-blocker in low risk post-AMI patients ¹⁰	15,600
Captopril in post-AMI patients with EF ≤ 40% ¹⁰	21,900
Reperfusion therapy	
Thrombolysis ¹³	1750
Streptokinase in elderly (≥75 years) AMI patients ¹⁰	21,400
Primary PTCA ^{13,33}	8800–15,400
Primary PTCA in patients with large infarct size ¹⁰	34,500
PTCA in patients with multivessel CAD and normal EF ³³	15,400
Non-elective PTCA with stenting ³⁶	14,500–33,900
PTCA in addition to optimal medical therapy in presence of stable angina ³⁵	24,805
CABG in patients with multivessel CAD and normal EF (CABG) ³³	14,100
CCU in patients with highly probable (≥50%) MI ¹⁰	27,000

Note: The strategy, along with its cost-effectiveness, expressed in 2012 Euros per year life saved or quality-adjusted life-year is reported.

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CCU, coronary care unit; CAD, coronary artery disease; EF, ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; YLS, year life saved; MI, myocardial infarction; QALYs, quality-adjusted life-years.

bypass grafting.^{10,13,31–36} In addition, the estimated cost-effectiveness of zofenopril compares well with that of other ACE inhibitors, although such a comparison, discussed in the next paragraphs, has limitations because the model used varies between studies. A recently published economic analysis of diverse cardiologic interventions from 2000 to 2010 in England and Wales showed reasonable cost-effectiveness for ACE inhibitors, ranging from approximately 2500 Euros up to 4400 Euros for secondary prevention in heart failure patients.¹³ Concerning a comparison with specific ACE inhibitors, the incremental cost per life-year gained using prophylactic captopril in survivors of AMI with a reduced left ventricular ejection fraction in the SAVE study ranged between 800 and 8000 Euros, depending on age, country, and time period considered.^{37–40} In the GISSI-3 trial, which assessed the efficacy of early (within 24 hours) treatment with lisinopril in unselected patients with AMI, the comparative cost-effectiveness ratio for use of lisinopril, expressed as cost per additional survivors among patients randomized to receive lisinopril, was approximately 1600 Euros per life saved.⁴¹ In the TRACE study, the ICER of treating post-AMI patients with LVD with trandolapril rather than with placebo was estimated at approximately 900 Euros.¹⁵ In the patients with stable coronary artery disease included in EUROPA, the median incremental cost of perindopril for each quality-adjusted life-year gained was estimated to be about 12,000 Euros.¹⁷

The cost-effectiveness of ramipril versus placebo has been estimated in two large, randomized, prospective studies, ie, HOPE and AIRE. In the HOPE study, which recruited patients with an increased risk of cardiovascular events, the estimated cost-effectiveness of ramipril ranged between 4000 and 14,000 Euros per life-year gained at five years, depending on the various local economic analyses, with costs consistently decreasing for lifetime treatment.^{42–48} In the USA and Canada, the majority of patients in the HOPE study

fell into a cost-effectiveness situation with an ICER < 8000 Euros per primary event saved.¹⁶ In the AIRE study, the incremental cost of ramipril per life-year gained in patients with heart failure following AMI ranged between 1300 and 3900 Euros after 3.8 years of follow-up in three European subanalyses.^{49–51}

There are a number of limitations to our economic analysis. First, and more importantly, this cost analysis was conducted after the randomized trial had been completed. Thus, a limited amount of variables were available to enable us to measure health care utilization in detail. Although some indicators useful for a more indepth pharmacoeconomic analysis, such as quality of life or life-years gained, were not assessed, hospitalizations and related causes were recorded prospectively at the time of the original study and were classified correctly using an event-driven system, ie, Diagnosis-Related Group code.

Second, a third-party payer perspective as an integrated public health care system where all costs are recorded was chosen for the cost analysis. Although it is suggested that a societal perspective be considered, it is recognized that use of other perspectives is acceptable and might be more appropriate in some cases.^{28,29} Unfortunately, we were forced to consider costs from the perspective of the health care system because of the limitations of the data available to us.

Third, one cost item (decline in left ventricular ejection fraction) was missing, but the assumption made does not appear to have had a major impact on the positive cost-benefit ratio of use of zofenopril versus ramipril. In fact, the number of patients with a significant reduction in left ventricular ejection fraction was larger in the ramipril-treated group, so the cost-benefit ratio of zofenopril would have been still in favor of this drug, even if the actual number of hospital admissions per year was significantly different from the number assumed in the calculations.

Fourth, our economic analysis applies to a relatively limited time horizon (one year), and we do not know whether the cost-effectiveness ratio remains favorable even if clinical benefit is assumed to stop at the end of the clinical trial follow-up period. Whilst this lack of continuing effect is implausible, any quantification of benefit beyond this period is not possible, and we cannot address the issue of how long zofenopril should be taken.

Fifth, in common with most economic analyses of this type, cost calculations were limited to the medical costs of both treatments, and nonmedical costs, direct and indirect, such as those due to productivity losses, were not evaluated or taken into account. In addition, due to the perspective and

time span of the observation, we did not assess direct costs, such as rehabilitation and long-term care.

Finally, we did not compare the cost-effectiveness of zofenopril versus placebo, but versus another ACE inhibitor. However, zofenopril was cost-saving compared with ramipril, a drug already proven to be cost-effective in patients at high risk of cardiovascular disease, including post-AMI patients.^{42–51}

Conclusion

The use of zofenopril in patients with LVD following AMI is not only associated with a 30% reduction in the risk of major cardiovascular events over one year, but also appears to be a good strategy from a health economics perspective. The incremental cost of zofenopril in the SMILE-4 Study was lower than the apparent threshold used to define a cardiac treatment as highly cost-effective (15,000–30,000 Euros). In addition, the cost-effectiveness of zofenopril in our study (just over 2000 Euros) compares favorably with that observed for ramipril in high cardiovascular risk and post-AMI patients (1300–14,000 Euros) and for other ACE inhibitors, such as captopril (800–8000 Euros), lisinopril (1600 Euros), trandolapril (900 Euros), and perindopril (12,000 Euros). Therefore, our results place zofenopril among the viable and cost-effective options for treating post-AMI patients with LVD.

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Disclosure

CB is a shareholder in Abbott and BMS, and a consultant to Boehringer Ingelheim and Menarini International Consultancy. DZ is an employee of Istituto Lusofarmaco d'Italia SpA. None of the other authors have any conflicts of interest to disclose.

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