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Zofenopril versus ramipril in the early phase of acute myocardial infarction with systolic dysfunction: A retrospective study

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Abstract

Introduction: Prognostic benefits of zofenopril over ramipril in the early phase of acute myocardial infarction have been reported by the SMILE study, but these benefits have not been tested in clinical practice in the Chinese population. The objective of this study was to compare the effectiveness and safety of zofenopril plus aspirin against ramipril plus aspirin in patients with acute myocardial infarction.

Methods: Patients in the early phase of acute myocardial infarction received 30 mg zofenopril (ZF cohort, *N*=191) or 5 mg ramipril (RP cohort, *N*=256) b.i.d. plus 100 mg aspirin/day. Data regarding hospitalisation for cardiovascular disease, non-cardiovascular events and mortality were collected and analysed.

Results: During 1 year of treatment, 47 (25%) patients in the ZF cohort and 97 (40%) patients in the RP cohort were hospitalised due to cardiovascular disease (p=0.002), and three (2%) patients in the ZF cohort and 14 (6%) patients in the RP cohort died (p=0.043). Lower incidences of dry cough (p=0.001) and anaemia (p=0.049) were reported in the ZF cohort.

Conclusions: The study recommends zofenopril with 100 mg aspirin for a longer period in patients with acute myocardial infarction with systolic dysfunction.

Keywords

Acute myocardial infarction, aspirin, cardiovascular events, cardio-protective action, ramipril, zofenopril

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Introduction

Acute myocardial infarction causes necrosis of cardiac myocytes by activation of the renin–angiotensin–aldosterone system.[1] Therefore, current guidelines recommended angiotensin-converting enzyme inhibitors in patients presenting in the early phase of acute myocardial infarction with[2] and without[3] ST-segment elevation. Angiotensin-converting enzyme inhibitors in combination with aspirin (acetylsalicylic acid) are preferred in the early phase of acute myocardial infarction.[4] However, angiotensin-converting enzyme inhibitors and aspirin both interfere with the prostaglandin-mediated pathway.[5] Angiotensin-converting enzyme inhibitors, such as captopril and lisinopril, improve the antiplatelet response of aspirin.[6] The SMILE-4 trial also reported that angiotensin-converting enzyme inhibitors, such as example zofenopril and ramipril, improved the antiplatelet response of aspirin.[5] However, aspirin plus ramipril is associated with haemodynamic deficiencies.[7] Moreover, there is a gap between clinical trials and clinical practice, for example inclusion criteria. To overcome such controversies regarding guidelines for treatment in acute myocardial infarction, there is a need for a retrospective study based on clinical practice.

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Zofenopril is a sulphhydryl containing angiotensin-converting enzyme inhibitor and is highly lipophilic in nature.[1] Ramipril is a carboxylic containing angiotensin-converting enzyme inhibitor[8] and has cardio-protective effects by inhibiting kinin metabolism[9] as well as being a well-established cost-effective angiotensin-converting enzyme inhibitor for high-risk cardiovascular diseases.[1] The efficacy of both of these angiotensin-converting enzyme inhibitors is different in the presence of aspirin.[5] The SMILE study reported prognostic benefits of zofenopril over ramipril.[4] In short, prognostic benefits of zofenopril have been reported, but clinical evidence is absent in the Chinese population.

The objective of this retrospective study was to compare the effectiveness and safety of zofenopril plus aspirin against ramipril plus aspirin in patients in the early phase of acute myocardial infarction with systolic dysfunction.

Methods

Ethics approval and consent to participate

The design protocol (reg. no.: AFMU150420 dated 19 May 2020) of this study was approved by the Second Affiliated Hospital of the Air Force Medical University review board. Informed consent was waived by the local Institutional Review Board because this was a retrospective study.

Patient population

Patients (⩾18 years of age) with acute myocardial infarction with or without ST-segment elevation, treated or not treated with thrombolysis and recommended for pharmacological treatments at the Second Affiliated Hospital of the Air Force Medical University (Xi'an, Shaanxi, PR China) were included in the study. From 9 August 2018 to 1 April 2019, clinical and echocardiographic evidence showed left ventricular systolic dysfunction in 457 patients with <45% left ventricle ejection fraction and who had an acute myocardial infarction. Among them, seven patients reported sensitivity to angiotensin-converting enzyme inhibitors, and three patients have reported sensitivity to aspirin. Therefore, they were not put on the angiotensin-converting enzyme inhibitor plus aspirin treatment. A total of 447 patients were put on either zofenopril (n=191) or ramipril (n=256) plus aspirin treatment.

Study design

A retrospective design was selected for this study, considering a two-sided Fisher's exact test with 80% power calculation and 5% error, with an expected minimum 1-year event rate of 15% and a maximum of 25% lost.

Cohorts

All patients received 325 mg aspirin (Zorprin-325; Bayer Healthcare, Leverkusen, Germany) for 2 days. After 2 days, patients received either 30 mg zofenopril (Zocardis® 30; Merck Sharp & Dohme, Haarlem, The Netherlands) b.i.d. plus 100 mg aspirin (Zorprin-100; Bayer Healthcare) q.d.[10] (ZF cohort, N=191) or 5 mg ramipril (Cardace; Sanofi Aventis, Paris, France) b.i.d. plus 100 mg aspirin q.d.[10] (RP cohort, N=256).

Hospitalisation for cardiovascular disease, cardiovascular events, haemodynamic parameters, concomitant cardiovascular drugs, non-cardiovascular events and mortality of patients during 1 year of treatment was recorded. Pathological and sonographic data were evaluated by experts in the field.

Statistical analysis

InStat v3.0 (GraphPad Software, Inc., San Diego, CA) was used for statistical analysis. An unpaired t-test for continuous data and Fisher's exact test for constant data were performed for statistical analysis. All results were considered significant at a 95% confidence level.

Results

Demographical and clinical conditions

A total of 18 patients (6 from the ZF cohort and 12 from the RP cohort) reported severe hypotension (systolic blood pressure <90 mmHg) and/or the other serious adverse effects. Therefore, treatment for these patients was discontinued, and they were switched to the standard treatment for acute myocardial infarction (as per current institute guidelines). The remaining patients (185 in the ZF cohort and 244 in the RP cohort) continued therapy (Figure 1). All patients were Killip class ⩾1. There was no statistical difference between the demographical and clinical characteristics of patients between cohorts at the start of treatment (p>0.05). The detailed demographical and clinical characteristics of patients at the start of the treatment are reported in Table 1.

Cardiovascular events

During 1 year of treatment, 47 (25%) patients in the ZF cohort and 97 (40%) patients in the RP cohort were hospitalised at least once due to cardiovascular disease (Figure 2). Patients who received ramipril were more likely to be hospitalised due to cardiovascular disease (p=0.002). In addition, during 1 year of treatment, three (2%) patients in the ZF cohort and 14 (6%) patients in the RP cohort died (Figure 3). Patients in the RP cohort had a higher risk of death (p=0.043). During 1 year of treatment, fatal (p=0.406) and non-fatal (p=0.336) cardiovascular events were the same between both cohorts, but there were fewer total cardiovascular events in the ZF cohort than in the RP cohort (Table 2).

Haemodynamic parameters

After 1 year of treatment, systolic blood pressure and diastolic blood pressure were reduced in both cohorts. N-terminal

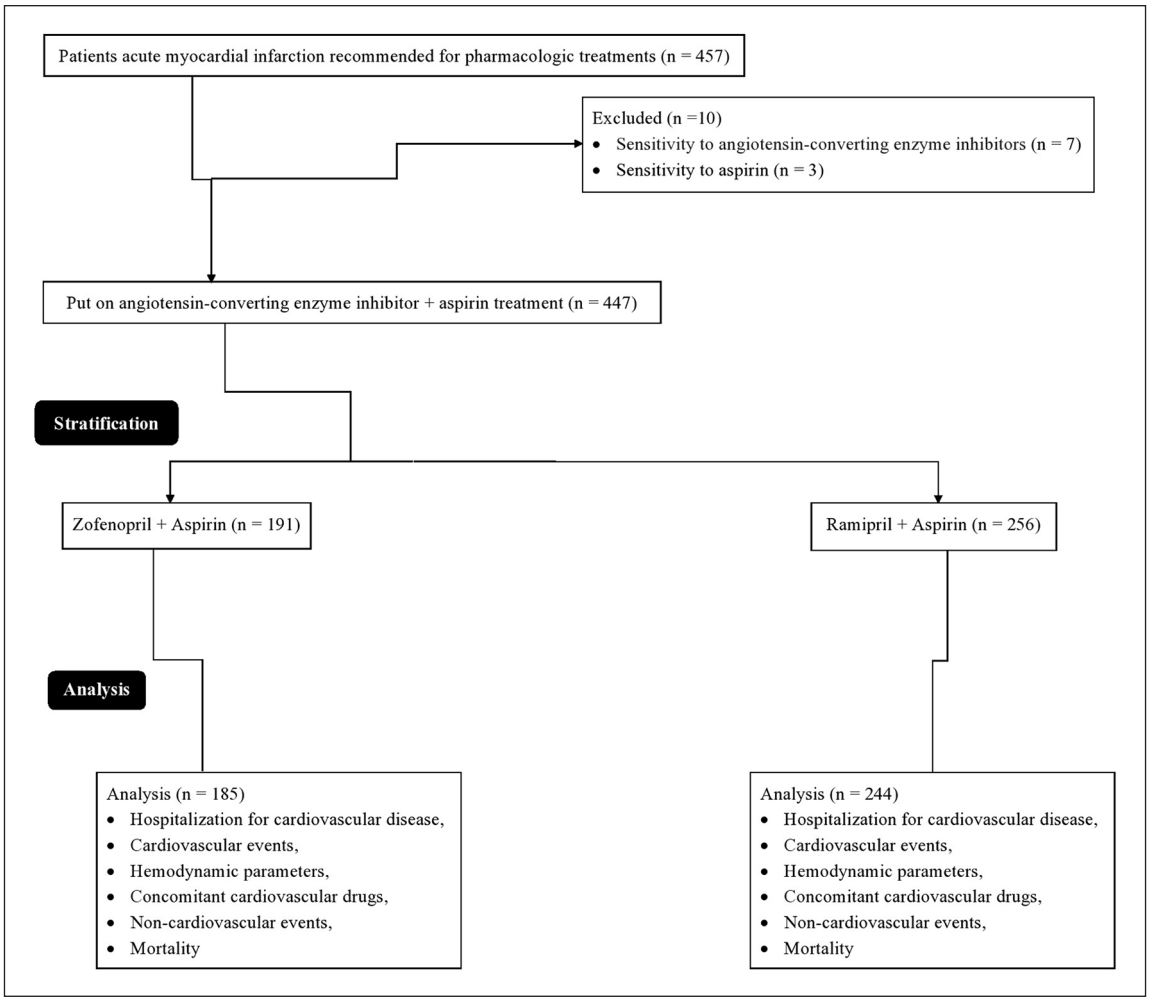

Figure 1. Flow diagram of the clinical practice.

pro-brain natriuretic peptide was also reduced in both cohorts. The left ventricle ejection fraction as improved by >5% in both cohorts. However, renal function deteriorated more. There were no significant differences between cohorts for the other haemodynamic parameters after 1 year of follow-up ($p>0.05$; Table 3).

Concomitant treatment

A total of 175 (95%) patients in the ZF cohort and 228 (93%) patients in the RP cohort were put on at least one concomitant cardiovascular drug during 1 year of treatment. Most patients were put on a lipid-lowering agent followed by beta-blockers and nitrates (Table 4).

Non-cardiovascular events

The most frequently reported non-vascular event was a dry cough. The detailed non-cardiovascular events during 1 year of treatment are reported in Table 5.

Discussion

This study reports fewer events of hospitalisation due to cardiovascular disease during 1 year of treatment for patients treated with zofenopril plus aspirin than for those treated with ramipril plus aspirin. These results agree with those of the SMILE-4 study.[5] Zofenopril is a sulphhydryl,[1] and it maintains its cardiovascular protective effect in the presence of aspirin, whereas ramipril does not maintain its cardiovascular protective effect in the presence of aspirin.[11] Zofenopril also has antioxidant properties in clinically achievable tissue concentrations.[11] Moreover, the area under the curve of plasma concentration of zofenopril/zofenoprilat is higher than ramipril/ramiprilat, leading to longer-lasting activity of zofenopril compared to ramipril.[12] The study recommends prescribing zofenopril instead of ramipril if cardiologists want to prescribe 100 mg aspirin for a longer period in the early phase of acute myocardial infarction.

The study reports reduced patient mortality due to cardiovascular disease during 1 year treatment in patients

Table 1. Demographical and clinical conditions of patients at the start of treatment.

Characteristics		Cohorts		Comparison between cohorts
		ZF cohort	RP cohort	(*p*-value)
		zofenopril+aspirin	ramipril+aspirin	
		(*N*=185)	(*N*=244)	
Age (years)	Minimum	25	27	0.054
	Maximum	62	65	
	M±*SD*	48.12±8.56	49.91±10.15	
Sex	Male	142 (77)	198 (81)	0.281
	Female	43 (23)	46 (19)	
Ethnicity	Han Chinese	168 (91)	221 (91)	0.989
	Mongolian	15 (8)	20 (8)	
	Tibetan	2 (1)	3 (1)	
Body mass index (kg/m^2)		24.98±1.89	25.02±1.88	0.828
Diabetes		47 (25)	49 (20)	0.199
Previous myocardial infarction		43 (23)	51 (21)	0.634
Co-morbidity	Atrial fibrillation	2 (1)	3 (1)	0.997
	Peripheral arterial occlusive disease	11 (6)	14 (6)	
	Angina pectoris	31 (17)	41 (17)	
	Congestive heart failure	15 (8)	21 (9)	
Prior percutaneous transluminal coronary angioplasty		14 (8)	19 (8)	0.988
Prior coronary artery bypass graft		5 (3)	6 (2)	0.995
Killip class	I	61 (33)	79 (32)	0.917
	II–IV	124 (67)	165 (68)	
Infarct location	Anterior	99 (53)	127 (52)	0.496
	Posterior	20 (11)	25 (10)	
	Lateral	19 (10)	24 (10)	
	Infero-posterior	42 (23)	52 (21)	
	Other	5 (3)	16 (7)	
Estimated glomerular filtration rate (mL/min)		71±21	72±17	0.586
Left ventricle ejection fraction (%)		42±2.9	42.5±2.4	0.052
Systolic blood pressure (mmHg)		135±15	132±22	0.112
Diastolic blood pressure (mmHg)		79±11	81±10	0.051
Heart rate (bpm)		73±11	72±9	0.301
N-terminal pro-brain natriuretic peptide (pG/mL)		135±21	139±23	0.065

Discrete data shown as numbers (frequency), and continuous data shown as *M*±*SD*.
Unpaired *t*-test for continuous data and Fisher's exact test for discrete data were performed for statistical analysis. A *p*-value of <0.05 was considered significant.

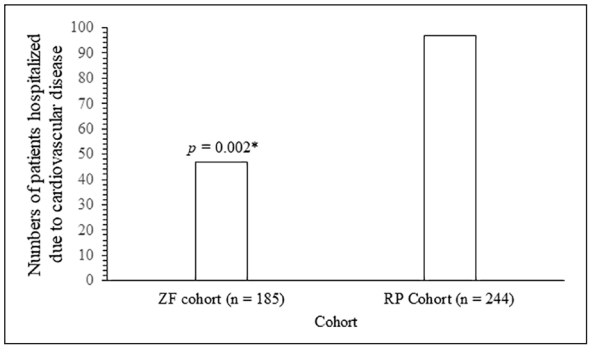

Figure 2. Hospitalisation due to cardiovascular disease during the 1 year of treatment. Data are presented as numbers. Fisher's exact test was performed for statistical analysis. A *p*-value of <0.05 was considered significant. *Significantly less than the RP cohort.

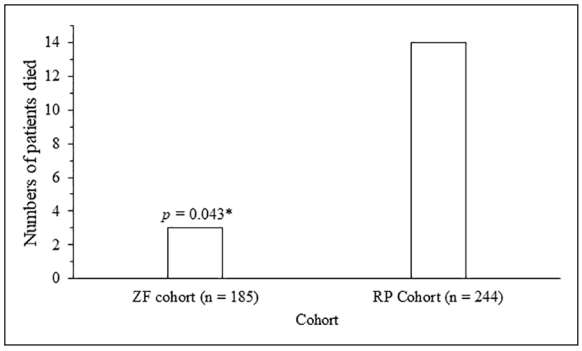

Figure 3. Patients who died during 1 year of treatment. Data are presented as numbers. Fisher's exact test was performed for statistical analysis. A *p*-value of <0.05 was considered significant. *Significantly less than the RP cohort.

Table 2. Fatal and non-fatal cardiovascular events during the 1 year of follow-up.

Type of events	Events	Cohorts		Comparison between cohorts
		ZF cohort	RP cohort	(*p*-value)
		zofenopril+aspirin	ramipril+aspirin	
		(*N*=185)	(*N*=244)	
Fatal	Congestive heart failure	2 (1)	4 (2)	0.406
	Cardiac rupture	2 (1)	4 (2)	
	Stroke	1 (1)	3 (1)	
	Angina pectoris	7 (4)	18 (7)	
	Decline in >15% left ventricular ejection fraction	8 (4)	21 (9)	
Non-fatal	Revascularisation	13 (6)	23 (9)	0.336
	Other causes related to cardiovascular for hospitalisation	16 (8)	24 (10)	
Total		47 (25)	97 (40)	0.002

Data shown as numbers (frequency). Fisher's exact test was performed for statistical analysis. A *p*-value of <0.05 was considered significant.

Table 3. Other haemodynamic parameters after 1 year of follow-up.

Parameters	Cohorts		Comparison between cohorts
	ZF cohort	RP cohort	(*p*-value)
	zofenopril+aspirin	ramipril+aspirin	
	(*N*=182)	(*N*=230)	
Systolic blood pressure (mmHg)	131±13	129±18	0.208
Diastolic blood pressure (mmHg)	76±10	78±11	0.057
N-terminal pro-brain natriuretic peptide (pG/mL)	139±20	137±22	0.341
Left ventricle ejection fraction (%)	48±5	47.1±5	0.071
Estimated glomerular filtration rate (mL/min)	77±23	76±19	0.629

Data shown as *M*±*SD*. Unpaired *t*-test performed for statistical analysis. A *p*-value of <0.05 was considered significant.

Table 4. Concomitant cardiovascular drugs during 1 year of follow-up.

Cardiovascular drugs	Cohorts		Comparison between cohorts
	ZF cohort	RP	(*p*-value)
	zofenopril+aspirin	ramipril+aspirin	
	(*N*=185)	(*N*=244)	
Lipid-lowering drugs	161 (87)	218 (89)	0.544
β-blockers	139 (75)	176 (72)	0.441
Nitrates	102 (55)	130 (53)	0.769
Diuretics	81 (44)	97 (40)	0.429
Calcium channel blockers	23 (12)	27 (11)	0.762
Anti-arrhythmics	12 (6)	21 (9)	0.468
Cardiac glycosides	6 (3)	6 (2)	0.769

Data shown as numbers (frequency). Fisher's exact test performed for statistical analysis. A *p*-value of <0.05 was considered significant.

treated with zofenopril plus aspirin compared with ramipril plus aspirin. These results do not agree with the SMILE-4 study.[5] The reasons for the contradictory results are the differences in the study populations, the retrospective non-randomised nature of the current study and different follow-up times between the current study and the

Table 5. Non-cardiovascular events during 1 year of follow-up.

Events	Cohorts		Comparison between cohorts
	ZF cohort	RP cohort	(*p*-value)
	zofenopril+aspirin	ramipril+aspirin	
	(*N*=185)	(*N*=244)	
Dry cough	128 (69)	217 (89)*	0.001
Asthenia	7 (4)	11 (5)	0.811
Vertigo	6 (3)	10 (4)	0.799
Gastrointestinal bleeding	3 (2)	7 (3)	0.526
Gastrointestinal ulcer	2 (1)	5 (2)	0.704
Mouth ulcer	12 (6)	21 (9)	0.469
Anaemia	7 (4)	21 (9)*	0.049
Toothache	7 (4)	12 (5)	0.642

Data shown as number (frequency). Fisher's exact test performed for statistical analysis. A *p*-value of <0.05 was considered significant.
*Significantly higher in the RP cohort.

SMILE-4 study.[5] However, the results of the current study for mortality do agree with the results for mortality after a 5-year follow-up period in the SMILE-4 study.[11] This study concludes that zofenopril may increase the active survival (patients with diseased condition) of patients with acute myocardial infarction by providing more sustained and favourable cardio-protective effects.

The most frequently reported non-vascular event was a dry cough, and fewer patients in the ZF cohort reported a dry cough (p=0.001) and anaemia (p=0.049) compared with the RP cohort. The results of the study agree with another retrospective study.[7] A dry cough is a typical side effect of angiotensin-converting enzyme inhibitors.[13] Zofenopril leads to a reduced accumulation of bradykinin and prostaglandins at the lung level.[8,14] In addition, ramipril shows airway inflammation, whereas zofenopril does not, especially in hypertensive patients.[12] Therefore, patients of the ZF cohort reported a lower incidence of dry cough compared to the RP cohort. Aspirin with ramipril has risk of developing anaemia.[7] The current finding suggested that zofenopril is a more appropriate treatment option in patients with acute myocardial infarction.

The major limitation of the study is that patients put on 325 mg/day aspirin for 2 days and then switched to 100 mg aspirin q.d. The dose of 100 mg/day spirin is a low dose to observe angiotensin-converting enzyme inhibitor–aspirin interaction,[5] but the safest dose for long-term use is $\leqslant$100 mg.[15,16] In addition, this was a retrospective study, and there was no control group. The study was performed for just 1 year, while the results of the SMILE study were evaluated after 5 years of follow-up. A daily dose of 60 mg zofenopril may lead to symptomatic or asymptomatic heart failure with long-term use.[11] Therefore, clinicians decided upon treatment for 1 year only and then switching to the other drug (data are not reported). It is possible to obtain equally beneficial effects from ramipril compared to zofenopril if given along with a cyclooxygenase inhibitor other than aspirin, but the study did not use drugs other than aspirin in the RP cohort (this is our future study).

Conclusions

Zofenopril plus 100 mg aspirin may have result in reduced mortality, fewer hospitalisation events due to cardiovascular disease and a reduced incidence of dry cough and anaemia compared to ramipril plus 100 mg aspirin. The study recommends zofenopril as an angiotensin-converting enzyme inhibitor if cardiologists want to prescribe 100 mg aspirin for a longer period in patients in the early phase of acute myocardial infarction and systolic dysfunction. A long-term trial of 60 mg/day zofenopril plus 100 mg/day aspirin compared with 10 mg/day ramipril plus cyclooxygenase inhibitor (the other than aspirin) is required to assess their performance for better cardio-protective action.

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Supplemental material

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