Original Article

An investigation of the effectiveness of oral cyclosporine on perioperative myocardial injury (PMI) in patients who undergo the surgical procedure of coronary artery bypass graft (CABG): A Randomized Controlled Clinical Trial

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Abstract

Background: Routine clinical strategies for the prevention of myocardial infarction (MI) during the surgical procedure of CABG include cross-clamp fibrillation and cardioplegia have failed to decrease the risk of perioperative myocardial injury (PMI). Cyclosporine-A (CsA) might be able to prevent mitochondrial dysfunction and PMI. **Methods:** In the present clinical trial, patients were divided into two groups (Case receive 2.5 mg/kg CsA and Control receive a placebo) randomly. Moreover, patients were controlled by placebo through a double-blind, single-center trial 4-12 h before anesthesia. Perioperative blood tests include bilirubin, complete blood count, the amount of hemoglobin in whole blood, liver transaminases, and glomerular filtration rate (GFR). Blood samples were taken before surgery and at 24, 48, and 72 h after surgery and serum Troponin-I and CK-MB levels were determined in all blood samples using ELISA. **Results:** There were no significant differences between the two groups in the results of routine pre-operative blood results, intraoperative variables, and baseline characteristics ($P > 0.05$). There are significant correlations between cross clamp time and cTnI and CKMB levels in patients taking CsA. In patients with both diabetes and hypertension, postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24, 48, and 72 h ($P < 0.05$). Moreover, patients with old MI, both postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24 h and 48 h ($P < 0.05$). **Conclusions:** In patients with a long cross-clamping period, using an oral CSA single dose before conducting CABG surgery, the risk of PMI could be decreased. Also, oral CsA has protective effect for CABG in diabetic patients with hypertension.

Keywords: CABG, clinical trial, Cyclosporine A, perioperative myocardial injury

Introduction

In developed countries, one of the main reasons for cardiovascular diseases that cause death is coronary heart disease (CHD). In a similar way, in developing countries, CHD could cause such diseases that are difficult to treat and impose high costs for individuals and society.[1-3] Nearly in all patients with multivessel coronary artery disease, one of the most effective treatment options for revascularization is CABG surgery.[4] In these patients, conducting routine CABG surgery decreases the perioperative risk of surgery. Anyway, recently, it's proved that any increase in the

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prevalence of hypertension, and diabetes, and the aging population increases the rate of perioperative risks, perioperative myocardial injury (PMI), and worse clinical symptoms. The most important reasons are related to the cardiomyocyte damages caused by acute ischemia-reperfusion injury (IRI), CPB induced inflammatory injury and direct myocardial damage due to the surgery and coronary micro-embolization.[5,6] Two main strategies of myocardial protection are blood cardioplegia and cross-clamp fibrillation that unfortunately have not fully succeeded in reducing PMI risks. Consequently, aiming to improve clinical outcomes, there is a high need for novel therapeutic strategies for restricting PMI risks and preserving the normal left ventricular ejection fraction (LVEF).[5] Additionally, in patients undergoing CABG surgery, the serum levels of cardiac enzymes such as cardiac troponin T (cTnT), cardiac troponin I (cTnI), and creatine kinase-MB (CK-MB) have a significant role in determining the magnitude of PMI risks and also associated with worse short and long-term prognosis among them.[7,8] As demonstrated by Venugopal *et al.*,[5] the opening of the mitochondrial permeability transition pore (MPTP) could cause mitochondrial dysfunction and consequent cardiomyocyte death during acute IRI. Based on some clinical and experimental studies, MI limitation and MPTP opening could be prevented by Cyclosporin A (CsA) at the onset of reperfusion.[9-13] The current randomized controlled clinical trial is mainly aimed to determine the capability of oral CsA in decreasing perioperative myocardial injuries in patients who undergo CABG surgery.

Methods

Study design and participants

A randomized double-blind placebo-control (RDBPC) single-center trial was conducted at the Golestan Hospital of Ahvaz University of Medical Sciences, Ahwaz, Iran. The protocol of this study that was approved by the Ethics Committees of Ahvaz University of Medical Sciences and Golestan Hospital was implemented according to the Declaration of Helsinki (DoH). The recruiting process was carried out only amongst consecutive adults who were attended the hospital for CABG surgery from February 2016 and February 2017. All the participants were informed about the trial aim, then their written consent was obtained. After that their medical history, laboratory analyses, and physical examination were recorded. The exclusion criteria of the study were; patients older than 85 years, patients with liver disease, unstable angina, myocardial infarction within two weeks of screening, patients with immunocompromised disorders, elevated liver enzymes (the enzyme of alanine aminotransferase (ALT) more than three times the upper reference limit), and kidney failure (glomerular filtration rate (GFR) of less than 45 mL/min/m2). Moreover, patients who take derivatives of xanthine or dipyridamole and glibenclamide or nicorandil were excluded from the study for their role in interfering with preconditioning.

Randomization and masking

The process of randomized assignment of patients (1:1) to pretreatment with either placebo or CsA was performed through a randomization sequence generated by an independent computer (Department of Medicine, Ahvaz University of Medical Sciences, Ahvaz, Iran) and opaque numbered envelopes were used for the allocation of blinded treatment by one of the investigators. Aiming to allocate treatments, all the staff, statisticians, and patients were equipped with masks. CsA capsules were over encapsulated under manufacturing practice conditions to obtain masking.

Procedures

The process of patient's allocation was carried out randomly for receiving 2.5 mg/kg placebo of CsA, 4-12 h before anesthesia. Normal general anesthesia induction and maintenance was performed on all patients. The results of routine preoperative blood tests included bilirubin testing, liver transaminases, GFR, complete blood count, and measurements of hemoglobin. Blood samples were taken before surgery at specific time periods of 24, 48, and 72 hours after surgery, then the serum Troponin-I (RapiCard™ InstaTest Troponin I kit - Woodland Hills, California, USA) and CK-MB (AccuDiag™ CK-MB ELISA Kit- Woodland Hills, California, USA) levels were determined in all blood samples using ELISA test according to manufacturer's protocol.

Statistical analysis

This study was aimed to assess the role of oral cyclosporine in the protection of patients with myocardial injuries through assessing serum CK-MB and cTnI as two main indicators of the MI magnitude. Statistical analysis was carried out with (SPSS) version 22. To compare continuous and categorical variables, the T-test and $\chi 2$ tests were administered, respectively. The achieved information is presented as mean ± SD or SEM. The significance threshold was determined statistically as $P < 0.05$ and all reported P values were two-tailed and the sample size was determined based on previous studies[13] and using Med-Calc software with an error of 5% and the power of 92%, which led to a total of 46 patients.

Results

Primarily, a total of 88 patients undergoing CAPG were found to be eligible for recruitment to the study. However, 28 patients dropped out for meeting exclusion criteria. As could be seen from Figure 1, in the final step, 60 patients were chosen randomly for treatment (for each of placebo and CsA options, 30 patients were selected). For comprehensive analysis of quantitative and qualitative variables, two separate tables were drawn. Based on the data presented in Tables 1 and 2, between these two groups, there were no significant differences between the two groups in the results of routine pre-operative blood results, intraoperative variables, and baseline characteristics. After releasing the aortic cross-clamp, the serum levels of CsA in 12 patients were assessed immediately, and it declared that it was in the therapeutic range (531 ± 154 ng/ml).

Mean comparison of cTnI and CKMB before surgery and on the 24, 48, and 72 h postsurgical day in drug and placebo

Table 1: Preoperative and postoperative qualitative variables

Variable	Group	Standard deviation	Mean	*t*-statistics	*P*
Age	Drug	9.47	60.57	-0.014	0.989
	Placebo	9.00	60.60		
BMI	Drug	5.46	26.19	-0.592	0.556
	Placebo	3.12	26.87		
GFR	Drug	20.87	86.54	0.434	0.666
	Placebo	22.61	84.10		
Preoperative EF	Drug	9.51	46.05	0.363	0.718
	Placebo	8.80	45.00		
Postoperative EF	Drug	8.81	44.64	0.432	0.667
	Placebo	8.40	43.67		
Preoperative Hb	Drug	2.01	12.62	-0.193	0.848
	Placebo	1.86	12.72		
Postoperative Hb	Drug	1.09	9.64	0.632	0.530
	Placebo	1.32	9.44		
Preoperative WBC	Drug	2568.60	8023	-0.941	0.351
	Placebo	3457.57	8763		
Postoperative WBC	Drug	4756.91	12906	0.411	0.683
	Placebo	5047.82	12386		
Preoperative BUN	Drug	5.37	17.37	-0.806	0.423
	Placebo	7.85	18.77		
Postoperative BUN	Drug	8.36	20.97	-0.033	0.974
	Placebo	7.12	21.03		
Preoperative CV	Drug	0.18	0.89	-0.884	0.380
	Placebo	0.20	0.94		
Postoperative CV	Drug	0.29	0.95	-1.009	0.317
	Placebo	0.25	1.02		
Preoperative BILL	Drug	0.41	0.89	1.110	0.271
	Placebo	0.29	0.79		
Postoperative BILL	Drug	0.29	0.93	1.074	0.287
	Placebo	0.20	0.86		
Preoperative ALP	Drug	7.98	22.83	-1.362	0.178
	Placebo	11.59	26.33		
Postoperative ALP	Drug	7.56	23.70	-0.684	0.496
	Placebo	12.58	25.53		
Bypass time	Drug	28.57	80.68	1.329	0.190
	Placebo	16.85	72.11		
Cross Clamp Time	Drug	16.61	36.28	0.600	0.551
	Placebo	14.79	33.67		
Operation Time	Drug	55.14	196.67	0.622	0.536
	Placebo	33.52	189.33		
Preoperative AST	Drug	18.09	28.63	-0.420	0.676
	Placebo	19.36	30.67		
Postoperative AST	Drug	18.26	30.77	0.269	0.789
	Placebo	18.25	29.50		

groups is shown in Table 3. Serum CKMB and cTnI levels on the first postsurgical day were at their pick level in both patient groups, showing PMI occurrence during the surgery. The mean comparison of both CKMB and cTnI levels in postsurgical days show a more decrease in patients receiving oral CsA than placebo group. However, the results are not statistically significant.

Ameliorative correlation between reduction of both Troponin and CKMB with operation time in drug group was shown in Tables 4 and 5. We also found that there are significant

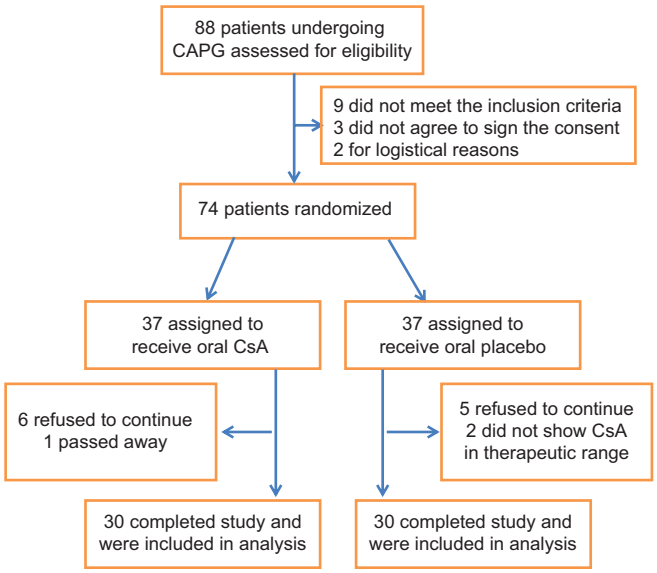

Figure 1: Consort diagram

correlations between cross clamp time and cTnI and CKMB levels in patients taking CsA [Tables 4 and 5]. Results also indicate that in patients with diabetes and hypertension, postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24, 48, and 72 h [Table 6]. Moreover, in patients with MI history, both postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24 h and 48 h [Table 6].

Discussion

Direct manipulation of heart tissues, reperfusion, cardiopulmonary bypass, and micro-embolization of coronary arteries are common known causes of myocardial injuries during CAPG.[5,14,15] Several studies have shown that impaired mitochondrial permeability due to opening of mitochondrial transition pore (MPTP), is a determining factor for cardiomyocytes death in acute cardiac IRI.[16,17]

Studies on animal models have reported that CsA reduces the MI size.[9-11] Ex vivo studies on human heart tissue also demonstrated that CsA has cardio protective effects following IRI stimulation in isolated human atrial trabecular tissue.[18] As demonstrated by Piot *et al.*, in STEMI patients, MI size could be limited using a single intravenous bolus of cyclosporine about 10 minutes before the PPCI procedure.

The most recent update of clinical trials in this regard was carried out by Hausenloy *et al.* who demonstrated that using a single dose of intravenous CsA before conducting the CABG procedure could decrease PMI in higher-risk patients with longer time of operation, cardiopulmonary bypass, and aortic cross-clamp time. In this clinical trial, the effect of oral CsA in patients undergoing CABG surgery was investigated. The data achieved from the present study demonstrated that using a single dose of oral CsA (2.5 mg/kg) before the surgery,

Table 2: Preoperative quantitative variables

Variables	Placebo (*n*=30)	CsA (*n*=30)	*P*
Male, Sex	20	21	0.781
Angina	8	10	0.573
DLP	22	24	0.542
DM	11	13	0.598
Hypertension	21	24	0.571
Stroke history	3	4	0.688
PAD	1	1	1.000
Family history	18	16	0.301
MI history	11	11	1.000
Current Smoker	8	7	0.766
Aritmia history	1	1	1.000
Angina	8	10	0.573
Thyroid disorders	1	2	0.554
CABG	28	29	0.554
Defibrillation	5	3	0.448
Inotrope	6	6	1.000
Pump off	3	2	0.640
Lima used	27	25	0.486

Table 3: Mean comparison of Troponin and Also CKMB in different times between drug and placebo groups

Variable	Time	Groups	Standard deviation	Mean	*t*-statistics	*P*
Troponin	24 h before	Drug	0.33	1.23	0.378	0.707
		Placebo	0.32	1.20		
	24 h after	Drug	0.69	2.04	0.136	0.893
		Placebo	1.13	2.08		
	48 h after	Drug	0.61	1.84	0.094	0.926
		Placebo	0.92	1.81		
	72 h	Drug	0.53	1.67	0.694	0.491
		Placebo	1.04	1.83		
CKMB	24 h before	Drug	4.65	17.32	-0.034	0.973
		Placebo	6.08	17.37		
	24 h after	Drug	8.67	28.78	-0.718	0.476
		Placebo	8.85	30.48		
	48 h after	Drug	7.78	26.25	-1.255	0.215
		Placebo	8.45	29.00		
	72 h	Drug	8.26	24.46	-1.234	0.222
		Placebo	9.61	27.44		

reduces the extent of PMI (measured by serum cTnI and CKMB levels) 24, 48, and 72 h after the surgery compared with placebo. Moreover, our data also show that CsA is significantly correlated with less myocardial injury during long operation and cross clamp time.

Clough *et al.* found 64.3% prevalence rate of comorbidity in a study with 27,239 patients with hypertension undergone CABG, showing significant association with increased risk of death after coronary artery bypass graft surgery.[19] Our results indicate that administration of oral CsA in patients with both diabetes and hypertension significantly reduces post-operative levels of both cTnI and CKMB that might be further protective, improve the surgery outcomes and morbidity rate in these patients.

In their study Bottle *et al.*[20] investigating the preoperative risk factors in patients with a prior myocardial infarction who undergo CABG procedure. The declared that there is a close association between perioperative risks and myocardial infarction. In present study, we found that postoperative levels of both cTnI and CKMB patients receiving oral CsA are significantly reduced.

Conclusion

In conclusion, considering the limitations such as the relatively small sample size, lack of information about the major adverse cardiovascular events (MACE), and normal LVEF, we demonstrated that using a single dose of oral CsA before conducting the CABG procedure could effectively decrease PMI risks in patients with long cross-clamp and operation time. We also indicated that oral CsA has protective effect for CABG in diabetic patients with hypertension.

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Table 4: Correlation between operation time, cross clamp time and CKMB levels in Tow groups

Group	Variables	Indexes	CKMB Ratio 24 h after to 24 before	CKMB Ratio 48 h to 24 h	CKMB Ratio 72 h to 48 h	CKMB Ratio 72 h to 24 h
drug group	Operation Time	Correlation Coefficient	0.302*	-0.290*	-0.274*	-0.343*
		P	0.025	0.032	0.043	0.010
		Number	30	30	30	30
	cross clamp time	Correlation Coefficient	0.302*	-0.274*	0.292	-0.553 *
		P	0.025	0.043	0.034	0.02
		Number	30	30	30	30
Placebo group	Operation Time	Correlation Coefficient	0.216	-0.170	-0.129	-0.256
		P	0.113	0.215	0.349	0.059
		Number	30	30	30	30
	cross clamp time	Correlation Coefficient	0.216	-0.170	-0.129	-0.266
		P	0.113	0.215	0.349	0.175
		Number	30	30	30	30

Table 5: Correlation between operation time, cross clamp time and Troponin levels in Tow groups

Group	Variables	Indexes	Troponin Ratio 24 h after to 24 before	Troponin Ratio 48 h to 24 h	Troponin Ratio 72 h to 48 h	Troponin Ratio 72 h to 24 h
drug group	Operation Time	Correlation Coefficient	0.435*	-0.383*	-0.255*	-0.530**
		P	0.016	0.036	0.049	<0.001
		Number	30	30	30	354
	cross clamp time	Correlation Coefficient	0.463*	-0.383*	-0.290*	-0.586**
		P	0.010	0.036	0.032	0.001
		Number	30	30	30	30
placebo group	Operation Time	Correlation Coefficient	0.220	-0.187	-0.103	-0.259
		P	0.107	0.172	0.053	0.056
		Number	30	30	30	30
	cross clamp time	Correlation Coefficient	0.119	-0.190	-0.119	-0.267
		P	0.532	0.314	0.532	0.155
		Number	30	30	30	30

Table 6: Mean comparison of Troponin levels and CKMB in diabetic patients with hypertension and Also MI History patients in two groups

Variable	Co-Exist disease	Time	Group	Number	Mean	Standard deviation	*P*
Troponin	diabetic patients with hypertension	Before operation	Drug	24	1.18	0.35	0.812
			Placebo	21	1.21	0.36	
		24 h	Drug	24	1.99	0.75	0.038*
			Placebo	21	2.36	0.53	
		48 h	Drug	24	1.67	0.38	0.037*
			Placebo	21	2.16	0.79	
		72 h	Drug	24	1.62	0.41	0.009*
			Placebo	21	2.07	0.46	
	MI history	Before operation	Drug	11	16.70	5.04	0.579
			Placebo	11	16.60	4.08	
		24 h	Drug	11	23.70	3.79	0.043*
			Placebo	11	27.80	2.00	
		48 h	Drug	11	21.00	8.82	0.029*
			Placebo	11	25.80	3.27	
		72 h	Drug	11	19.60	5.04	0.205
			Placebo	11	24.00	4.08	
CKMB	diabetic patients with hypertension	Before operation	Drug	24	17.32	4.03	0.932
			Placebo	21	17.28	5.15	
		24 h	Drug	24	29.59	7.67	0.031*
			Placebo	21	34.00	5.34	
		48 h	Drug	24	26.72	7.18	0.023*
			Placebo	21	32.10	6.34	
		72 h	Drug	24	24.32	7.79	0.005*
			Placebo	21	30.29	7.08	
	MI history	Before operation	Drug	11	16.70	5.04	0.579
			Placebo	11	16.60	4.08	
		24 h	Drug	11	23.70	3.79	0.043*
			Placebo	11	27.80	2.00	
		48 h	Drug	11	21.00	8.82	0.029*
			Placebo	11	25.80	3.27	
		72 h	Drug	11	19.60	5.04	0.205
			Placebo	11	24.00	4.08	

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35:72-115.
2. Allen NB, Zhao L, Liu L, Daviglus M, Liu K, Fries J, *et al.* Favorable cardiovascular health, compression of morbidity, and healthcare costs. Circulation 2017;135:1693-701.
3. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: A historical perspective. Lancet 2014;383:999-1008.
4. Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: Meta-analysis of randomized clinical trials of the arterial grafting and stenting era. JAMA Intern Med 2014;174:223-30.
5. Venugopal V, Ludman A, Yellon DM, Hausenloy DJ. 'Conditioning' the heart during surgery. Eur J Cardiothorac Surg 2009;35:977-87.
6. Thielmann M, Dörge H, Martin C, Belosjorow S, Schwanke U, van de Sand A, *et al.* Myocardial dysfunction with coronary microembolization. Circ Res 2002;90:807-13.
7. Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G, *et al.* Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. Circulation 2006;114:1468-75.
8. Fellahi J-L, Gué X, Richomme X, Monier E, Guillou L, Riou B. Short-and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. Anesthesiology 2003;99:270-4.
9. Hausenloy DJ, Maddock HL, Baxter GF, Yellon DM. Inhibiting mitochondrial permeability transition pore opening: A new paradigm for myocardial preconditioning? Cardiovasc Res 2002;55:534-43.
10. Hausenloy DJ, Duchen MR, Yellon DM. Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia–reperfusion injury. Cardiovasc Res 2003;60:617-25.
11. Argaud L, Gateau-Roesch O, Muntean D, Chalabreysse L, Loufouat J, Robert D, *et al.* Specific inhibition of the mitochondrial permeability transition prevents lethal reperfusion injury. J Mol Cell Cardiol 2005;38:367-74.
12. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, *et al.* Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008;359:473-81.
13. Hausenloy DJ, Boston-Griffiths E, Yellon D. Cyclosporin A and cardioprotection: From investigative tool to therapeutic agent. Br J Pharmacol 2012;165:1235-45.
14. Skyschally A, Schulz R, Erbel R, Heusch G. Reduced coronary and inotropic reserves with coronary microembolization. Am J Physiol Heart Circ Physiol 2002;282:H611-4.
15. Marzilli M, Huqi A. Cardioprotective therapy in reperfusion injury: Lessons from the European Myocardial Infarction Project—Free Radicals (EMIP-FR). Heart Metab 2010;46:35-7.
16. Leung AW, Halestrap AP. Recent progress in elucidating the molecular mechanism of the mitochondrial permeability transition pore. Biochim Biophys Acta (BBA)-Bioenergetics2008;1777:946-52.
17. Hausenloy DJ, Yellon DM. The mitochondrial permeability transition pore: Its fundamental role in mediating cell death during ischaemia and reperfusion. Academic Press; 2003.
18. Shanmuganathan S, Hausenloy DJ, Duchen MR, Yellon DM. Mitochondrial permeability transition pore as a target for cardioprotection in the human heart. Am J Physiol Heart Circ Physiol 2005;289:H237-42.
19. Clough RA, Leavitt BJ, Morton JR, Plume SK, Hernandez F, Nugent W, *et al.* The effect of comorbid illness on mortality outcomes in cardiac surgery. Arch Surg 2002;137:428-32; discussion 32-3.
20. Bottle A, Mozid A, Grocott HP, Walters MR, Lees KR, Aylin P, *et al.* Preoperative risk factors in 10 418 patients with prior myocardial infarction and 5241 patients with prior unstable angina undergoing elective coronary artery bypass graft surgery. Br J Anaesth 2013;111:417-23.