International Journal of Medical and Health Sciences

Journal Home Page: http://www.ijmhrs.net ISSN:2277-4505

Original article

Effect of Pharmacological treatment on cardiac biomarkers in patients with acute coronary syndrome of non–ST segment elevation with Type-2 diabetes

Agustín N. JOISON[1], and Gustavo BAIARDI[2]*

[1]Faculty of Chemical Sciences, Catholic University of Córdoba, Córdoba, Argentina.

Avenida Armada Argentina 3555 X5016DHK Córdoba, Argentina,

[2]Institute of Biological and Technological Research (IIBYT-CONICET), National University of Córdoba, Faculty of Chemical Sciences, Catholic University of Córdoba, Córdoba, Argentina, Avenida Armada Argentina 3555 X5016DHK Córdoba, Argentina

ABSTRACT

Background: The acute coronary syndrome is a consequence of coronary artery disease. Creatine Kinase MB is a cardiac biochemical marker used in the diagnosis and risk stratification of patients. The diabetes is a pathology associated to acute coronary syndrome non–ST segment elevation that change the cardiac conditions, in this sense, our objective was to evaluate the modifications of cardiac biomarkers values in diabetic patients. **Materials and methods**: A retrospective study included 155 patients of both sexes, ages ranging from 31 to 92 years old, admitted to the coronary unit of the "Reina Fabiola" Clinic, Córdoba, Argentina was performed in the period 2014-2015. Body mass index, time consultation pain, plasmatic Creatine Kinase isoenzyme MB activity and Troponin I levels were measured. The patients were stratified into two groups: without cardiovascular risk pathologies (Control group), n = 7; and with only type II diabetes, n = 64 treated with therapeutic doses of metformin (n= 37), and glibenclamide plus glizipide (n= 27). **Results:** cTnI levels were lower in both pharmacological treatments at 12 hrs when the values in control reach the highest. Similarly, CK-MB activity was lower at 8 hrs in both treatments; however at 12 hrs these values were lower only with metformin but not in glibenclamide plus glizipide treatment. These results could be showing an interaction between diabetes and pharmacological treatment upon the biomarkers values. **Conclusion:** The use of hypoglycemic drugs and the glycometabolic state are conditions that could modify CK-MB and cTnI release/clearance balance at 8 and 12 hrs after admission to the coronary unit.

KEYWORDS: Coronary syndrome; Creatine Kinase MB; Diabetes; Troponin I.

INTRODUCTION

The acute coronary syndrome (ACS) is a consequence of coronary artery disease, characterized by myocardial ischemia and reduction of the artery diameter with inflammation of endothelial wall cell. The ACS can be caused by unstable angina with non–ST segment elevation (NSTEMI) or myocardial infarction with ST-segment elevation (STEMI) [1]. Cardiac molecular markers are used in the diagnosis and risk stratification of patients with chest pain and suspected ACS. Creatine Kinase-MB (CK-MB) values are important to define unstable angina or NSTEMI, even in the absence of electrocardiogram (ECG) changes [2, 3]. Actually CK-MB and troponin I (cTnI) are used as markers of myocardial injury cardiospecific for correct diagnosis [4]. cTnI is one of predictive markers more sensitive used in the stratification of necrosis myocardial and the subsequent therapeutic efficacy [5]. In pathologies such as decompensated diabetes several cardiac markers including cTnI are elevated in patients without ACS [6].

There are factors that influence the risk of coronary artery disease such as age, sex, family history and ethnicity. But there are risk factors that can be modified, including elevated levels of serum cholesterol, LDL cholesterol, triglycerides, lower levels of HDL cholesterol, diabetes type II, smoking, obesity, sedentary lifestyle, hypertension and stress [7].

Diabetes is a risk factor for cardiovascular disease and according to epidemiological data death in the diabetic population caused by cardiovascular disease reached 65%. This disease has one of the highest morbidity and mortality levels and the prevalence of NSTEMI increases to double [8], although the incidence of ACS can be decreased with preventive treatments [9].

Studies associating factors like angiogenic changes, oxidative stress and diabetes are important when evaluating cardiac tissue response to ischemic injury. In diabetic patients with unstable angina, the expression of hypoxia-inducible factor-1α (HIF) and vascular endothelial growth factor (VEGF) are reduced in parallel with lower levels of nitric oxide synthase (NOS) activity. All these together, lead to an increased oxidative stress worsening the angiogenesis process [10]. Diabetic patients have less collateral vessels and this condition causes a more severe injury during coronary ischemia [11].

There are many contradictions regarding the response of the diabetic heart to ischemia. In this sense, there are data suggesting an increased vulnerability of the diabetic myocardium to the ischemic injury [12]. The diabetes as pathology associated to NSTEMI could change the physiological cardiac conditions; in this sense our objective was to evaluate the effect of pharmacological treatment on cardiac biomarkers in patients with acute coronary syndrome of non–ST segment elevation with Type-2 diabetes.

MATERIALS AND METHODS

A retrospective study included 155 patients of both sexes, ages ranging from 31 to 92 years old, and admitted to the coronary unit of the "Reina Fabiola" Clinic, Córdoba, Argentina with an ACS diagnosis in the period 2014-2015.

The patients were separated into two groups: without cardiovascular risk pathologies (Control group), n = 7; and only with type II diabetes, n = 64 treated with therapeutic doses of metformin (n= 37), and glibenclamide plus glizipide (n= 27). Seventy-four patients with other associated pathologies and five diabetic patients treated with another drugs were excluded from the study.

An uncorrected weight was estimated using the body mass index (BMI) measured by height (in meters) and weigh (Kg) relation (weigh/height^2). Time consultation pain (TCP) was taken into account: the time (in hours) elapsed from the onset of chest pain until the inquiry to the coronary unit. Plasmatic CK-MB activity was measured by the kinetic method Biosystem ®. Plasmatic cTnI levels were measured by Enzyme Linked Fluorescent Assay (ELFA) Biomeriux (France). The amount of enzyme required to transform a µmol of substrate per minute was considered as an international unit (IU). The normal reference values of the CK-MB were considered less than 25 IU [13]. The normal reference value of cTnI was considered ≤ 0.01 ng/ml. To study the kinetics of markers, the values were obtained at admission to the coronary unit (0 hs), after 8, 12 and 24 hours for CK-MB and 0, 8, 12, 24 and 36 for cTnI; thereafter the patients were submitted to coronary angiography.

Multiple correlation analysis and ANOVA II followed by the Sidak's post hoc test, and Chi square were performed. The values of $p < 0.05$ were considered significant.

Limitations of this study

Our court of patients as control group has low number of them because they have acute coronary syndrome without cardiovascular risk pathologies. This condition is uncommon, but allows to discard the effects of other frequent pathologies in patients with NSTEMI.

Ethical statement

The current study protocol was approved by the Bioethical Committee of the "Reina Fabiola" Clinic and the Catholic University of Córdoba. All participants were enrolled upon signing written informed consent. All governmental and institutional regulations regarding the ethical involvement of human volunteers in clinical studies were respected.

RESULTS

Positive correlation was found between CK-MB activity in the plasma and TPC at 12 hours (Table 1). No differences were found between sexes and biomarkers in all studied times (Figure 1 A, B).

Table 1: Pearson correlation between CK- MB, cTnI and age, BMI, TPC at the time of admission to the coronary care unit (0 hours), 8, 12, 24 and 36 hours

Hours		0	8	12	24	36
CK-MB(UI/L)	Age	0.09	-0,12	-0,027	0,03	
	BMI	0,03	-0,07	-0.08	-0,16	
	TPC	0,03	-0,003	0,25 †	0,20	
cTnI (µg/ml)	Age	-0.01	-0,03	-0,07	-0,008	-0.14
	BMI	0.03	-0.06	-0.16	0.20	-0.05
	TPC	0.06	-0.14	0.03	0.01	0.12

BMI (body mass index), TPC (time consultation pain). †p <0.05

Figure 1: Values of the plasma CK-MB (Panel A) and cTnI levels (panel B) of both sexes studied at the time of admission to the coronary care unit (0 hours), and after 8, 12, 24 and 36 hours. The values represent the mean ± SEM.

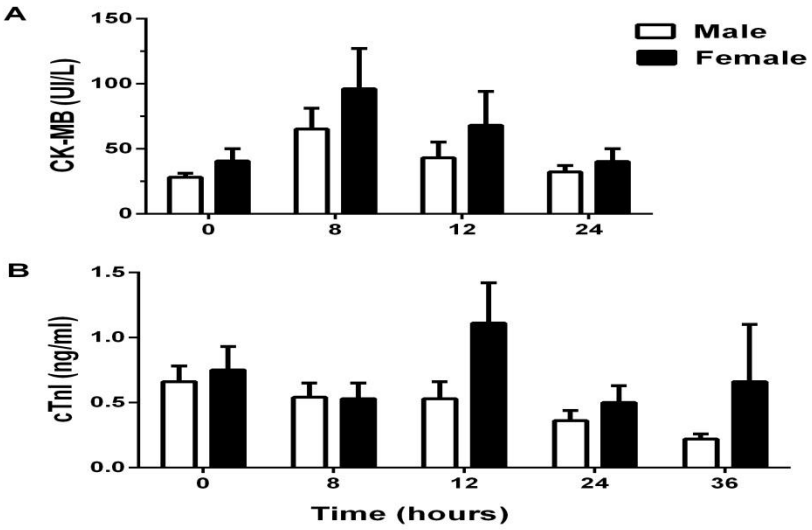


Table 2: Percent of patients who have high or low values CK- MB and cTnI respect to the references values in control and diabetes groups at the time of admission to the coronary care unit (0 hours), 8, 12, 24 and 36 hours.

	Time (hours)	0	8	12	24	36
	CK-MB					
Control	≤ 25UI/L	71.4	42.8	57.1	33.3	-
	> 25UI/L	28.5	57.1	42.8	66.6	-
Diabetes	≤ 25UI/L	69.5	80.9	84.4	75.7	-
	> 25UI/L	28.9	19.0	15.5	24.2	-
		P= 0.6	P<0.05	P=0.1	P=0.1	
	cTnI					
Control	≤0,01ng/ml	14.2	14.2	14.2	50.0	33.3
	>0,01ng/ml	85.7	85.7	85.7	50.0	66.6
Diabetes	≤0,01ng/ml	53.6	55.2	60.3	50.0	73.3
	>0,01ng/ml	44.7	46.3	39.6	50.0	26.6
		P=0.5	P=0.06	P<0.05	P=0.6	P=0.07

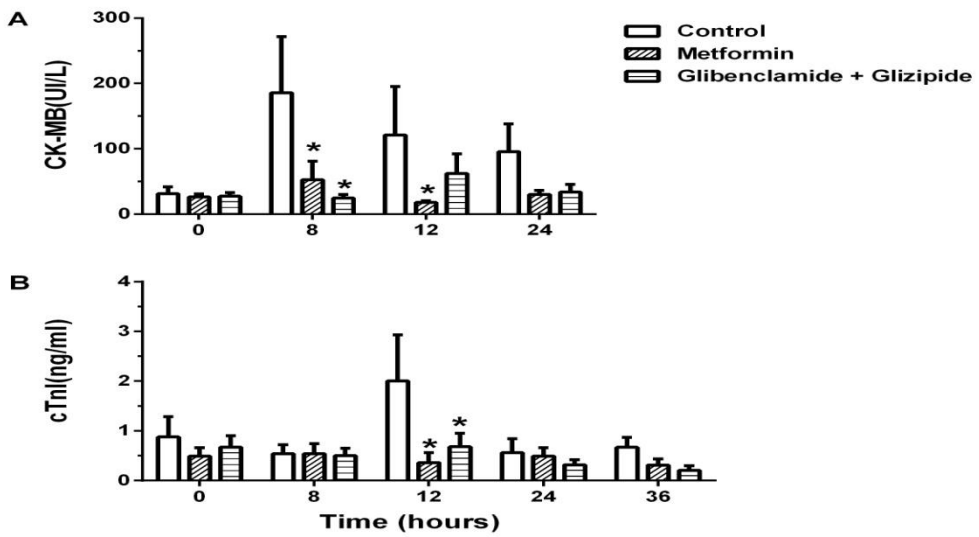
P < 0.05 diabetes vs control group

The percentage of patients that have high /low ratio values of CK-MB (>25UI/L)/(≤ 25UI/L) and cTnI (>0.01ng/ml)/(≤ 0.01 ng/ml) are lower in diabetic group at 8 hs; (chi^2 = 5. 19) p < 0.05 and 12 hs (chi^2 = 5. 36) p < 0.05 respectively; (Table 2). When diabetics patients were separated in metformin and glibenclamide plus glizipide treatment, the analysis of CK-MB activity two-way ANOVA showed significant differences in treatment condition, F (2, 218) = 8.08; P< 0.05.

Multiple comparisons Sidak's post hoc test indicated that there were significant low levels of metformin treated diabetic patients respect to the control group 52.7 ± 28.4 vs 185.9 ± 85.7, t= 3.45, P < 0.05, glibenclamide plus glizipide 24.5 ± 5.5 vs 185.9 ± 85.7, t= 4.12, p < 0.05 at 8 hs and metformin 17.9 ± 2.5 vs 121.0 ± 74.3, t= 2.48 at 12 hs after admission to the coronary care unit (Figure 2 A).

cTnI levels showed significant differences in treatment condition F (2, 259) = 4.59 P < 0.05. Multiple comparison Sidak's post hoc test indicated that there was a decreased in the cTnI levels in metformin treatment respect to the control group at 12 hs 0.36 ± 0.20 vs 2.00 ± 0.93, t = 3.85, P < 0.05, glibenclamide + glizipide 0.68 ± 0.27 vs. 2.00 ± 0.93, t = 3.06 P < 0.05. (Figure 2 B).

Figure 2. Values of the plasma CK-MB activity (Panel A) and cTnI levels (Panel B) in control group and patients treated with metformin or glibenclamide plus glizipide at the time of admission to the coronary care unit (0 hours), and after 8, 12, 24 and 36 hours. The values represent the mean ± SEM. * p< 0.05 Control vs. treatment group.



DISCUSSION

Biochemical cardiac markers as CK-MB and cTnI are used in the diagnosis and risk stratification of patients with chest pain and suspected ACS [13]. Studies of diseases as heart failure and others highlight the positive correlation between either age, sex and cTnI levels [14]. Although the range of age (31-92 years) of studied patients was large, we did not found correlation between these parameters in diabetic patients. In this way, no differences were found in CK-MB activity and cTnI levels in both sex.

Keller, et al showed that increased troponin levels are related to the early diagnosis of ACS according to the time of consultation after the onset of chest pain [15]. In patients with NSTEMI the evaluation during the admission to care unit is important and the reperfusion therapy should not be delayed pending to the biomarkers, they are used only if the symptoms persist after 6-8 hours. For this reason, is not recommendable to use biomarkers in the diagnostic at the moment of pain consultation [16]. In this way, cTnI specifically has the most sensibility in the early cardiovascular risk stratification to diagnosis and prognosis at the same time. It is recommended to increase the cTnI sensitivity in the diagnosis of myocardial injury to take samples in emergency room and 6 to 9 hours later, since it is not reliable within 2 to 4 hours taking into account the delay in time of pain consultation [17].

TPC range in patients in our study was from 1 to 8 hours and results showed that there were no correlations between CK-MB, cTnI and TPC and in this way the delay in the biomarkers measure is not relevant in the damage prognosis although there was a positive correlation in TPC with CK-MB at 12 hours of coronary unit admission.

It is known that CK-MB and cTnI have different sensibility in the ACS diagnosis confirmation but their levels can be modified by comorbidities and muscle injuries.

The percentage of patients with CK-MB values above 25 IU/L is similar in the control (28.5%) and diabetic group (28.9%) at 0 hours, but there was an increase in the number of patients with high levels of CK-MB in control group (66.6%) and lower (24.8%) of diabetic patients within 24 hours. Analyzing the corresponding cTnI results the percentage of patients with values greater that 0.01 ng/ml was higher (85.7%) in controls, but it is important to remake the decrease to 39.6% of diabetic patients at 12 hours, indicating that type II diabetes will be implicated in the loss of biomarkers sensibility.

CK-MB is diagnostic specific for myocardial injury, but it depends on the muscle mass and it has also been reported that it increases with exercise or in patients with respiratory difficulties, whose chest muscles have more activity. This feature affects the specificity, particularly in patients with concomitant myocardial and skeletal muscle injury [18]. cTnI is important to evaluate the muscle ischemia because is the most specific and sensitive laboratory marker of myocardial cell injury. [19].

Diabetic patients in our study were treated with metformin or glibenclamide plus glizipide. cTnI levels were lower in both treatments at 12 hs when the control values reach the highest. Similarly, CK-MB activity was lower at 8 hs in both treatments; however at 12 hs this value was lower only with metformin but not in glibenclamide plus glizipide treatment. These results could be showing an interaction between diabetes and pharmacological treatment on the biomarkers values.

The use of effective normoglycemic drugs as metformin acquires importance in diabetic patients with risk of coronary events. In these cases, it has been shown that the use of metformin reduces the CK-MB activity and cTnI levels compared to untreated metformin diabetic patients [18, 20]. Besides, benefits in chronic coronary disease have been observed [21]. The cardio protective effect of

metformin in the preconditioned ischemia was associated to the activation of kinases, which increases the intracellular adenosine.

One of the end effectors of preconditioned ischemia that protects cells such as cardiomyocytes against ischemic cell death seems to be the mitochondrial hexokinase II, that is increased by metformin [22]. When the episode of angina pectoris precedes the appearance of the acute myocardial infarct, it is found to be associated with a smaller size of the infarction, improvement of left ventricular function and survival. However, the possibility that patients with diabetes type II were protected by ischemic preconditioning is still discussed. There are divergences regarding the cardio protective effects of ischemic preconditioning where some authors suggest that this effect is lost and others that the diabetic hearts are more protected[23].

In preclinical studies using diabetic rats induced by streptozotocin, the infarct size was similar to those of non-diabetic rats after 45 minutes of ischemia, and the release of CK-MB in plasma was higher in diabetic rats. Other studies showed that the infarct size, ischemia intensity and CK-MB levels do not reach their maximum values at the same time. Other deleterious effects of diabetes have also been described such as left valvular ejection fraction decrease, after 30 minutes of ischemia, which was reduced in diabetic rats respect to non-diabetic control group [24].

Prospective clinical trials analyzed the release of cardiac enzymes, as preconditioning by angina pandromal, as an assessment of the size of the infarction, but did not found beneficial effects. Thus, there is insufficient evidence that allows to conclude that the mechanism has a relevant role in diabetic patient. Therefore, more clinical trials will be necessary to observe the relationship between myocardial preconditioning and diabetes.

There are discussions about the previous ischemic preconditioning with lower percutaneous coronary intervention related to cTnI release respect to major adverse cardiac events. Diabetic patients require a higher threshold of preconditioning due to metabolic and ATP sensitive potassium channels alterations. The reduction in cTnI was also observed in cycles of the ischemic conditioning stimulus [25]. Others authors suggest that the evolution of ischemic damage and the possible release of cardiac enzymes show similar values in diabetic and non-diabetic patients [26].

It is important to stand out that in our diabetic patients treated with hypo and normoglycemic drugs, there was a decreased CK-MB activity (8hs) and cTnI levels (12hs) respect to control group. This possibly could be a consequence of the interaction between the use of hypoglycemic drugs and the glycometabolic state that could modify the CK-MB and cTnI release/clearance balance at 8 and 12 hs after admission to the coronary unit.

DISCLOSURES

The Authors declares that there is no conflict of interest. Agustín N. Joison MHS are established researcher of the Catholic University of Córdoba (UCC) Argentina and Gustavo Baiardi, PhD are established researcher of the National Council of Research, Science and Technology (CONICET), Argentina.

ACKNOWLEDGEMENTS: To all the staff of coronary unit, “Reina Fabiola” Clinic.

REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):e21-181.

2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33(20):2551-67.

3.Collinson PO, Gaze DC, Thokala P, Goodacre S. Randomised Assessment of Treatment using Panel Assay of Cardiac markers--Contemporary Biomarker Evaluation (RATPAC CBE). Health Technol Assess 2013;17(15):1-122.

4. Welsh TM, Kukes GD, Sandweiss LM. Differences of creatine kinase MB and cardiac troponin I concentrations in normal and diseased human myocardium. Ann Clin Lab Sci 2002;32(1):44-9.

5. Wiviott SD, Cannon CP, Morrow DA, Murphy SA, Gibson CM, McCabe CH, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. Circulation 2004;109(5):580-6.

6. Eubanks A, Raza F, Alkhouli M, Glenn AN, Homko C, Kashem A, et al. Clinical significance of troponin elevations in acute decompensated diabetes without clinical acute coronary syndrome. Cardiovasc Diabetol 2012;11(154):1-8.

7. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352(16):1685-95.

8. Theroux P, Alexander J, Jr., Pharand C, Barr E, Snapinn S, Ghannam AF, et al. Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infarction: results from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. Circulation 2000;102(20):2466-72.

9. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362(23):2155-65.

10. Marfella R, Esposito K, Nappo F, Siniscalchi M, Sasso FC, Portoghese M, et al. Expression of angiogenic factors during acute coronary syndromes in human type 2 diabetes. Diabetes 2004;53(9):2383-91.

11. Abaci A, Oguzhan A, Kahraman S, Eryol NK, Unal S, Arinc H, et al. Effect of diabetes mellitus on formation of

coronary collateral vessels. Circulation 1999;99(17):2239-42.

12. Ravingerova T, Neckar J, Kolar F. Ischemic tolerance of rat hearts in acute and chronic phases of experimental diabetes. Mol Cell Biochem 2003;249(1):167-74.

13. Wurzburg U, Hennrich N, Orth HD, Lang H, Prellwitz W, Neumeier D, et al. Quantitative determination of creatine kinase isoenzyme catalytic concentrations in serum using immunological methods. J Clin Chem Clin Biochem 1977;15(3):131-7.

14. Kusumoto A, Miyata M, Kubozono T, Ikeda Y, Shinsato T, Kuwahata S, et al. Highly sensitive cardiac troponin T in heart failure: comparison with echocardiographic parameters and natriuretic peptides. J Cardiol 2012;59(2):202-8.

15. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361(9):868-77.

16. O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, et al. Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122(18 Suppl 3):787-817.

17. Brogan RA, Malkin CJ, Batin PD, Simms AD, McLenachan JM, Gale CP. Risk stratification for ST segment elevation myocardial infarction in the era of primary percutaneous coronary intervention. World J Cardiol 2014;6(8):865-73.

18. Lexis CP, Wieringa WG, Hiemstra B, van Deursen VM, Lipsic E, van der Harst P, et al. Chronic metformin treatment is associated with reduced myocardial infarct size in diabetic patients with ST-segment elevation myocardial infarction. Cardiovasc Drugs Ther 2014;28(2):163-71.

19. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). G Ital Cardiol (Rome) 2012;13(3):171-228.

20. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 2008;29(2):166-76.

21. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008;168(19):2070-80.

22. Rahmi Garcia RM, Rezende PC, Hueb W. Impact of hypoglycemic agents on myocardial ischemic preconditioning. World J Diabetes 2014;5(3):258-66.

23. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, et al. Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. J Am Coll Cardiol 2001;38(4):1007-11.

24. Li H, Liu Z, Wang J, Wong GT, Cheung CW, Zhang L, et al. Susceptibility to myocardial ischemia reperfusion injury at early stage of type 1 diabetes in rats. Cardiovasc Diabetol 2013;12(133):1-11.

25. Davies WR, Brown AJ, Watson W, McCormick LM, West NE, Dutka DP, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up. Circ Cardiovasc Interv 2013;6(3):246-51.

26. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. Lancet 2013;381(9861):166-75.

*Corresponding author: Dr Gustavo BAIARDI
E-Mail: gbaiardi@efn.uncor.edu