**Dear Editor,**

**World Journal of Diabetes**

We are very glad to send these answers to the questions and suggestions made by the reviewers. After all the corrections, we think that the paper improved substantially. Specific responses are stated in this letter and changes in the manuscript are highlighted in red.

## Reviewer 1

The reviewer has some comments that need to be addressed.

Dear Reviewer 1,

Thank you very much for your excellent suggestions. After all the changes made based on the comments of the reviewers, we think that the paper improved substantially. The answers are after each question and the changes in the manuscript were written in red after the answer. They were also written in red into the edited copy of the manuscript. The manuscript was submitted to a full English review.

### Question 1

1. In the section Abstract, the authors provide a brief description of protective signaling taking place with ischemic preconditioning. Please, note that the current consensus is that protein kinase C is not the major signaling molecule and its place is now considered downstream of a number of recently discovered signaling factors and/or pathways. On page 4, in the section “Cellular Mechanisms of Classical Preconditioning”, the authors correctly summarize current views on the mechanism of ischemic preconditioning. Please, edit the paragraph in the section Abstract accordingly.

### Answer to question 1

Thank you very much for your excellent suggestion. We have changed the Abstract section as requested and in accordance with the section “Cellular Mechanisms of Classical Preconditioning”. All the changes are shown in red.

Murry et al, in 1986, discovered the intrinsic mechanism of profound protection named ischemic preconditioning. The complex cellular signaling cascades underlying this phenomenon remain controversial and are only partially understood. However, evidencesuggests that adenosine, released during the initial ischemic insult, activates a variety of G protein-coupled receptors, such as opioids, bradykinin and catecholamines, which results in the activation of protein kinases, especially protein kinase C (PKC). This leads to the translocation of PKC from the cytoplasm to the sarcolemma, where it stimulates the opening of the ATP-sensitive $K^+$ channel, which confers resistance to ischemia. It is known that a range of different hypoglycemic agents that activate the same signaling cascades at various cellular levels can interfere with protection from ischemic preconditioning. This review examines the effects of several hypoglycemic agents on myocardial ischemic preconditioning in animal studies and clinical trials.

**Question 2**

2. A Table summarizing all discussed hypoglycemic drugs and their effects would be appreciated by the readers.

**Answer to question 2**

Again, thank you for this suggestion. We have added a Table summarizing the effects of hypoglycemic drugs in ischemic preconditioning, as follows.

**TABLE 1. Effects of hypoglycemic drugs on ischemic preconditioning**

| Study | Model | Diabetic drug | Effect |
|---|---|---|---|
| Animal studies | | | |

| | | | |
|---|---|---|---|
| Gross (1992)[23] | Dogs | Glibenclamide(glyburide) | Abolished |
| Toombs (1993)[50] | Rabbits | Glibenclamide | Abolished |
| Mocanu (2001)[47] | Rats | Glimepiride | Preserved |
| Maddock (2004)[51] | Rats | Glibenclamide | Abolished |
| | | Glimepiride | Preserved |
| Hausenloy (2013)[62] | Rats | Glimepiride | Preserved |
| Ye(2008)[63] | Rats | Pioglitazone | Preserved |
| | | Glibenclamide (glyburide) | Abolished |
| | | Glimepiride | Preserved |
| Horimoto (2002)[64] | Rabbits | Glibenclamide | Abolished |
| | | Glimepiride | Preserved |
| Bose (2005)[70] | Rats | Native sequenced human GLP-1 | Preserved |
| ZHU Qi-wei (2011)[74] | Rats | Pioglitazone | IPC mimic |
| Sasaki (2007)[75] | Rats | Pioglitazone | IPC mimic |
| Ahmed (2011)[76] | Rats | Pioglitazone | IPC mimic |
| Li (2008)[77] | Rats | Pioglitazone | Preserved |
| Wynne (2005)[78] | Rats | Pioglitazone | IPC mimic |
| Sarraf (2012)[79] | Porcine | Pioglitazone | Abolished |
| | | Rosiglitazone | Abolished |
| Human studies | | | |
| Cleveland (1997)[52] | atrial muscle trabeculae | Glibenclamide (glyburide) | Abolished |
| Tomai (1994)[53] | Human | Glibenclamide | Abolished |
| Klepzig (1999)[54] | Human | Glibenclamide | Abolished |

| | | | |
|---|---|---|---|
| | | Glimepiride | Preserved |
| Lee (2002)[55] | Human | Glibenclamide | Abolished |
| Tomai (1999)[56] | Human | Glibenclamide | Abolished |
| Ovünc (2000)[57] | Human | Glibenclamide | Abolished |
| Ferreira (2005)[58] | Human | Glibenclamide | Abolished |
| Bilinska (2007)[59] | Human | Glibenclamide | Abolished |
| | | Gliclazide | Partially preserved |
| Bogaty (1998)[60] | Human | Glibenclamide | Preserved |
| Correa (1997)[61] | Human | Glibenclamide | Preserved |
| Loubani (2005)[65] | right atrial appendages | Glibenclamide | Abolished |
| | | Gliclazide | Preserved (but abolished in supratherapeutic concentrations ) |
| Hueb (2007)[67] | Human | Repaglinide | Abolished |
| Rahmi (2013)[71] | Human | Repaglinide | Abolished |
| | | Vildagliptin | Preserved |

**Reviewer 2**

The authors review the current literature on effect of hypoglycemic agents in myocardial ischemic preconditioning. This is an area of high priority and in need of more clinical and basic research. This review is well-written and should make readers well aware of the importance of consideration of prescribing hypoglycemic agents to diabetic patients.

Dear Reviewer 2,
Thank you for all your excellent suggestions. After all the changes made based on the comments of the reviewers, we believe that the paper improved substantially. The answers are after each question and the changes were written in red after the answer. They were also written in red into the edited copy of the manuscript. We have also send the manuscript to a full English review.

**Question 1**

1. The authors should check the manuscript more carefully regarding English, make it easy to read and understand. For example, “it is of great interest the available data from clinical studies, ...” in 3rd paragraph on page 8; “It`s well established the fundamental role of adenosine in IP” in 2nd paragraph on page 12; “it`s demonstrated ...” in 2nd paragraph on page 11; “In view of the widely difference ... “ in 3rd paragraph on page 10; etc.

**Answer to question 1**

Thank you for your suggestion. The manuscript passed through a full English review. We have changed these expressions and others in the text. Changes are shown in red.

“... Indeed, data from clinical studies are of great interest since experimental findings...”

"… The fundamental role of adenosine in IPC is well established."

"… In studies using rat models, pioglitazone was associated with beneficial effects on cardiomyocyte injury, limiting infarct size and ventricular arrhythmias[74-76]. These beneficial effects may be related to the opening of the mitochondrial (ATP)-sensitive potassium channel …"

"Due to the great difference of in vitro selectivity ratios of repaglinide…"

**Question 2**

2. The authors should check the references and put a little more details in the manuscript. For example, in text "Bilinska and co-workers [59] evaluated 64 men, allocated in 3 groups, and performed two consecutive ET" in 1st paragraph on page 8, the authors should give more details about the 3 groups and the study design, which will make readers easy to follow when discussing the study results.

**Answer to question 2**

Thank you again for this important suggestion. We have rewritten this part of the text and put more details about this study. Changes are shown in red.

"… Bilinska and co-workers [59] evaluated 64 men, 17 non-diabetic and 47 diabetic patients, aged 54±5 years. Diabetic patients were allocated into 3 groups: one treated with glibenclamide, one with gliclazide, and the other with diet. All patients performed 2 consecutive exercise tests, with 30 minutes between them. The authors compared the improvement in ischemic parameters among these groups of patients and concluded that the warm-up effectwaspreserved in diabetic patients treated with diet, partially preserved in patients treated with gliclazide, and abolished in patients treated with glibenclamide."

**Question 3**

3. What does PCI on page 5 mean? What does IPC on page 3 mean? Don`t assume everyone know these abbreviations. What is Protective PCI pathways (3rd paragraph on page 5)? Any reference? What is fosfatidil-inositol 3 kinase (1st paragraph on page 12)? Is this commonly used in the literature? The authors need to further check into the basic literature referenced and make sure they get it right when refering to the research.

**Answer to question 3**

Thank you for these observations. All the abbreviations cited by the reviewer mean “Ischemic Preconditioning” and have been corrected. In the entire text, the term “Ischemic Preconditioning” was referred to as “IPC”.

Such as Protein kinase C, phosphatidylinositol 3 kinase (PI3K) is an important kinase involved in the mechanisms of IPC. Reference 78 is an elegant study in a rat model by Wynne AM, Mocanu MM and Yellon DM, which demonstrates a possible benefit of pioglitazone, reducing the damage tothe myocardium produced by ischemia, probably mediated by the activation of phosphatidylinositol 3 kinase cascades.