To: Editor in Chief
World Journal of Cardiology

Athens, October 22th, 2018

Dear Editor,

We would like to thank the reviewers for their comments on our manuscript: ***"Current evidence of drug-elution therapy for infrapopliteal arterial disease"*** that was submitted for publication in World Journal of Cardiology.

We have followed the comments and we hope that we have addressed their questions adequately. Please find below a point-by-point list of all the changes and revisions made.

If there is any question regarding this resubmission, please do not hesitate to contact us.

Sincerely,

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Point by point reply

Reviewer #1:

Reviewer #1 Comment: Data about comparison between bypass surgery and percutaneous procedures are not reported. If data are lacking this should be reported in the conclusions.

Authors' Response: We would like to thank the reviewer for this comment. Indeed, data comparing BTK bypass surgery and percutaneous procedure outcomes are limited. This was added in the Introduction section, pages 4-5, lines 79-84, as follows: *"Although direct comparison data between bypass surgery and percutaneous procedures below the knee are limited, with only one randomized, multi-center trial available in the literature, the evolution of interventional techniques along with the development of novel devices, contributed to a paradigm shift in the treatment of CLI; nowadays endovascular methods can be used for multiple vessel recanalization and are related with comparable clinical outcomes to open surgery."*

Reviewer #1 Comment: The bibliography is complete, but references are not in the requested format. There are also differences among the different citations in the format used.

Authors' Response: Again we thank the reviewer for this comment. The references have been corrected and changed to requested format.

Reviewer #2:

Reviewer #2 Comment: DES section: The authors need to mention which segments of the crural arteries were treated in the randomized trials (proximal / mid or distal by study protocols). Treatment of proximal crural segments with DES is much more frequent and possibly associated with better outcomes than treatment of the mid part of crural vessels. As the authors mention stent placement in the distal part of crural arteries or in pedal arteries is associated with short- and long-term complications and should be avoided.

Authors' Response: The YUKON- BTX, the DESTINY and the ACHILLES trials included patients suffering from infrapopliteal arterial occlusive disease. Infrapopliteal trifurcation lesions, lesions in juxta-articular regions or lesions subject to external compression were excluded. The use of DES in anatomic flexion points such as the the distal third of the anterior tibial artery should be avoided as stated in Drug-Eluting Stents (DES) section, page 9, lines 185-191: *"Despite the fact that the safety and superiority of DES compared to standard balloon angioplasty and bare metal stents in short to medium length lesions has been demonstrated by level IA evidence in short to medium length lesions, the polymorphic nature of BTK disease, which usually presents with very long lesions (>20 cm) and requires treatment of bifurcations and flexion points, such as the distal anterior tibial artery and the pedal arch, certainly requires further investigation, as several controversies remain. Specifically, the YUKON- BTX, the DESTINY and the ACHILLES trials excluded patients with infrapopliteal trifurcation lesions, lesions in juxta-articular regions or lesions subject to external compression."* and page 10, lines 204-208: *"Another challenging issue, commonly faced by medical providers, is the deployment of DES in anatomic flexion points. Severe compression resulting to DES fracture at the distal third of the anterior tibial artery has been related with in-stent restenosis/reocclusion, as well as inability to recanalize the lesion with either endovascular or surgical means. Therefore, stent placement in this area as well as the pedal arteries must be avoided."*

Reviewer #2 Comment: The parallelism to coronary DES for late stent thrombosis needs to be reevaluated. According to recent data, the rate of late stent thrombosis is higher with BMS than with DES. The question why this may not be the case with placement of the same stent devices in the infrapopliteal regions needs to be addressed.

Authors' Response: Indeed, this an issue that needs to be addressed. Unfortunately, little is known about late stent thrombosis following infrapopliteal BMS placement. The authors have introduced an appropriate comment in page 10, lines 221-228, of the annotated manuscript as follows: "*In the field of coronary disease, the phenomenon of neoatherosclerosis following both bare metal or drug-eluting stents has been correlated with very late acute stent thrombosis, and many authors advocate the prescription of long-term dual antiplatelet therapy to avoid late thrombotic events. Nevertheless, late stent thrombosis has never been investigated following infrapopliteal bare metal stent placement and therefore whether this phenomenon is as frequent as in cases of DES placement remains to be addressed .[38] However, according to current knowledge the need for long-term antiplatelet coverage to reduce the risk of acute or late thrombosis after DES placement might pose some restrictions on the use of these devices[20]."*

Reviewer #2 Comment: In recent years percutaneous atherectomy by rotational, orbital, directional or hybrid devices has broadened the spectrum of invasive angiology. Some data on atherectomy in BTK lesions (technical challenges, higher probability of spasm,

slow flow due to small lumen or vessel tortuosity) need to be mentioned and discussed (e.g. Lee-MS et al, Cath. Cardiovasc. Interv. 2016)

Authors' Response: We thank the reviewer for this comment. The combination of DCB use with orbital or directional atherectomy devices is supported by an increasing level of evidence and could possibly improve outcomes of infrapopliteal DCB angioplasty. This was added in "DES vs DCB for infrapopliteal arterial disease" section, page 15, lines 342-348: *"Having said that, better vessel preparation, using atherectomy devices or less traumatic semi-compliant balloon catheters could improve outcomes of infrapopliteal DCB angioplasty. Indeed, the combination of DCB use with debulking atherectomy devices for the management of long, heavily calcified femoropopliteal de novo or restenotic lesions is supported by an increasing level of evidence. Orbital as well as directional atherectomy has been employed to remove the occlusive intimal or neointimal tissue, allowing drug-coated balloons to act straight to the vessel wall. [53]"*
The authors believe that a further discussion about atherectomy devices would be beyond the scope of our article.

Reviewer #2 Comment: In addition, so overview articles on drug eluting balloons for femoropopliteal lesions need to be mentioned and discussed (Korosoglou et al, J Cardiovasc Surg, 2018).

Authors' Response: These information were added as requested. Please refer to the previous comment.

Reviewer #2 Comment: Furthermore, the authors need to discuss why drug eluting balloons did not achieve the same favorable results with BTK compared to femoropopliteal lesions. Some details need to be discussed and mentioned in terms of different anatomy, components of atherosclerotic plaque, circumferential calcification ect.) or pathophysiology.

Authors' Response: This is another good comment that needs to be adressed. Distal embolization due to loss of the balloon's coating during insertion could be a possible reason for IN.PACT DEEP study failure. This was added in the "Drug-Coated Balloons (DCB)" section, page 13, lines 299-300 as follows: *"It has been suggested that distal embolization due to loss of balloon's coating during insertion may have contributed to these poor outcomes".* In addition, we believe that the patency rates of plain balloon angioplasty in the IN.PACT DEEP and the BIOLUX P-II studies were unexpectedly high, a fact that has possibly contributed to the inability to prove the antirestenotic effect of PCB as stated in the "Drug-Coated Balloons (DCB)" section, page 14, lines 309-313: *"The authors would like also to comment that in both studies the patency rates of plain balloon angioplasty were unexpectedly high, taking into consideration reported data from previous infrapopliteal plain balloon angioplasty studies, a fact that has possibly contributed to the inability to prove the antirestenotic effect of PCB. The reason for this discrepancy remains to be clarified".*
Finally, following the 6-month results of the IDEAS RCT, in which restenosis but not LLL was inferior in the DES group compared to DCB, the authors support the notion that in small vessel disease, a superior acute luminal gain achieved by DES, leads to less short-term binary restenosis. This was further highlighted in page 15, lines 339-342 of the annotated manuscript, as follows: "*The authors can assume that reduced binary restenosis following DES deployment was due to a significantly superior initial luminal gain compared to DCB angioplasty and that for small-vessel disease, maximizing the initial luminal gain could lead to less short-term binary restenosis."*

Reviewer #2 Comment: Overall, it needs to be mentioned that current guidelines propagate the interventional treatment of infrapopliteal lesions in patients with ischemic pain at rest and critical limb ischemia but not in patients with claudication symptoms.

Authors' Response: According to recent guidelines, revascularization should be attempted in every patient with ischemic rest pain, diabetic or non-healing foot ulcers or gangrene involving any portion of the lower limbs, after assessment with the WIfI classification system. This was added in the "Introduction" section, page 4, lines 71-75: "Patients with ischemic rest pain, diabetic or non-healing foot ulcers or gangrene involving any portion of the lower limbs should be evaluated with the WIfI classification system that assesses the three primary factors that contribute to the risk of limb threat: wound (W), ischemia (I) and foot infection (fI). [6-7] After considering these components and staging each patient, revascularization should be attempted."
Furthermore, a table summarizing the WIFI classification was created.

Reviewer #2 Comment: Reference #16 is followed by reference #12. Please correct. 8. Reference #27 (PADI trial) does not match with the reference in the text. Please correct. 9. Some further typos and errors need to be corrected

Authors' Response: We thank the reviewer for this comment. The references have been corrected and the manuscript was checked for typos and errors.

Reviewer #3:

Reviewer #3 Comment: I suggest to add some sentences about novel drug delivery catheters (Catheter Cardiovasc Interv. 2018 Feb 1;91(2):296-301).

Authors' Response: We would like to thank the reviewer for this suggestion. Catheters that can deliver therapeutic agents directly to the vessel wall are discussed in "Drug Infusion Catheters" section, page 16 and the reference was added in lines 374-377 as follows: *"The Occlusion Perfusion Catheter (Advanced Catheter Therapies, Chattanooga, TN) is a universal delivery catheter capable of delivering paclitaxel to the media by forming a treatment chamber between two occlusion balloons. Results from a small multi-center study are promising."*

Reviewer #3 Comment: Better to point you some recommendations related with this topic from our recent guidelines Aboyans et al. Eur Heart J. 2018 Mar 1;39(9):763-816

Authors' Response: Guideline recommendations about the WIfI classification system were added in the "Introduction" section, page 4, lines 71-75: *"Patients with ischemic rest pain, diabetic or non-healing foot ulcers or gangrene involving any portion of the lower limbs should be evaluated with the WIfI classification system that assesses the three primary factors that contribute to the risk of limb threat: wound (W), ischemia (I) and foot infection (fI).(mils) After considering these components and staging each patient, revascularization should be attempted."*
Furthermore, a table summarizing the WIFI classification was introduced. Please see previous comment of Reviewer #2

Reviewer #3 Comment: CrI needs to be defined as Credible interval in the text.

Authors' Response: CrI was defined as Credible interval in the text.