Cardiovascular Revascularization Medicine 20 (2019) 621–623

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Letters to the Editor

Letter Regarding "The Prostacyclin Analogue Iloprost as an Early Predictor of Successful Revascularization in Diabetic Patients Affected by Critical Limb Ischemia and Foot Ulcers"

Critical Limb Ischemia (CLI) is a very common condition in my practice and multiple interventions within the same lesion is a clinical situation that I encounter rather frequently.

Objective markers that indicate which subset of patients would benefit from re-intervention have the potential of saving resources and preventing hospitalizations. Having the opportunity to review "The prostacyclin analogue Iloprost as an early predictor of successful revascularization in diabetic patients affected by critical limb ischemia and foot ulcers" is of high personal value for my area of expertise. This manuscript discussion is based on the use of Transcutaneous oximetry (TcPO2) as an outcome monitor when using a prostacyclin analogue shortly after revascularization [1].

TcPO2 has been established as a reliable tool for assessing limb ischemia, and in selective patients with arterial calcinosis, it is can be more accurate than ABI and segmental toe pressures [2]. Arroyo et al. evaluated post bypass patients by measuring TcPO2 and concluded that waiting 3 or more days could give adequate time for tissue reperfusion to promote healing of the surgical site [3]. Although the usability of non-invasive measurements in peripheral artery disease (PAD) is supported by numerous studies. Patients and providers often endure up to a 4–6 week wait to appreciate full treatment response after revascularization [4,5].

It is important to note that there might be other markers with higher predictive value as described by Arroyo et al. They found that transcutaneous carbon dioxide tension (TcPCO2) monitoring may be more useful to identify the negative outcome of a revascularization procedure and that TcPCO2/TcPO2 ratio > 1.3 is a strong predictor of healing failure [3].

Pharmacologically, Iloprost is a synthetic analogue of prostacyclin PGI2 that vasodilates arterial vascular beds and hinders platelet aggregation and blood clotting. Ismael et al. describes the pathology associated with the elevated oxidative stress that overwhelms the body's innate antioxidant system after revascularization, which perhaps explains how Iloprost and other prostanoids may assist with blunting reperfusion injury [6].

Meloni et al. discovered a 24% clinical recurrence rate of limb ischemia in a prospective study using PTA and endovascular stenting in CLI patients with diabetic foot ulcers. HbA1c and dialysis status were significant independent factors contributing to recurrent limb ischemia [7]. It is known that PTA is beneficial and cost effective as a treatment for limb salvage in diabetics [8], but diabetes is often accompanied by multiple comorbidities (e.g. renal disease, coronary artery disease, poor wound healing) that may act as confounders for data analysis.

A low risk side effect profile makes Iloprost an appropriate choice for use as a possible outcome marker and a helpful tool for clinical decision making. Adverse side effects mainly include flushing, headache, and gastrointestinal symptoms, which may stop shortly after the infusion begins or titration of the infusion [6]. Additionally, Iloprost has shown promising results in the treatment of CLI patients who are unable to undergo surgical or endovascular revascularization. As demonstrated by Melillo et al., investigators observed a 71.5% response rate in CLI patients who were solely treated with repeated Iloprost infusions. They included TcPCO2 as a monitor outcome and found a significant correlation with mortality and other outcomes such as major amputation rate [9].

As discussed above, TcPCO2 and TcPCO2/TcPO2 ratio may be of better use for analysis of outcomes and should be included as part of a more comprehensive study. I would like to conclude that in studies including multifactorial diseases such as Diabetes Mellitus, the studied subjects should be controlled for their variables in order to identify high risk groups for a specific hypothesis. Our study of interest had a small sample size and extrapolation of the results to the general population may not be feasible at this point. Nonetheless, the preliminary results are optimistic and an attempt to reproduce these results should be considered on a larger scale with perhaps impactful change in the CLI endovascular practice clinical decision making.

Michael Patel
Sofia C.D. Vianna
Robert E. Beasley*
Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, FL 33140, United States of America
*Corresponding author.
E-mail address: bbeaz@aol.com (R.E. Beasley).

https://doi.org/10.1016/j.carrev.2019.05.009

References

[1] Izzo V, Meloni M, Giurato L, Uccioli L. The prostacyclin analogue Iloprost as an early predictor of successful revascularization in diabetic patients affected by critical limb ischemia and foot ulcers. Cardiovasc Revasc Med 2018:1–3.
[2] Tsai FW, Tulsyan N, Jones DN, Abdel-al N, Castronuovo JJ, Carter SA. Skin perfusion pressure of the foot is a good substitute for toe pressure in the assessment of limb ischemia. J Vasc Surg 2000;32(1):32–6.
[3] Arroyo CI, Tritto VG, Buchbinder D, et al. Optimal waiting period for foot salvage surgery following limb revascularization. J Foot Ankle Surg 2002;41(4):228–32.
[4] Caselli A, Latini V, Lapenna A, et al. Transcutaneous oxygen tension monitoring after successful revascularization in diabetic patients with ischaemic foot ulcers. Diabet Med 2005;22(4):460–5.
[5] Stalc M, Poredos P. The usefulness of transcutaneous oximetry in assessing the success of percutaneous transluminal angioplasty. Eur J Vasc Endovasc Surg 2002;24(6):528–32.
[6] Ismaeel A, Lavado R, Smith RS, et al. Effects of limb revascularization procedures on oxidative stress. J Surg Res 2018;232:503–9.
[7] Meloni M, Izzo V, Giurato L, et al. Recurrence of critical limb ischemia after endovascular intervention in patients with diabetic foot ulcers. Adv Wound Care (New Rochelle) 2018;7(6):171–6.

[8] Ferraresi R, Centola M, Ferlini M, et al. Long-term outcomes after angioplasty of isolated, below-the-knee arteries in diabetic patients with critical limb ischaemia. Eur J Vasc Endovasc Surg 2009;37(3):336–42.
[9] Melillo E, Ferrari M, Balbarini A, Pedrinelli R. Transcutaneous oxygen and carbon dioxide levels with iloprost administration in diabetic critical limb ischemia. Vasc Endovascular Surg 2006;40(4):303–11.

Letter by Bilazarian et al. regarding the article, "Adverse events and modes of failure related to Impella RP: Insights from the Manufacturer and User Facility Device Experience (MAUDE) database" by Khalid et al.

We read with interest the study by Khalid N et al. [1], reporting on the most common complications and failure modes with Impella RP based on analysis of the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database. In this article, 35 medical device reports on Impella RP were identified between Jan 2009 and Dec 2018. Of the 35 MAUDE reports, commonly reported complications included bleeding ($n = 15$) and vascular complications ($n = 8$). Also, failure modes with Impella RP included fracture/damage of device ($n = 12$), thrombus in the device ($n = 6$), and device detachment ($n = 3$).

We have the following concerns:

1. It should be noted that the United States FDA approved the Impella RP for providing temporary support of right ventricular function in patients with right ventricular failure on Sep 20, 2017 [2]. Thus, the intent behind the query of the MAUDE database from 8 years before the actual approval of the device seems unclear.
2. Considering that likely several hundreds of Impella RP devices were implanted since Sep 20, 2017, and the 35 reports could include duplicate reports both by the user and the manufacturer, the overall incidence of patient complications and device failure modes with Impella RP is extremely low. Moreover, the FDA clearly states that the number of MDR reports cannot be interpreted to reach conclusions about the frequency or severity of problems associated with devices [3]. The authors themselves state that the complete analysis of the failure modes of Impella RP following the procedure could not be performed as only a minority of the devices were returned to the manufacturer. Given the limitations of the MAUDE database and the inability to establish the cause-and-effect relationship, we disagree with the conclusion by Khalid et al. that "the failure modes of the Impella RP device needs to be addressed to improve device performance and clinical outcomes."
3. A recent publication from the JACC scientific expert panel highlighted the dramatic increase in the use of VA-ECMO for cardiopulmonary failure since 2009 [4]. Despite the increased used of VA-ECMO during this time period and the reported rates of bleeding complications with VA-ECMO of about 60% [5], there are no reports on the complications rates or failure modes with VA-ECMO from the MAUDE database. Which begs the question of the appropriateness and intent of this analysis of the MAUDE database for the newly approved Impella RP devices.

Given that the MAUDE database was established to aid in the identification of complications associated with a new medical device not yet reported in the published literature [6], and the lack of a noteworthy finding of this study, we question the utility and validity of this study.

Seth Bilazarian*
William Bolt
Abiomed, Inc., Danvers, MA, United States of America
*Corresponding author at: Abiomed, Inc., 22 Cherry Hill Drive, Danvers, MA 01923, United States of America.
E-mail address: sbilazarian@abiomed.com (S. Bilazarian).

https://doi.org/10.1016/j.carrev.2019.04.020

☆ Conflict of interest: All authors are employees of Abiomed, Inc.

References

[1] Khalid N, Rogers T, Shlofmitz E, Chen Y, Musallam A, Khan JM, et al. Adverse events and modes of failure related to Impella RP: insights from the Manufacturer and User Facility Device Experience (MAUDE) database. Cardiovasc Revasc Med 2019;20(6):503–6.
[2] Impella RP® System - P170011. Available at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm581165.htm. Accessed April 9, 2019.
[3] MAUDE: Manufacturer and user facility device experience. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm. Accessed April 9, 2019.
[4] Guglin M, Zucker MJ, Bazan VM, et al. Venoarterial ECMO for Adults. JACC Scientific Expert Panel J Am Coll Cardiol 2019;73(6):698–716.
[5] Keebler ME, Haddad EV, Choi CW, et al. Venoarterial extracorporeal membrane oxygenation in cardiogenic shock. JACC Heart Fail 2018;6(6):503–16.
[6] Gurtcheff SE. Introduction to the MAUDE database. Clin Obstet Gynecol 2008;51(1):120–3.

Response to the letter by Bilazarian et al. regarding the article, "Adverse events and modes of failure related to Impella RP: Insights from the Manufacturer and User Facility Device Experience (MAUDE) database"

We appreciate the comments by Bilazarian and Bolt [1] regarding our manuscript analyzing the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) reports of the Impella RP published in the recent issue of *Cardiovascular Revascularization Medicine* [2]. The Impella RP (Abiomed, Danvers, Massachusetts) received FDA approval for short-term right ventricular support on September 20, 2017; however, 13 reports were submitted to the MAUDE database before that date. The Impella RP system received the CE Mark in Europe on April 4, 2014, was in limited clinical use in Canada, under Health Canada's Special Access Program, and was tested in clinical trials in the United States (US) [3]. The MAUDE database reporting is worldwide and not limited to the US; therefore, our report included the totality of the available reports inputted into the database, including those preceding the FDA approval date for marketing, as they represent the initial operator experience with the device.

In the Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health, the FDA outlined a vision for enhancing device innovation and assuring safety. Some of the key elements of this plan include to "*establish a robust medical device patient safety net in the US, explore regulatory opportunities to streamline and modernize timely implementation of postmarket mitigations and spur innovation towards safer medical devices*" [4]. The FDA depends on several mechanisms for post-marketing surveillance and monitoring of long-term safety outcomes of devices. The MAUDE database is one of these mechanisms but has well-recognized inherent limitations including underreporting, lack of event adjudication, duplicate reporting, and inability to estimate the incidence of adverse events because of the lack of a denominator. We believe that, despite these limitations and in the absence of robust post-marketing studies, the MAUDE database is a helpful source to identify the types and trends of device adverse events in real-world clinical practice. Reports from the MAUDE database have been useful in fostering awareness among physicians and patients on the myriad adverse events and malfunctions of a wide variety of devices, including drug-eluting stents, inferior vena cava filters, transcatheter aortic valves, guide extension catheters, and percutaneous left ventricular assist devices [5–10]. With the lack of systematic post-marketing studies, the MAUDE database is the only tool to inform publicly on these events related to the devices.

Bilazarian and Bolt question the utility of our study. However, as already stated in our study, the totality of the events is not reported, as there is no available denominator of the Impella RP used in the market. Therefore, our study details only proportions of reported complications and not incidence rates [2]. Interestingly, most