Circulation

LETTER TO THE EDITOR

Letter by O'Neill and Burkhoff Regarding Article, "The Evolving Landscape of Impella Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention With Mechanical Circulatory Support"

William W. O'Neill, MD
Daniel Burkhoff, MD, PhD

To the Editor:

Amin and colleagues[1] accessed administrative claims data from the Premier Healthcare Database and used statistical tools to assess clinical outcomes in patients treated with mechanical circulatory support on the day of percutaneous coronary intervention. They concluded, after propensity score adjustment, that outcomes (death, stroke, and bleeding) were worse in patients treated with Impella than those treated with intra-aortic balloon pump (IABP). The topic of this article is of critical importance. However, we believe that detailed analysis illustrates important limitations of using claims data for this purpose. Most assuredly, analyses based on large claim databases can be useful for tracking treatment trends over time and assess variability of treatment practices. However, claims data that rely solely on administrative *International Classification of Diseases* (ICD) codes to characterize patient factors and clinical outcomes have obvious limitations and are prone to misclassification. For example, the authors' claim of Impella use in less sick patients was based on a designation of "critically ill" defined as the presence of cardiogenic shock (CS) or mechanical ventilation, or post-cardiac arrest, without any supportive data. CS, which accounted for much of the difference between groups, is a broad category[2] in which mortality varies dramatically according to The Society for Cardiovascular Angiography and Interventions subgroup, ranging from 3% in Stage A to 67% in Stage E.[3] Thus, it seems inappropriate to apply the single diagnosis of CS to all patients, without adjudication, to classifying disease severity.[4] Similarly, mortality rates after cardiac arrest and with mechanical ventilation also depend on many factors not available in the database. Sole reliance on ICD-9 and ICD-10 codes to compare acuity of illness in CS has not been validated, to our knowledge. Moreover, based on the baseline descriptors provided, there are many more high-risk features in the patients with Impella versus IABP, including age, diabetes mellitus, hypertension, heart failure, chronic renal failure, multivessel disease, bifurcation lesions, chronic total occlusions, and calcified lesions requiring atherectomy. The use of a statistical propensity adjustment strategy cannot overcome the lack of required granular hemodynamic and clinical data in comparing populations. Further to this point, how can a 33% use of bare metal stents in patients with IABP (Table 1) be accounted for, unless there was a high frequency of low-risk type A lesions in the IABP cohort? Exclusion of patients who received IABP first and transitioned to Impella could have also introduced bias into the analysis.

The inability to properly account for differences in baseline characteristics using an inadequate, unvalidated propensity scoring system raises questions as to the validity of comparing outcomes between groups. Given the challenges in performing high-quality studies in the settings of CS or assisted percutaneous coronary intervention in high-risk patients, wherein accurate conclusions can only be derived from granular accounting of patient, hemodynamic, laboratory, and anatomic variables, we should require a level of data scrutiny beyond retrospective

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administrative codes. Although the use of retrospective analysis of "big" claims data may be appealing, we believe that this study lacks the required data and adjudication needed to advance our understanding of mechanical circulatory support in CS or in the setting of percutaneous coronary intervention.

ARTICLE INFORMATION

Affiliations

Henry Ford Hospital, Detroit, Michigan (W.W.O.). Cardiovascular Research Foundation, New York (D.B.).

Disclosures

Dr O'Neill is a consultant to Edwards Life Sciences and Abiomed. Dr Burkhoff reports an institutional grant and travel reimbursement from Abiomed, consulting with BackBeat Medical and Corvia Medical, and equity interest in Impulse Dynamics.

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LETTER TO THE EDITOR

Letter by Khalid et al Regarding Article, "The Evolving Landscape of Impella Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention With Mechanical Circulatory Support"

Nauman Khalid, MD
Evan Shlofmitz, DO
Ron Waksman, MD

To the Editor:

Amin et al report temporal trends for Impella use in 48 306 patients undergoing percutaneous coronary intervention at 432 hospitals by analyzing the Premier Healthcare Database from 2004 to 2016.[1] The following important findings were noted: increased use of Impella over time, significant site-level variation in Impella use, escalated costs and adverse outcomes in the Impella era (2004–2007) compared with the pre-Impella era (2008–2016) and at hospitals with higher Impella use, and last, an increased rate of death, bleeding, and stroke with Impella use (compared with intra-aortic balloon counterpulsation) despite robust propensity score adjustment. The present study is useful for providing the preliminary data and in guiding the development of future prospective randomized studies. We wish to highlight a few relevant points.

First, the analysis of this longitudinal study spans a timeframe of approximately 14 years divided into 2 epochs—the "pre-Impella era" and the "Impella era." In this time scale, considerable evolution in device technology, iterations of existing technology, and rapid technological advancements have emerged. Parallel to this, contemporary percutaneous coronary intervention practices have also expanded to include more patients with greater comorbidity burden and anatomic complexity as they are deemed ineligible for surgical revascularization. While the present study allows us to understand the degree and direction of change over time, the results lack generalizability given concurrent evolving changes in the policy landscapes, patient profiles, and practice patterns. Second, in the present study, all the indications for mechanical circulatory support are pooled together—including patients with stable ischemic heart disease presenting for an elective high-risk intervention, as well as patients with cardiogenic shock or cardiac arrest—thereby making the overall patient cohort largely heterogeneous, which compromises the ability to fastidiously propensity-match such patients. A more pragmatic approach would be to investigate these 2 subgroups separately, as these are 2 inherently distinct patient subsets. Last, there is large variability not only in the quantity but also the "quality" of mechanical circulatory support utilization. As alluded to in the present study, the bleeding complications in quartile 4 (highest use) hospitals were reduced by almost half in comparison to quartile 1 (lowest use) hospitals. We anticipate that with emphasis on training and appropriate use, the other adverse events related to the mechanical circulatory support devices will decline as well. Furthermore, the decision to use support appears to be linked to hospitals rather than patient characteristics, suggesting that there is far more to the processes and hospital practice patterns rather than the device itself.

Notwithstanding the ongoing deliberation on the merits and demerits of mechanical circulatory support use, there is little doubt that these devices

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have an important role in carefully defined patient populations. The role of mechanical circulatory support should be individualized and tailored for each patient, weighing the benefits of hemodynamic support against the risk of device-related complications. Prospective randomized studies with proper adjudication are needed to elucidate a cause-and-effect relationship between the device and the outcome.

ARTICLE INFORMATION

Affiliation

Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC.

Disclosures

Dr Waksman discloses the following Advisory Board positions (all modest): Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; the following Consultancies: Amgen (modest), Biotronik (significant), Boston Scientific (modest), Cardioset (modest), Cardiovascular Systems Inc. (modest), Medtronic (modest), Philips (modest), Pi-Cardia Ltd. (modest); the following Grant Support: AstraZeneca (modest), Biotronik (significant), Boston Scientific (modest), Chiesi (modest); the following Speakers Bureau (both modest): AstraZeneca, Chiesi; and that he is an investor in MedAlliance (modest). The other authors report no conflicts.

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LETTER TO THE EDITOR

Letter by Vincent et al Regarding Article, "The Evolving Landscape of Impella Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention With Mechanical Circulatory Support"

Flavien Vincent, MD, PhD
Eric Van Belle, MD, PhD
Sophie Susen, MD, PhD

To the Editor:

We read with great interest the work of Amin et al[1] on the nationwide experience of mechanical circulatory support (MCS) with Impella in percutaneous coronary intervention in 48 306 patients at >400 hospitals in USA between 2004 and 2016.

Compared with the intra-aortic balloon pump, Impella was associated with higher adverse event rates including higher in-hospital mortality and major bleeding. These findings drawn retrospectively from the administrative Premier Healthcare Database (representing only a fraction of patients implanted with Impella in the United States) must be carefully interpreted, because the meticulous propensity-scoring analysis improved the comparability between the groups but cannot rule out potential unmeasured confounding. However, these results have been recently confirmed by a study following the same methodology exclusively in patients in cardiogenic shock and undergoing percutaneous coronary intervention for acute myocardial infarction.[2] Together, these studies highlight a signal that should not be ignored.

The bleeding risk observed is obviously multifactorial in such high-bleeding-risk patients requiring large bore access for MCS implantation and concomitant anticoagulant treatment. However, this study is a reminder that continuous-flow designed pumps like Impella, contrary to the intra-aortic balloon pump, rely on the continuous high-speed rotation of an impeller that has 2 major effects on the blood flow: a diminution of arterial pulsatility and the generation of high shear-stress forces. These latter produce a defect of the most potent multimers of a main primary hemostasis protein, the von Willebrand factor. Also known as acquired von Willebrand syndrome, it has been associated with an increased bleeding frequency in high shear conditions.[3,4] These 3 phenomena (loss of pulsatility, high shear, von Willebrand factor defect) are intimately related, given that the preservation of pulsatility under Impella has been shown to mitigate the von Willebrand factor defect.[5] This has potential important clinical consequences as observational studies have demonstrated that high-pulsatile heart-mate II recipients were less prone to bleeding events.[3]

The work of Amin et al did not include biological end points, which precludes further conclusions on the association between the disturbance of hemostasis and bleeding events. However, this study adds to the plethoric literature on the high number of nonsurgical bleeding events observed in patients requiring various short- and long-term MCS including extracorporeal membrane oxygenation and Heartmate.[3] These bleeding events occur in almost 50% of patients and strongly impact quality of life and survival and reduce the cost-effectiveness of these treatments.

Overall, bleeding complication appears once again as the main pitfall of MCS devices. The hemodynamic efficacy of Impella has been demonstrated, and many

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clinicians have experienced life-saving rescue that could have not been possible without this device. We certainly should not remove this tool from our catheterization laboratory, but we must optimize our use of this technology by adopting the best practice in large bore access management while increasing our understanding of the device's effects on blood components for hemostasis including von Willebrand factor. A win for the heart should not be lost at the groin. This study should be received as a call both for specific training before use of MCS devices and for further research on their hemocompatibility.

ARTICLE INFORMATION

Affiliations

CHU Lille, Institut Coeur Poumon, Cardiology, Department of Interventional Cardiology for Coronary, Valves, and Structural Heart Diseases, France (F.V., E.V.B.). Inserm, U1011, Institut pasteur de Lille, EGID, France (F.V., E.V.B., S.S.). Université de Lille, France (F.V., E.V.B., S.S.). CHU Lille, Hematology and Transfusion Department, France (S.S.).

Disclosures

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LETTER TO THE EDITOR

Letter by Helgestad et al Regarding Article, "The Evolving Landscape of Impella Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention With Mechanical Circulatory Support"

Ole K.L. Helgestad, MD, PhD
Sören Möller, PhD
Jacob E. Møller, MD, PhD, DMSc

To the Editor:

We read with interest the recent article by Amin and associates describing temporal changes in the use of mechanical circulatory support (MCS) from 2004 to 2016 among patients receiving percutaneous coronary intervention based on registry data.[1] The study has several important findings, perhaps most notably the sustained high use of intra-aortic balloon pump (IABP), in contrast to other countries such as Denmark, where IABP was abandoned in patients with acute myocardial infarction and cardiogenic shock after the neutral results of the IABP-SHOCK II trial (Intraaortic Balloon Pump in Cardiogenic Shock) in 2012.[2,3] In the present study, patients requiring MCS escalation were excluded from analysis. Given the lack of efficacy of IABP, which has also been seen in patients without shock, it raises a potential selection bias as one could speculate that escalation was more frequent in the IABP group and this subgroup might be at a particularly high risk.

In the present study, Impella was associated with higher costs and risk of adverse outcomes compared with IABP.[1] We acknowledge the authors for emphasizing that their findings should not be causally linked. They also state that Impella was used more commonly in low-risk patients in whom the likelihood of any mortality benefit is lower while still carrying costs and complication risks. Using diagnostic codes to define "low-risk" is questionable because a patient's risk profile is more likely to rely on the degree of cardiac dysfunction and hemometabolic state than diagnostic codes used for billing.

The developed propensity score was used as an adjustment factor instead of adjusting for the separate variables used to generate the propensity score. This has some unfortunate interpretation consequences because the estimated odds ratio relates to the marginal effects of holding the propensity score constant.[4] Also, interpreting the estimated odds ratios is difficult because there are no crude frequencies of the outcomes or total numbers of observed outcomes. If the specific outcome were relatively frequent, odds ratio is *not* equal to risk, and the missing crude information prevents the reader from interpreting the direction of bias.

The article lacks information on how the variables used for the propensity score were selected. Variables included should preferably be true confounders, or at least strongly associated to outcome, to prevent the unintended consequence of *increasing* bias.[5] Of the 37 variables selected, only age (and perhaps diabetes mellitus) are well-known risk factors in cardiogenic shock (for which MCS is probably used). No important hemometabolic variables are included in the propensity score or presented in the article. The propensity score includes medication given during treatment, which could be an intermediate factor instead of a confounder, in which case the propensity score could result in overadjustment.

We note that the observed association of higher costs and adverse events in patients receiving an Impella might be because those patients are in fact an entirely

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different patient population with a higher risk profile. We urge clinicians to be careful in selecting patients for MCS, regardless of type, but also not to be reluctant with MCS if a patient is severely hemodynamically compromised.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, Odense University Hospital, Denmark (O.K.L.H., J.E.M.). OPEN - Open Patient data Explorative Network, Odense University Hospital and Department of Clinical Research, University of Southern Denmark (S.M.). Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (J.E.M.).

Disclosures

Dr Helgestad has received travel compensation from Abiomed. Dr Møller has received research grants and speaker's fee from Abiomed. Dr Möller report no conflicts.

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RESPONSE TO LETTER TO THE EDITOR

Response by Amin et al to Letters Regarding Article, "The Evolving Landscape of Impella Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention With Mechanical Circulatory Support"

Amit P. Amin, MD, MSc, MBA
Sunil V. Rao, MD
Richard G. Bach, MD
Jeptha P. Curtis, MD
Nihar Desai, MD, MPH
Christian McNeely, MD
Firas Al-Badarin, MD, MSc
John A. House, MS
Hemant Kulkarni, MD
Frederick A. Masoudi, MD, MSc
John A. Spertus, MD, MPH

In Response:

We appreciate the opportunity to respond to several letters regarding our article.[1] Van Belle state "(our) study highlights a signal that should not be ignored." O'Neill and Chieffo raise concerns about potential misclassification with big data and billing codes, stating "randomized clinical trials are warranted." We concur and reemphasize our support for randomized clinical trials (RCTs) of mechanical circulatory support (MCS) devices.[1] We believe that observational data are complementary to RCTs for postmarketing studies of effectiveness, safety, and cost-effectiveness; they support regulatory decision making for drugs and devices; they quantify the translation of RCTs into practice, and their value should not be overlooked. In this regard, our study[1] stands independently of the results of RCTs.

O'Neill and Chieffo point out limitations of determining shock severity due to lack of hemometabolic variables. Whereas information on lactate, or SCAI shock score could have enriched our inferences, our data reflect how MCS is used in contemporary practice. Given the lower incidence of cardiac arrest, mechanical ventilation, or cardiogenic shock observed in the Impella group and the trend of more frequent Impella use among patients who were not critically ill, it seems unlikely that hemodynamic/metabolic variables would be worse in Impella patients. Furthermore, the falsification end point analysis—a validated method of examining unmeasured confounding—showed that important unmeasured confounding was unlikely. The consistency of higher adverse events within high- versus low-use hospitals and Impella era versus the pre-Impella era, add further strength to our findings. Last, our findings are congruent with analyses from NCDR[2] and BMC2[3] registries.

Chieffo et al raise an important point for patients with acute myocardial infarctions, "the timing of MCS and type of support might play an important role." While those factors may theoretically affect outcomes, no RCTs demonstrate that MCS timing affects outcomes. The best evidence comes from Dhruva,[2] where the association of Impella with higher rates of bleeding and mortality were consistent, regardless of device timing. We conducted additional analysis restricted to ST-elevation myocardial infarction (62% patients), the risks of death, bleeding, and acute kidney injury were uniformly higher with Impella versus intra-aortic balloon pump, irrespective of the presence or absence of cardiogenic shock (odds ratio [OR] ranging from 1.5–2.7, $P<0.001$ for all outcomes). To our knowledge, there is no RCT showing that earlier MCS use, in the setting of acute myocardial infarction shock improves outcomes. The ongoing Door-to-Unload trial (ClinicalTrials.gov. Unique identifier: NCT03947619) may shed further light.

Helgestad et al question the exclusion of 828 patients who received both intra-aortic balloon pump and Impella. While "this subgroup might be particularly high-risk," these patients could not reliably be assigned to either treatment

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group. Retention of these patients would introduce a misclassification of exposure bias if outcomes were wrongly attributed to a single device. Thus, to minimize bias, we excluded this small group (≈1.5% of overall study sample).[1]

Helgestad and O'Neill question: (1) methods/validity of the propensity score; (2) using the propensity score as a covariate; and (3) and inclusion of treatment variables in the propensity score. In response: (1) the propensity score area under the curve was 0.83, considered a strong propensity score and variables were well-balanced after adjustment. (2) Pocock and colleagues compared propensity methods from 4 cardiovascular studies: matching, stratification, adjustment, and inverse propensity weighting.[4] They found that in all scenarios, using propensity score as a covariate approximated the true measure of risk. Nonetheless, we repeated the mortality analysis using inverse propensity weighting, which generates nearly perfect covariate balance between groups,[4] we found mortality associated with Impella was higher (OR, 1.64 [95% CI, 1.46–1.85], *P*<0.001). (3) We included glycoprotein inhibitors, prasugrel, ticagrelor, anticoagulants, bivalirudin, transradial access, and atherectomy in the propensity score. These drugs and devices are important confounders of bleeding and mortality on the basis of previous literature, hence we included to reduce confounding.

Helgestad et al suggest "higher costs and adverse events in Impella patients ... (are due to) ...a higher risk-profile" is not borne out by our data.[1] The patients receiving Impella in our cohort had a lower-risk profile (lesser incidence of cardiac arrest, mechanical ventilation, and shock), important drivers of cost and length of stay (LOS). Hence, we observed a shorter length of stay in Impella patients.[1] In this context, higher costs associated with Impella, cannot necessarily be attributed to a sicker population.

Khalid and Helgestad question pooling of MCS indications with both stable coronary artery disease and acute coronary syndrome. While we agree with a stratified analysis, ≈90% of our sample was acute coronary syndrome, with 62% ST-elevation myocardial infarctions, 22% non-ST-elevation myocardial infarctions, while only 12.8% were patients with 'other than acute coronary syndrome.' An analysis excluding 12.8% of patients did not affect the overall results for acute coronary syndrome with or without shock.

O'Neill and Burkhoff surmise that greater bare-metal stent use in intra-aortic balloon pump patients reflects "type-A" lesions. There are no data supporting this assertion. On the contrary, studies support that bare-metal stent use is more frequent in higher risk, not lower risk, patients,[5] potentially reflecting an intention to reduce duration of antiplatelet therapy in critically ill patients.

We would also like to clarify Khalid et al's comment that "bleeding complications in the Quartile 4 (highest use) hospitals were reduced by almost half in comparison to the Quartile 1 (lowest use) hospitals." In fact, the OR for bleeding comparing the highest versus lowest use hospitals was 1.17 (95% CI, 1.03–1.33, *P*=0.015), thus 17% higher, which was a statistically significant difference.[1]

Khalid's comment about evolving device technology spanning 14 years is relevant to any technology in rapidly evolving fields. As described in our article,[1] we included calendar year as a covariate in hierarchical models, which indirectly adjusts for changes in patient-complexity or device improvements over time. Consistently, post-Impella versus pre-Impella era outcomes did not show any improvements. Moreover, there are no data that the evolution of large-bore MCS devices has improved outcomes.

Despite a large investment in MCS devices, there is little consensus among physicians on the appropriate role of the technology in contemporary practice. The lack of an adequately powered RCT demonstrating the benefit of MCS contributes to practice variability. Observational data have found an association between Impella use and potential harm.[1–3] However, the limitations of observational data are well known and clearly stated in our article.[1] We endorse the adoption of best practices for the use of MCS to minimize complications and optimize patient selection and underscore Van Belle's comment that "a win for the heart should not be lost at the groin."

ARTICLE INFORMATION

Affiliations

Cardiovascular Division (A.P.A., R.G.B., C.McN.), Washington University School of Medicine, St Louis, MO. Barnes-Jewish Hospital, St Louis, MO (A.P.A., R.G.B., C.McN.). The Duke Clinical Research Institute, Durham, NC (S.V.R.). Yale University, New Haven, CT (J.P.C., N.D.). Saint Luke's Mid America Heart Institute, University of Missouri–Kansas City (F.A.-B., J.A.S.). Premier, Inc, Premier Applied Sciences, Charlotte, NC (J.A.H.). M&H Research, LLC, San Antonio, TX (H.K.). University of Colorado Anschutz Medical Campus, Aurora (F.A.M.).

Disclosures

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