EDITORIAL

Microaxial Left Ventricular Assist Devices
In Search of an Appropriate Indication

Holger Thiele, MD; Steffen Desch, MD; Anne Freund, MD

Since 1999, after the SHOCK trial demonstrated a reduction in mortality with early myocardial revascularization in patients with acute myocardial infarction complicated by cardiogenic shock,[1] intensive care specialists and interventionalists have searched for additional ways to reduce the persistently high mortality, often in the range of 40% to 50%.[2] After other reports demonstrated that intra-aortic balloon pump (IABP) support failed to reduce mortality,[3-5] the next step was development and evaluation of other approaches for active mechanical circulatory support, including microaxial left ventricular assist devices (LVADs), in the treatment of cardiogenic shock.

Related article

Microaxial LVADs consist of a small catheter-mounted pump that can be inserted percutaneously through a peripheral artery (often the femoral artery). The device is positioned across the aortic valve with its distal end in the left ventricle and its outlet in the proximal aorta. The device draws blood from the left ventricle and pumps it into the aorta and generates forward blood flow from the left ventricle to the aorta. In this manner, the device is intended to unload the left ventricle and improve forward blood flow. This approach is theoretically appealing as mechanical circulatory support devices might improve perfusion of critical organs such as the heart, brain, and kidneys. However, any invasive measure is also associated with complications. Since sufficiently powered randomized clinical trials (RCTs) of mechanical circulatory support devices are scarce,[6-8] large-scale registry studies with propensity matching represent an important data source and method to provide additional evidence.

In this issue of *JAMA*, Dhruva et al[9] report findings from an observational study that compared the outcomes associated with an intravascular microaxial LVAD vs the IABP in a propensity-matched analysis of patients with cardiogenic shock related to myocardial infarction. In the overall registry cohort of 28 304 patients with acute myocardial infarction who underwent percutaneous coronary intervention (PCI) from October 2015 to December 2017, 29.9% received treatment with IABP compared with 6.2% who received treatment with the microaxial LVAD (the Impella heart pump), with an increasing trend in use of the latter device over the study period. In the propensity-matched analyses, which included a total of 1680 matched pairs, the microaxial LVAD, compared with IABP, was associated with a significantly higher risk of in-hospital death (45.0% vs 34.1%; absolute risk difference, 10.9 percentage points [95% CI, 7.6-14.2]; $P < .001$) and in-hospital bleeding (31.3% vs 16.0%; absolute risk difference, 15.4 percentage points [95% CI, 12.5-18.2]; $P < .001$), irrespective of the timing of device implantation pre- or post-PCI. Further propensity-matched analyses confirmed the results of the IABP-SHOCK II trial by showing no benefit associated with IABP compared with optimal medical treatment.[3-5] In contrast to the IABP-SHOCK II trial, IABP treatment was associated with a higher risk of in-hospital death and an increased risk of major in-hospital bleeding than optimal medical treatment.

Despite propensity matching, the observed differences in outcomes between use of the microaxial LVAD and use of the IABP reported by Dhruva et al[9] may have been related to limitations in these registry-based analyses, and the findings should not be considered definitive. Since the indication for mechanical circulatory support strongly depends on the familiarity of the operator with the device and the severity of cardiogenic shock, findings derived from observational registries may be limited by selection bias and confounding, which cannot be completely accounted for even with sophisticated statistical matching and analyses.

The finding that IABP support was not associated with better outcomes compared with optimal medical treatment has been well known for years since the large-scale randomized IABP-SHOCK II trial.[3-5] In 2014, routine use of the IABP in patients with cardiogenic shock was subsequently downgraded in clinical guidelines and is no longer recommended by European guidelines (class III level of evidence B),[10,11] whereas US guidelines from the American College of Cardiology/American Heart Association in 2013 include a class IIa level of evidence B recommendation for use of IABP in patients with cardiogenic shock.[12] Against this background, a 30% rate of IABP use in the United States between 2015 and 2017 is surprising, and by comparison, adoption of the latest scientific evidence has been seemingly faster in European countries, as shown in several European registries with rates of IABP use of less than 10%, from 2012 to 2017.[13-15]

Approval of mechanical circulatory support devices by the US Food and Drug Administration (FDA) and by European regulatory agencies led to a steadily increasing use of these devices. In the study by Dhruva et al,[9] use of the microaxial LVAD increased from 3% to 8% between 2015 and 2017. However, no adequately powered RCT exists for any of the available active mechanical circulatory support devices in the setting of cardiogenic shock.[8] In 2008, an early version of the microaxial LVAD (the Impella 2.5 device) received FDA 510(k) clearance for high-risk PCI; subsequently, other models of the device (Impella CP, Impella 5.0) received FDA approval with an expanded indication for cardiogenic shock. Initially, this microaxial LVAD approval was granted for

high-risk PCI procedures for a duration of 6 hours. However, the only RCT that compared this device with IABP in stable patients (PROTECT II trial) was stopped prematurely for futility, and despite a lack of benefit regarding the primary end point (a composite of 11 intra- and postprocedural adverse events at 30 days) this device was approved.[16] In subsequent years, FDA approval for several models of the microaxial LVAD (Impella 2.5, 5.0, LD, and CP) was extended for use for up to 14 days in the management of cardiogenic shock related to acute myocardial infarction and postcardiotomy. For infarct-associated cardiogenic shock, the only available RCT at that point in time (ie, in 2008) was the ISAR-SHOCK trial (Impella 2.5 vs IABP), with a total of 26 patients. In 2017, the IMPRESS in Severe Shock trial (Impella CP vs IABP) randomized a total of 48 patients. Despite some benefit in hemodynamic variables, both trials showed no difference between the treatment groups in 30-day mortality.[17,18] Nevertheless, FDA approval was obtained, and the use of the microaxial LVAD has become an important component for temporary treatment of severe infarct-associated cardiogenic shock, despite limited data of improved patient outcomes.

The study by Dhruva et al[9] questions the approval of such devices without showing evidence for improvement in outcomes, and it challenges the increasingly frequent use of the microaxial LVAD in the United States. The results of the current analysis are consistent with the results of a multinational registry of 237 patients with infarct-related cardiogenic shock that were matched with 237 patients from the IABP-SHOCK II trial.[19] That study also showed significantly higher risks of bleeding (8.5% vs 3.0%) and peripheral vascular complications (9.8% vs 3.8%) in patients treated with this microaxial LVAD device (compared with IABP or no IABP) without any survival benefit (30-day mortality 48.5% vs 46.4%).[19] Another recent study using a US registry (the Premier Healthcare Database), which included 48 306 patients undergoing percutaneous coronary intervention and who were deemed to require circulatory support, also showed higher mortality with this microaxial LVAD than with the IABP (odds ratio, 1.24 [95% CI, 1.13-1.36]).[20] The mechanism of possible harm associated with this microaxial LVAD is likely an excess in device-related complications (which might outweigh any hemodynamic benefit). Furthermore, recent biomarker analyses support the theory that worse outcomes in cardiogenic shock at a certain stage are not related to impairment in cardiac function but more to a systemic inflammatory response syndrome associated with cardiogenic shock.[21]

The conflicting and insufficient evidence of active mechanical circulatory support in cardiogenic shock supports the need for large clinical trials to more definitively assess this important issue. Currently, no device, including the extracorporeal membrane oxygenator (ECMO), has been adequately studied in a well-powered RCT, which will be required to generate reliable evidence for use of mechanical circulatory support devices in clinical practice. Several ongoing clinical trials are currently examining the use of mechanical circulatory support devices: (1) the Danish-German Shock trial (DanGer; n = 360; NCT01633502); the Extracorporeal Life Support in Cardiogenic Shock trial (ECLS-SHOCK; n = 420; NCT03637205); the Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock trial (ANCHOR; n = 400; NCT04184635); the Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock trial (EUROSHOCK; n = 428; NCT03813134); and the ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock trial (ECMO-CS; n = 120; NCT02301819).

The results of these trials will help to define appropriate use of mechanical circulatory support devices. However, until reliable evidence from RCTs is available, the study by Dhruva et al,[9] together with other registry studies, provide evidence to support a more restrictive use of these devices and as based on current guidelines, only in selected patients with refractory cardiogenic shock.

ARTICLE INFORMATION

Author Affiliations: Heart Center Leipzig, University of Leipzig, Leipzig, Germany; Leipzig Heart Institute, Leipzig, Germany.

Corresponding Author: Holger Thiele, MD, Heart Center Leipzig, Department of Internal Medicine/Cardiology, University of Leipzig, Strümpellstr. 39, 04289 Leipzig, Germany (holger.thiele@medizin.uni-leipzig.de).

Published Online: February 10, 2020. doi:10.1001/jama.2019.22382

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock; SHOCK Investigators: should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med*. 1999;341(9):625-634. doi:10.1056/NEJM199908263410901

2. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation*. 2009;119(9):1211-1219. doi:10.1161/CIRCULATIONAHA.108.814947

3. Thiele H, Zeymer U, Neumann F-J, et al; Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial investigators. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12-month results of a randomised open-label trial. *Lancet*. 2013;382(9905):1638-1645. doi:10.1016/S0140-6736(13)61783-3

4. Thiele H, Zeymer U, Neumann F-J, et al; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367(14):1287-1296. doi:10.1056/NEJMoa1208410

5. Thiele H, Zeymer U, Thelemann N, et al; IABPSHOCK II Trial (Intraaortic Balloon Pump in Cardiogenic Shock II) Investigators. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II Trial. *Circulation*. 2018;139(3):395-403. doi:10.1161/CIRCULATIONAHA.118.038201

6. Sandhu A, McCoy LA, Negi SI, et al. Use of mechanical circulatory support in patients undergoing percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. *Circulation*. 2015;132(13):1243-1251. doi:10.1161/CIRCULATIONAHA.114.014451

7. Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med*. 2016;42(5):889-896. doi:10.1007/s00134-016-4273-z

8. Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of

randomized trials. *Eur Heart J*. 2017;38(47):3523-3531. doi:10.1093/eurheartj/ehx363

9. Dhruva SS, Ross JS, Mortazavi BJ, et al. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA*. doi:10.1001/jama.2020.0254

10. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394

11. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393

12. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425. doi:10.1161/CIR.0b013e3182742c84

13. Helgestad OKL, Josiassen J, Hassager C, et al. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study. *Eur J Heart Fail*. 2019;21(11):1370-1378; epub ahead of print. doi:10.1002/ejhf.1566

14. Rathod KS, Koganti S, Iqbal MB, et al. Contemporary trends in cardiogenic shock: Incidence, intra-aortic balloon pump utilisation and outcomes from the London Heart Attack Group. *Eur Heart J Acute Cardiovasc Care*. 2018;7(1):16-27. doi:10.1177/2048872617741735

15. Backhaus T, Fach A, Schmucker J, et al. Management and predictors of outcome in unselected patients with cardiogenic shock complicating acute ST-segment elevation myocardial infarction: results from the Bremen STEMI Registry. *Clin Res Cardiol*. 2018;107(5):371-379. doi:10.1007/s00392-017-1192-0

16. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation*. 2012;126(14):1717-1727. doi:10.1161/CIRCULATIONAHA.112.098194

17. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol*. 2008;52(19):1584-1588. doi:10.1016/j.jacc.2008.05.065

18. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol*. 2017;69(3):278-287. doi:10.1016/j.jacc.2016.10.022

19. Schrage B, Ibrahim K, Loehn T, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation*. 2019;139(10):1249-1258. doi:10.1161/CIRCULATIONAHA.118.036614

20. Amin AP, Spertus JA, Curtis JP, et al. The evolving landscape of Impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support. *Circulation*. 2020;141(4):273-284. doi:10.1161/CIRCULATIONAHA.119.044007

21. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation*. 2003;107(24):2998-3002. doi:10.1161/01.CIR.0000075927.67673.F2