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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Percutaneous Ventricular Assist Devices: A Health Technology Assessment

KEY MESSAGES

The Impella device is a percutaneous ventricular assist device that has a small pump at one end of a thin, flexible tube. It is implanted through an artery in the leg and pumps blood from the left ventricle through the heart valve into a blood vessel called the ascending aorta. The other end of the tube is connected to a special control system (console) outside the body that controls the pump rate.

This review looked at how well the Impella percutaneous ventricular assist device works and how safe it is for patients. It also considered how much the device costs.

Percutaneous ventricular support with Impella can help to maintain blood flow and blood pressure during high-risk heart procedures and when the heart suddenly cannot pump enough blood (cardiogenic shock). However, percutaneous ventricular support with Impella does not lower death rates; nor is it safer or cheaper than usual treatment with balloon pumps. The economic evaluation shows that Impella devices do not provide a better value for money than balloon pumps for treating patients who receive high-risk percutaneous coronary intervention.

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ABSTRACT

Background

Percutaneous coronary intervention (PCI)—using a catheter to place a stent to keep blood vessels open—is increasingly used for high-risk patients who cannot undergo surgery. Cardiogenic shock (when the heart suddenly cannot pump enough blood) is associated with a high mortality rate. The percutaneous ventricular assist device can help control blood pressure and increase blood flow in these high-risk conditions. This health technology assessment examined the benefits, harms, and budget impact of the Impella percutaneous ventricular assist device in high-risk PCI and cardiogenic shock. We also analyzed cost-effectiveness of the Impella device in high-risk PCI.

Methods

We performed a systematic search of the literature for studies examining the effects of the Impella percutaneous ventricular assist device in high-risk PCI and cardiogenic shock, and appraised the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria, focusing on hemodynamic stability, mortality, major adverse cardiac events, bleeding, and vascular complications. We developed a Markov decision-analytical model to assess the cost- effectiveness of Impella devices versus intra-aortic balloon pumps (IABPs), calculated incremental cost-effectiveness ratios (ICERs) using a 10-year time horizon, and conducted sensitivity analyses to examine the robustness of the estimates. The economic model was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Results

Eighteen studies (one randomized controlled trial and 10 observational studies for high-risk PCI, and one randomized controlled trial and six observational studies for cardiogenic shock) were included in the clinical review. Compared with IABPs, Impella 2.5, one model of the device, improved hemodynamic parameters (GRADE low–very low) but showed no significant difference in mortality (GRADE low), major adverse cardiac events (GRADE low), bleeding (GRADE low), or vascular complications (GRADE low) in high-risk PCI and cardiogenic shock. No randomized controlled trials or prospective observational studies with a control group have studied Impella CP and Impella 5.0 (other models of the device) in patients undergoing high-risk PCI or patients with cardiogenic shock.

The economic model predicted that treatment with the Impella device would have fewer quality-adjusted life-years (QALYs) and higher costs than IABP in high-risk PCI patients. These observations were consistent even when uncertainty in model inputs and parameters was considered. We estimated that adopting Impella would increase costs by $2.9 to $11.5 million per year.

Conclusions

On the basis of evidence of low to very low quality, Impella 2.5 devices were associated with improved hemodynamic stability, but had mortality rates and safety profile similar to IABPs in high-risk PCI and cardiogenic shock. Our cost-effectiveness analysis indicated that Impella 2.5 is likely associated with greater costs and fewer quality-adjusted life years than IABP.

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BACKGROUND

Health Condition

One treatment for coronary artery disease is percutaneous coronary intervention (PCI), where a physician typically uses a catheter to place a stent that will keep a blood vessel open. Another alternative is open-heart surgery. High-risk patients are increasingly being offered PCI rather than surgery. Although there is no unifying definition of high-risk PCI, reasons surgery is contraindicated fall into three general categories: patient-specific factors (e.g., prior myocardial infarction), anatomic-specific factors (e.g., stenosis of the left main artery of the heart), and clinical presentation–specific factors (e.g., acute coronary syndrome).[1]

Cardiogenic shock is defined as a state of systemic tissue hypoperfusion caused by left ventricular, right ventricular, or biventricular injury, resulting in failure of the heart to pump blood.[2] Cardiogenic shock attributable to acute myocardial infarction is associated with a high mortality rate.[3] Mortality from cardiogenic shock reaches 50% to 80% in patients treated conservatively.[4]

In fiscal year 2015/2016, the estimated prevalence of high-risk PCI and cardiogenic shock with the use of IABP or Impella devices in Ontario was 184 and 171, respectively (written communication, Anne Forsey, Cardiac Care Network of Ontario, June 2016).

Clinical Need and Target Population

Patients with poor left ventricular function undergoing high-risk PCI sometimes develop myocardial ischemia. This inadequate blood supply can cause hypotension (low blood pressure) and decreased cardiac output, which will eventually result in coronary hypoperfusion (poor blood circulation in the heart), heart failure, and hemodynamic collapse.[5]

Cardiogenic shock from various causes leads to systemic hypoperfusion (i.e., inadequate supply of oxygen and nutrients to the body tissues). If not reversed, it is followed by multiple organ dysfunction and eventually death. Patients in profound cardiogenic shock might not respond to increasing doses of inotropes (drugs that alter the contractility of the heart) or intra-aortic balloon pumps (IABPs).[6]

Percutaneous circulatory support systems include IABPs, extracorporeal membrane oxygenation (ECMO), TandemHeart, and Impella.[1] Although IABPs are often used in Ontario, they offer only modest hemodynamic support and myocardial protection. The effectiveness of IABP depends on timing of balloon inflation and deflation, as well as electrocardiographic rhythm or arterial pressure triggers. In contrast, the Impella device requires neither specific timing nor a trigger from an electrocardiographic rhythm or arterial pressure. The cardiac output from Impella devices (2.5–5.0 L/min) is greater than output from IABPs (0.5 L/min). While ECMO can provide full hemodynamic support, the device is complex and requires perfusion expertise to operate. It is seldom used in catheterization laboratories.[7] TandemHeart is a left atrial-to-femoral arterial–ventricular assist device driven by a low-speed centrifugal continuous flow pump to provide an uploading capacity of up to 4.5 L/min. It requires transseptal puncture (i.e., direct access to the left side of the heart) and arterial cannulation to insert a large 15- to 17-Fr sheath.[8]

Technology

The Impella percutaneous ventricular assist device is a minimally invasive, catheter-based rotary pump. It is placed retrogradely across the aortic valve into the left ventricle via the femoral artery. The device directly unloads the left ventricle by aspirating blood from the left ventricle and expelling it into the aorta to increase total cardiac output, reduce myocardial oxygen consumption, decrease pulmonary capillary wedge pressure, and improve coronary perfusion.[9,10]

Three models of the Impella device are available in Canada:

1. Impella 2.5: a 12-F device with maximal flow rates of 2.5 L/min, placed through a femoral percutaneous approach

2. Impella CP (cardiac power): a 14-F device with maximal flow rates of 3.5 L/min, placed through a femoral percutaneous approach

3. Impella 5.0: a 21-F device with maximal flow rates of 5.0 L/min; placement requires an open femoral artery cut down

All three models could be used as a circulatory support system 1) for patients with reduced left ventricular function, for example, after cardiotomy (surgical incision of the heart), in low cardiac output syndrome, for cardiogenic shock after acute myocardial infarction, and 2) during coronary bypass surgery on the beating heart, particularly in patients with limited preoperative ejection fraction with a high risk of postoperative low cardiac output syndrome. The Impella 2.5 and Impella CP could also be used as prophylactic circulatory support in high-risk PCI.

Impella devices are placed across the aortic valve which can increase the risk of valve injury or aortic regurgitation (blood flowing backwards into the heart). In addition, positioning the Impella catheter in the left ventricular cavity can increase the risk of ventricular arrhythmia. Hemolysis (rupture of red blood cells) is also a concern because of the high shear stress of the pump on red blood cells.[5] Given that inserting Impella devices requires femoral artery access with larger sheaths, there are potential risks of access site bleeding, hematoma, and vascular complications.[11] Impella devices are contraindicated for patients with left ventricular thrombus (blood clot in the heart) or severe aortic stenosis.

Regulatory Information

The Impella percutaneous ventricular assist device system (Abiomed, Inc.), including Impella 2.5, Impella 5.0, and Impella CP, is licensed by Health Canada (licence number 74175) as a Class 4 device. It is intended to provide hemodynamic support of the left ventricle in situations where a patient has hemodynamic impairment, or where hemodynamic instability is expected, in order to prevent the patient from experiencing hemodynamic collapse and shock (written communication, Marie Rochefort, Device Licensing Services Division, Medical Devices Bureau, Health Canada, October 2015).

Since initial approval from Health Canada, the names of the devices have been changed for marketing purposes, i.e., from Recover LP 2.5/5.0 to Impella LP (LP stands for left peripheral) 2.5/5.0, then to Impella 2.5/5.0. However, the technology itself remained the same (written communication, Mandy Ford, Clinical Consultant, Abiomed, Inc, March 2016).

In March 2015, the US Food and Drug Administration (FDA) approved Impella 2.5 for elective and urgent high-risk PCI conditional upon conducting a post-approval study: a new prospective multicentre, single-arm study to characterize the Impella 2.5 system outcomes at discharge and 90 days compared with outcomes from the PROTECT II trial (Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention) with a 1-year follow-up.[12]

In April 2016, the FDA approved Impella 2.5, Impella CP, and Impella 5.0 devices for cardiogenic shock after acute myocardial infarction or open-heart surgery. Approval was based on data from the Recover I study, the USpella registry, 17 clinical studies, and safety data from FDA's medical device reporting database.[13]

Context

The provinces of Ontario, Quebec, Alberta, New Brunswick, Nova Scotia, and Manitoba have general billing codes for inserting percutaneous ventricular assist devices; however, specific brands are not named. These billing codes could be used to claim for inserting Impella devices in Ontario. The Impella devices themselves are not publicly funded by provincial programs, although individual hospitals can purchase devices as they wish.

Table 1 lists cardiac centres currently implanting Impella percutaneous ventricular assist devices in Ontario. Although Impella 2.5 is available for sale in Canada, all six centres use Impella CP because of the higher flow rate at the same price as Impella 2.5 (written communication, Mandy Ford, Abiomed Inc., May 2016).

Table 1: Cardiac Centres Currently Implanting Impella Percutaneous Ventricular Assist Devices in Ontario

Cardiac Centres	Impella Models Used
Hamilton Health Sciences Centre	CP, 5.0
Health Sciences North	CP, 5.0
St Michael's Hospital	CP
University Health Network	CP, 5.0
University of Ottawa Heart Institute	CP, 5.0
Windsor Regional Hospital	CP

Abbreviation: CP, cardiac power.
Source: Mandy Ford, Clinical Consultant, Abiomed Inc., written communication, May 2016.

Table 2 shows the number of patients who received IABPs and Impella devices during their hospitalization in Ontario over the last 5 years.

Table 2: Number of Patients who Received Intra-Aortic Balloon Pump and Impella Percutaneous Ventricular Assist Devices in Ontario Within Last 5 Years

Fiscal Year[a]	IABPs	Impella Devices
2010	262	<5
2011	614	6
2012	569	8
2013	527	5
2014	568	12
2015	520	27

Abbreviation: IABP, intra-aortic balloon pump.

[a]Data could be under-reported, as it was not until July 2015 that procedures performed in cardiac catheterization laboratories and cardiac surgeries became a mandatory field in the Cardiac Care Network Registry. In addition, IABPs inserted in intensive care units and at nonadvanced cardiac hospitals were not reflected in registry.

Source: Cardiac Care Network of Ontario (written communication, June 2016).

Research Questions

- What are the benefits and harms of Impella percutaneous ventricular assist devices in providing hemodynamic support in (1) high-risk PCI and (2) cardiogenic shock?
- What is the cost-effectiveness of Impella percutaneous ventricular assist devices in providing hemodynamic support in (1) high-risk PCI and (2) cardiogenic shock?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this clinical evidence review was to assess the benefits and harms of Impella percutaneous ventricular assist devices in providing hemodynamic support in 1) high-risk percutaneous coronary intervention (PCI) and 2) cardiogenic shock.

Methods

Research questions are developed by Health Quality Ontario in consultation with experts, end users, or applicants in the topic area.

Sources

We performed a literature search on December 7, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database, for studies published from January 1, 1946, to December 7, 2015.

The websites of Canadian health technology assessment agencies (Canadian Agency for Drugs and Technologies in Health [CADTH], Institute of Health Economics, University of Calgary Institute for Public Health Technology Assessment Unit, Institut national d'excellence en sante et en services sociaux [INESS], Centre for Evaluation of Medicines at McMaster University, Centre for Health Services and Policy Research at the University of British Columbia, Institute for Clinical Evaluative Sciences Ontario, Technology Assessment Unit at McGill University Health Centre) were also searched for reports about Impella percutaneous ventricular assist devices used for high-risk PCI and cardiogenic shock.

In 2009, McGill University Health Centre published a health technology assessment on the Impella percutaneous ventricular assist device in high-risk PCI and cardiogenic shock.[14] This health technology assessment included a comprehensive literature search and identified 45 publications, which were virtually all case series and single case studies, except for only one randomized controlled trial published in 2008.[15] Because case series and single case studies were excluded from our review, we included the single randomized controlled trial published in 2008 and all studies published from 2009 onward that met the inclusion criteria.

Search strategies were developed by medical librarians using medical subject headings (MeSH). The final search strategy was peer-reviewed using the PRESS Checklist.[16] See Appendix 1 for details, including all search terms.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- randomized controlled trials, systematic reviews, meta-analyses, health technology assessments, observational studies (retrospective chart review, prospective registry) published from 2009 onward
- studies that examined Impella percutaneous assist devices in high-risk PCI or cardiogenic shock

Exclusion Criteria

- Nonhuman studies
- Case reports, case series, editorials, letters to editor, abstracts, nonsystematic reviews
- Concurrent use of other mechanical circulatory systems that support blood flow, for example, intra-aortic balloon pump (IABP) or ECMO, for patients with cardiogenic shock

Outcomes of Interest

- Hemodynamic stability
- Mortality
- Adverse events (i.e., myocardial infarction, stroke, revascularization, bleeding complications, and vascular complications)

Data Extraction

We extracted relevant data on study characteristics—including study design, sample size, follow-up duration, comparators, reported outcomes, and outcome definition—and summarized them in our tables.

Statistical Analysis

We did not pool the results of the studies because definitions of the composite outcomes and the varied time points of the outcomes were different in the various studies. Instead, we summarized results in tables.

Quality of Evidence

We examined the quality of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[17] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Expert Consultation

We asked experts about Impella percutaneous ventricular assist devices from December 2015 to June 2016. These experts included interventional cardiologists, heart failure specialists, and cardiac surgeons. Our expert advisors provided advice on research questions, review methods and review results, and placed the evidence on the benefits and harms of Impella percutaneous ventricular assist devices in context. However, statements, conclusions, and views expressed in this report do not necessarily represent the views of these experts.

Results

Literature Search

The database search yielded 2,376 citations published between January 1, 1946, and December 7, 2015. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment.

For the high-risk PCI population, 11 studies (one randomized controlled trial and 10 observational studies) met the inclusion criteria. For the cardiogenic shock population, seven studies (one RCT and six observational studies) met the inclusion criteria. We hand-searched the reference lists of included studies, along with health technology assessment websites and other sources but did not identify additional relevant studies.

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[18]

Identification

Records identified through
database searching (n = 3,440)

Additional records identified through
other sources (n = 0)

Records after duplicates removed
(n = 2,376)

Screening

Records screened
(n = 2,376)

Records excluded
(n = 2,307)

Eligibility

Full-text articles assessed
for eligibility (n = 69)

Full-text articles excluded (n = 51)
- Concurrent use of other mechanical circulatory systems (n = 12)
- Published before 2009 (n = 2)
- Report combined data for Impella and other mechanical circulatory systems (n = 10)
- Small sample size (n = 8)
- Populations not predefined (n = 2)
- Outcomes not predefined (n = 8)
- Research questions not predefined (n = 5)
- Case series (n = 4)

Included

Studies included in
qualitative synthesis
(n = 11 for high-risk PCI;
n = 7 for cardiogenic shock)

Studies included in
quantitative synthesis
(meta-analysis) (n = 0)

Figure 1: PRISMA Flow Diagram for Clinical Evidence Review

Abbreviations: PCI, percutaneous coronary intervention; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[18]

High-Risk PCI

Randomized Controlled Trial

Only one of the 11 included studies was a randomized controlled trial—the PROTECT II trial. This prospective, multicentre randomized trial was conducted in 112 sites in the United States, Canada, and Europe, and recruited symptomatic patients with complex three-vessel disease or unprotected left main coronary artery disease and severely depressed left ventricular function undergoing nonemergency high-risk PCI. The PROTECT II trial was terminated early for futility reasons, thus not meeting its target recruitment of 654 patients. The primary intent-to-treat analysis included 448 patients randomly assigned to Impella 2.5 (n = 225) or IABP (n = 223). The per-protocol population included 427 patients who met the eligbility criteria (216 for Impella 2.5 and 211 for IABP).[19]

The primary outcome was the composite rate of major adverse events during and after the procedure at discharge or at 30-day follow-up, whichever was longer. Components of the composite outcome included all-cause death, Q-wave or non–Q-wave myocardial infarction, stroke or transient ischemic attack, any repeat revascularization procedure (PCI or coronary artery bypass graft), need for a cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI.[19]

Observational Studies

In addition to the PROTECT II trial, 10 observational studies met the inclusion criteria. Seven of these studies were noncomparative[5,20-25]; one compared Impella 2.5 with IABP[11]; one compared Impella 2.5 with TandemHeart[8]; and one compared Impella with either IABP or TandemHeart.[26] Researchers reported various outcomes for benefits and harms.

Boudoulas et al[11] compared Impella 2.5 (n = 13) with IABP (n = 62) in a single-centre retrospective chart review from October 2008 to November 2010. There were significant differences in severity of disease at baseline between the Impella 2.5 and IABP groups (myocardial infarction: 15.3% vs. 59.6%; cardiogenic shock: 7.6% vs. 43.5%).

Kovacic et al[8] included 36 patients with Impella 2.5 and 32 patients with TandemHeart devices undergoing high-risk PCI in a single-centre prospective study. Device selection was performed on a temporal basis with exclusive use of TandemHeart from April 2005 to October 2007 and of Impella 2.5 from October 2007 to June 2010. This method of device selection did not allow direct comparison between devices. Therefore, only the group receiving Impella 2.5 was analyzed in this review as a noncomparative study.

Schwartz et al[26] reviewed the medical charts of 50 patients from January 2008 to June 2010 in a single-centre retrospective study. Among these patients, five had IABP, 13 had Impella 2.5, and 32 had TandemHeart devices. Device selection was a measure of disease severity (i.e., least risk for IABP, intermediate risk for Impella 2.5, and highest risk for TandemHeart). Because of the different patient characteristics in each group at baseline, outcomes were not directly comparable. Therefore, only the group receiving Impella 2.5 was analyzed in this review as a noncomparative study.

Among the noncomparative studies, there were two multicentre registries funded by the manufacturer of Impella devices—the USpella registry and the Europella registry.[22,24,25] The USpella registry involved 47 sites in the United States and two sites in Canada. Two studies

from the USpella registry met the inclusion criteria of this review.[22,24] The study by Cohen et al[22] included 637 patients from June 2007 to September 2013 and reported only in-hospital outcomes, whereas the study by Maini et al[24] included 175 patients from June 2009 and March 2010 and reported both in-hospital and 30-day outcomes. It is possible that these two studies contain overlapping data. The Europella registry comprised 144 patients from 10 sites in Europe.[25] The USpella registry included patients who underwent elective or emergency PCI, while the Europella registry included patients who underwent elective PCI only.

The remaining four noncomparative observational studies were single-centre retrospective chart reviews or observational studies with a sample size of 20 to 60 patients.[5,20,21,23] The study by Alasnag et al[20] was on elective PCI, and the study by Iliodromitis et al[23] was on emergency PCI only. The other two noncomparative studies did not specify whether the PCI was elective or emergency or both.[5,21]

In a single-centre retrospective chart review of all patients who had Impella-assisted procedures between October 2008 and January 2014, 45 patients were at high risk.[27] Of the 44 patients with successful Impella implantation, 34 received Impella 2.5 and 10 received Impella 3.8 (the UK brand of Impella CP). Since this study did not report outcomes by the model of Impella device, and each model has a different flow rate and gauge, the outcomes of this study are not compared with studies that reported outcomes by model. The 30-day outcomes for mortality, bleeding requiring blood transfusion, stroke, and periprocedural myocardial infarction were 18%, 5%, 2%, and 2%, respectively. No vascular complications were reported.[27]

The literature search also identified two systematic reviews on percutaneous ventricular assist devices in high-risk PCI.[28,29] Both reviews included the PROTECT II trial as the single randomized controlled trial on Impella devices for high-risk PCI.[19] Because the methodologic quality of the PROTECT II trial was assessed separately in this review, the quality of these two published reports[28,29] was not assessed and will not be discussed further in this review.

Based on small case series and single case reports, a health technology assessment conducted by the McGill University Health Centre in 2009[14] reported that the Impella device was more clinically effective with higher survival rate than IABP or ECMO as circulatory support in high-risk PCI. However, this health technology assessment did not assess the quality of the included studies.

Table 3 summarizes the characteristics of the included studies on Impella percutaneous ventricular assist devices in high-risk PCI.

Table 3: Characteristics of Studies on Impella Percutaneous Ventricular Assist Devices in High-Risk PCI

Author, Year	Sample Size, n	Study Design	Elective or Emergency PCI?	Additional Information
Comparison of Impella 2.5 With IABP				
Boudoulas et al, 2012[11]	13 (Impella 2.5), 62 (IABP)	Single-centre retrospective chart review	NR	• Included patients with cardiogenic shock (7.6% in Impella 2.5, 43.5% in IABP)
O'Neill et al, 2012[19] PROTECT II trial	ITT population 225 (Impella 2.5), 223 (IABP)	Multicentre RCT	Elective	• Funded by manufacturer
Noncomparative Observational Studies on Impella 2.5				
Alasnag et al, 2011[20]	60	Single-centre retrospective chart review	Elective	
Anusionwu et al, 2012[21]	25	Single-centre retrospective chart review	NR	
Cohen et al, 2015[22] USpella registry	637	Multicentre retrospective observational study	Elective and emergency	• Funded by manufacturer
Dixon et al, 2009[5] PROTECT I study	20	Multicentre prospective observational study	NR	• Funded by manufacturer
Iliodromitis et al, 2011[23]	38	Single-centre prospective observational study	Emergency	• Patients with acute coronary syndrome required urgent revascularization
Kovacic et al, 2013[8]	36 (Impella 2.5), 32 (TandemHeart)	Single-centre prospective observational study	NR	• Device selection of Impella 2.5 or TandemHeart on temporal basis[a]. Not comparable between groups. Only Impella 2.5 group was reviewed
Maini et al, 2012[24] USpella registry	175	Multicentre retrospective observational study	Elective and emergency	• Funded by manufacturer
Schwartz et al, 2011[26]	13 (Impella 2.5), 5 (IABP), 32 (TandemHeart)	Single-centre retrospective chart review	Elective	• Device selection of Impella 2.5 or TandemHeart based on disease severity. Not comparable between groups. Only Impella 2.5 group was reviewed. • Included patients stabilized after cardiogenic shock (23% in Impella 2.5 group)
Sjauw et al, 2009[25] Europella registry	144	Multicentre retrospective observational study	Elective	• Funded by manufacturer

Abbreviations: IABP, intra-aortic balloon pump; ITT, intent-to-treat; NR, not reported; PCI, percutaneous coronary intervention; PROTECT, Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention; RCT, randomized controlled trial.
[a]Device selection was performed on a temporal basis with exclusive use of TandemHeart from April 2005 to October 2007 and of Impella 2.5 from October 2007 to June 2010.

Methodologic Quality of Included Studies
Complete results of the methodology checklist for included studies on high-risk PCI are presented in Appendix 2. Eleven studies were deemed directly applicable or partially applicable to the research question. The quality of evidence was assessed as low for hemodynamic stability, mortality, and major adverse cardiac events (MACEs), and as very low for bleeding complications and vascular complications when Impella 2.5 was compared with IABP.

Results for Hemodynamic Stability
Table 4 presents findings for the outcome of hemodynamic stability.

Table 4: Hemodynamic Stability

Author, Year	Hemodynamic Stability
Comparison of Impella 2.5 With IABP	
O'Neill et al, 2012[19]	Maximal decrease in cardiac power output Impella: −0.04 ± 0.24 W
	IABP: −0.14 ± 0.27 W
	P = .001
Noncomparative Observational Studies on Impella 2.5	
Cohen et al, 2015[22]	Transient hypotension during support: 7.1% (5.1%–9.1%)
Dixon et al, 2009[5]	Freedom from hemodynamic compromise[a]: 100%
Iliodromitis et al, 2011[23]	Hemodynamic stability: 100%
Maini et al, 2012[24]	Transient hypotension during support: 3.4%

Abbreviations: IABP, intra-aortic balloon pump.
[a]Defined as a decrease in mean arterial pressure below 60 mmHg for >10 min.

Various outcomes were used to measure hemodynamic stability. In the PROTECT II trial, patients randomized to receive Impella 2.5 support had a significantly lower maximal decrease in cardiac power output than those using IABPs, indicative of better hemodynamic stability.[19]

The two studies published from the USpella registry reported that 3.4% to 7.1% of patients had transient hypotension while receiving Impella 2.5 support.[22,24] In the PROTECT I clinical study, all patients were free from hemodynamic compromise, defined by a decrease in mean arterial pressure below 60 mmHg for more than 10 min.[5] Similarly, the single-centre study by Iliodromitis et al[23] also did not report any hemodynamic instability, as indicated by severe hypotension, during the entire PCI.

The quality of evidence was assessed as low for hemodynamic stability when Impella 2.5 was compared with IABP (Table 5).

Table 5: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in High-Risk PCI—Hemodynamic Stability

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
4 observational studies[5,22-24]	Serious limitations[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

[a]Optimal sample size not met. Trial was terminated early for futility reasons; at risk of selection bias.

[b]Insufficient statistical power.

[c]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of study conduct.

Results for Mortality

Table 6 presents findings for the outcome of mortality at various time points.

Table 6: Mortality

Author, Year	Mortality		
	In-Hospital	**30-Day**	**12-Month**
Comparison of Impella 2.5 With IABP			
O'Neill et al, 2012[19]	NR	ITT: 7.6% vs. 5.9% ($P = .47$) PP: 6.9% vs. 6.2% ($P = .74$)	NR
Boudoulas et al, 2012[11]	0% vs. 20.9% ($P = .10$)	NR	15.3% vs. 25.8% ($P = .72$)
Noncomparative Observational Studies on Impella 2.5			
Alasnag et al, 2011[20]	NR	5%	NR
Cohen et al, 2015[22]	2.8%	NR	NR
Dixon et al, 2009[5]	NR	10%	NR
Iliodromitis et al, 2011[23]	NR	2.9%	NR
Kovacic et al, 2013[8a]	0%	2.8%	NR
Maini et al, 2012[24]	3.4%	4%	12%
Schwartz et al, 2011[26b]	NR	0%	NR
Sjauw et al, 2009[25]	NR	5.5%	NR

Abbreviations: IABP, intra-aortic balloon pump; ITT, intent-to-treat; NR, not reported; PP, per protocol.

[a]In the study by Kovacic et al[8], patients received hemodynamic support from either Impella 2.5 or TandemHeart. Device selection was on temporal basis. The groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.

[b]In the study by Schwartz et al[26], patients received hemodynamic support from Impella 2.5, IABP, or TandemHeart. Device selection was based on disease severity. The groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.

In the PROTECT II trial, the 30-day mortality rate was not significantly different between the Impella 2.5 and IABP groups in intent-to-treat analysis and per-protocol analysis. The 90-day mortality between Impella 2.5 and IABP was similar (intent-to-treat analysis: 12.1% vs. 8.7%, P = .24; per-protocol analysis: 11.6% vs. 9.0%, P = .38).[19]

In a single-centre retrospective chart review of patients with acute coronary syndrome undergoing high-risk PCI treated with Impella 2.5 (n = 13) or IABP (n = 62), the in-hospital mortality rate was 0% and 20.9%, respectively (P = .10). At 1-year follow-up, mortality rates were 15.3% in the Impella group and 25.8% in the IABP group (P = .72).[11]

Eight noncomparative observational studies on using Impella 2.5 to support high-risk PCI reported mortality rates.[5,8,20,22-26] The 30-day mortality rates ranged from 0% to 10%. The study that reported a 10% mortality rate[5] had a smaller sample (n = 20) than other studies. The two studies from the USpella registry reported in-hospital mortality rates of 2.8% to 3.4%.[22,24] The similar mortality rates could be due to overlapping populations.

The quality of evidence for mortality was assessed as low when Impella 2.5 was compared with IABP (Table 7).

Table 7: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in High-Risk PCI—Mortality

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
1 observational study[11]	Serious limitations (−1)[c,d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Noncomparative Observational Studies on Impella 2.5							
8 observational studies[5,8,20,22-26]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

[a]Optimal sample size not met. The trial was terminated early for futility reason; at risk of selection bias.

[b]Insufficient statistical power.

[c]Boudoulas et al[11]: significant difference in disease severity at baseline between Impella and IABP groups.

[d]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Major Adverse Cardiac Events

Table 8 presents findings for the outcome of overall and individual rates of MACEs, including myocardial infarction, stroke, and revascularization. The included studies used different definitions for the composite outcome, making comparison across studies difficult.

Table 8: Major Adverse Cardiac Events

Author, Year	Major Adverse Cardiac Events			
	In-Hospital		30-Day	
	Overall	**Individual Events**	**Overall**	**Individual Events**
Comparison of Impella 2.5 With IABP				
O'Neill et al, 2012[19a]	NR	NR	ITT: 35.1% vs. 40.1% (*P* = .28) PP: 34.3% vs. 42.2% (*P* = .092)	ITT MI: 13.8% vs. 10.4% (*P* = .29) Stroke: 0% vs. 1.8% (*P* = .043) RR: 1.3% vs. 4.1% (*P* = .29) PP MI: 13.4% vs. 10.9% (*P* = .43) Stroke: 0% vs. 1.9% (*P* = .042) RR: 1.4% vs. 4.3% (*P* = .072)
Noncomparative Observational Studies on Impella 2.5				
Alasnag et al, 2011[20b]	NR	NR	5%	MI: 0% Stroke: 0% RR: 0% Urgent CABG: 0%
Cohen et al, 2015[22]	NR	MI: 1.3% RR: 0.78%	NR	NR
Dixon et al, 2009[5b]	NR	NR	20%	MI: 10%
Iliodromitis et al, 2011[23]	NR	MI: 63.6%	NR	NR
Kovacic et al, 2013[8c,d]	NR	MI: 6%	8.3%	NR
Maini et al, 2012[24e]	NR	MI: 1.1% Stroke: 0.6%	8%	MI: 1.1% Stroke: 0.6% RR: 0.6%
Schwartz et al, 2011[26f,g]	NR	NR	15%	MI: 0% Stroke: 0%
Sjauw et al, 2009[25h]	NR	NR	12.4%	Stroke: 0.7%

Abbreviations: CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; ITT, intent-to-treat; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; PP, per protocol; RR, revascularization.

[a]Major adverse cardiac events included all-cause death, MI, stroke or transient ischemic attack, repeat revascularization, need for a cardiac or a vascular operation, acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia, aortic insufficiency, and angiographic failure of PCI.

[b]Major adverse cardiac events included death, MI, stroke, target lesion revascularization, and urgent bypass surgery.

[c]Major adverse cardiac events included death, MI and target lesion revascularization.

[d]In the study by Kovacic et al,[8] patients received hemodynamic support from either Impella 2.5 or TandemHeart. Device selection was on temporal basis. Groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.

[e]Major adverse cardiac events included death, MI, stroke or transient ischemic attack, revascularization, and emergency cardiac or vascular surgical operation.

[f]Major adverse cardiac events included death, recurrent ischemia, MI, and stroke.

[g]In the study by Schwartz et al,[26] patients received hemodynamic support from Impella 2.5, IABP, or TandemHeart. Device selection was based on disease severity. The groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.

[h]Major adverse cardiac events included death, MI, stroke, urgent bypass surgery, and major bleeding requiring transfusion.

In the PROTECT II trial, the overall 30-day MACE[*] rate for Impella 2.5 was not significantly different when compared with IABP in intent-to-treat analysis and per-protocol analysis. Both groups have similar rates of myocardial infarction and revascularization. The IABP group has a significantly higher stroke rate than the Impella 2.5 group. However, the absolute number of stroke events was low.[19] At 90-day follow-up, the overall MACE rate for Impella 2.5 was significantly lower than for IABP in per-protocol analysis (40% vs. 51%, P = .023), but not in intent-to-treat analysis (40.6% vs. 49.3%, P = .066).

Because of the difference in radiographic appearance, it was impossible to blind attending physicians to the treatment assignments. Attending physicians used rotational atherectomy, a method of lesion preparation, in patients randomized to the Impella 2.5 group more frequently and more vigorously, resulting in fewer revascularizations but higher incidence of periprocedural myocardial infarction than the IABP group.[19,30] However for patients receiving IABP, physicians in clinical practice would likely use aggressive predilation to prepare the lesion for high-risk PCI. Therefore, the different modality of lesion preparation in Impella 2.5 and IABP did not constitute a bias toward developing MACEs (expert consultation, Dr. Harindra Wijeysundera, Interventional Cardiologist, Sunnybrook Health Sciences Centre, May 2016).

Six noncomparative observational studies reported an overall 30-day MACE rate of 5% to 20%.[5,8,22,24-26] In the study by Iliodromitis et al,[23] approximately 64% of patients had a periprocedural myocardial infarction. The population of this study was patients with acute coronary syndrome requiring emergency revascularization. Because of the complexity of the interventions and the large number of stents used, troponin I increased more than three times the upper limit of normal range 48 hours after the PCI, resulting in type 4a myocardial infarction in approximate two thirds of the patients. In contrast, the periprocedural myocardial infarction rate in the USpella registry was 1.1% to 1.3%.[22,24]

The quality of evidence for MACEs was assessed as low when Impella 2.5 was compared with IABP (Table 9).

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[*]Many trials specified major adverse cardiac and cerebrovascular events (i.e., MACCE in the PROTECT II trial); we include this broader definition in the abbreviation MACE.

Table 9: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in High-Risk PCI—Major Adverse Cardiac Events

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
8 observational studies[5,8,20,22-26]	Serious limitations[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

[a]Optimal sample size not met. Trial was terminated early for futility reason; at risk of selection bias.

[b]Insufficient statistical power.

[c]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Bleeding Complications
Table 10 presents findings for the outcome of bleeding complications, including access site hematoma and major bleeding that required blood transfusion.

Table 10: Bleeding Complications

| | Bleeding Complications | | | |
| | In-Hospital | | 30-Day | |
Author, Year	Femoral Hematoma	Bleeding Requiring Blood Transfusion	Femoral Hematoma	Bleeding Requiring Blood Transfusion
Comparison of Impella 2.5 With IABP				
Boudoulas et al, 2012[11]	NR	38.4% vs. 32.2% (*P* = .74)	NR	NR
Noncomparative Observational Studies on Impella 2.5				
Alasnag et al, 2011[20]	NR	NR	8.3%	10%
Anusionwu et al, 2012[21]	8%	NR	NR	NR
Cohen et al, 2015[22]	11%	NR	NR	NR
Dixon et al, 2009[5]	40%	10%[a]	NR	NR
Iliodromitis et al, 2011[23]	15.8%	34.2%	NR	NR
Kovacic et al, 2013[8b]	3%[a,c]	NR	NR	NR
Maini et al, 2012[24]	8.6%	9.7%	NR	NR
Schwartz et al, 2011[26d]	8%	39%	NR	NR
Sjauw et al, 2009[25]	NR	NR	NR	5.5%

Abbreviations: IABP, intra-aortic balloon pump; NR, not reported.
[a]Time point was not specified in report.
[b]In the study by Kovacic et al,[8] patients received hemodynamic support from either Impella 2.5 or TandemHeart. Device selection was on temporal basis. The groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.
[c]Large hematoma (>4 cm) with blood transfusion.
[h]In the study by Schwartz et al[26], patients received hemodynamic support from Impella 2.5, IABP, or TandemHeart. Device selection was based on disease severity. The groups were not directly comparable. Therefore, only results from the Impella 2.5 group were reviewed.

The PROTECT II trial did not report bleeding complications.[19] The in-hospital rate of blood transfusion due to major bleeding was not statistically different between Impella 2.5 and IABP in the study by Boudoulas et al.[11]

Among the noncomparative observational studies,[5,20-25] the rate of major bleeding requiring blood transfusion ranged from 9.7% to 34.2%. The study[23] that reported a 34.2% of blood transfusion rate comprised patients with acute coronary syndrome undergoing emergency PCI. The rate of femoral hematoma ranged from 8.6% to 40%. The study[5] that reported a 40% of femoral hematoma rate had a small sample size (n = 20) compared with other studies.

The quality of evidence for bleeding complications was assessed as very low when Impella 2.5 was compared with IABP (Table 11).

Table 11: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in High-Risk PCI—Bleeding Complications

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 observational study[11]	Serious limitations (−1)[a,b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Noncomparative Observational Studies on Impella 2.5							
9 observational studies[5,8,20-26]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

[a]Boudoulas et al[11]: significant difference in disease severity at baseline between Impella 2.5 and IABP groups.

[b]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Vascular Complications
In the PROTECT II trial, vascular complications, such as aortic insufficiency and need for a vascular operation, were grouped into the composite outcome of MACEs and were not reported separately.[19] In an observational study by Boudoulas et al,[11] there was no significant difference in in-hospital vascular complication rates between Impella 2.5 and IABP (15.3% vs. 6.4%, P = .27).

In both the USpella registry and the Europella registry, there was a 4% in-hospital rate for major vascular complications, defined as pseudo-aneurysm, arterio-venous fistula, or access site infection.[24,25] The USpella registry also reported that 2.5% of patients with vascular complications required surgery and 5.2% did not require surgery.[22]

Among other noncomparative observational studies, Alasnag et al[20] reported no valve injury and aortic valve regurgitation at 30-day follow-up. The rates for pseudo-aneurysm were 2.6% from the study by Iliodromitis et al[23] and 3% from the study by Kovacic et al.[8]

The quality of evidence for vascular complications was assessed as very low when Impella 2.5 was compared with IABP (Table 12).

Table 12: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in High-Risk PCI—Vascular Complications

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 observational study[11]	Serious limitations (−1)[a,b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Noncomparative Observational Studies on Impella 2.5							
6 observational studies[8,20,22-25]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

[a]Boudoulas et al[11]: significant difference in disease severity at baseline between Impella 2.5 and IABP groups.

[b]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Cardiogenic Shock

Randomized Controlled Trial

Only one of the seven included studies was a randomized controlled trial—the ISAR-SHOCK (Efficacy Study of Left Ventricular Assist Device to Treat Patients With Cardiogenic Shock). This two-centre trial randomized 26 patients with cardiogenic shock caused by acute myocardial infarction into two treatment arms—Impella 2.5 (n = 13) and IABP (n = 13). One patient died before device implantation, leaving 12 patients in the Impella 2.5 arm. The primary outcome was the change of cardiac index from baseline to 30 minutes after implantation. Secondary outcomes were lactate acidosis, hemolysis, and mortality at 30-day follow-up.[15]

Observational Studies

In addition to the ISAR-SHOCK trial, six observational studies met the inclusion criteria.[31-35] One study compared Impella 2.5 with IABP.[36] Among the five noncomparative observational studies, three were on Impella 2.5[31-33] and two were on Impella 5.0.[34,35]

Manzo-Silberman et al[36] compared Impella 2.5 (n = 35) with IABP (n = 43) in a single-centre retrospective study between January 2007 and October 2010. At baseline, patients who received Impella 2.5 support had significantly higher heart rate, but lower left ventricular ejection factor, than those who received IABP support.

Among the three noncomparative observational studies on Impella 2.5, the USpella registry included 154 consecutive patients with acute myocardial infarction and cardiogenic shock who underwent high-risk PCI.[31] The Impella-EUROSHOCK multicentre registry retrospectively included 120 patients with cardiogenic shock from acute myocardial infarction receiving Impella 2.5 support from 2005 to 2010. Ten of these patients required upgrading to other circulatory assist devices with a higher maximum pump flow (Impella 5.0, ECMO, or surgical left ventricular assist device).[32] Casassus et al[33] reviewed the medical charts of 22 patients with acute myocardial infarction complicated by refractory cardiogenic shock from July 2008 to December 2012 in a single-centre retrospective study. The remaining two noncomparative observational studies were either a multicentre retrospective chart review[35] or a multicentre prospective clinical study[34] on Impella 5.0 in patients with refractory cardiogenic shock after cardiotomy.

Three observational studies included patients supported by different models of Impella devices but did not report outcomes by model.[37-39] This did not allow delineation of the effects from each model. In addition, the results were not directly comparable to other studies that reported outcomes by specific model. Therefore, the results of these three studies are described separately here. In a study by Higgins et al[37] of 35 patients, two patients received Impella 2.5, 29 patients received Impella 5.0, and six patients received Impella RD/5.0. The 30-day mortality rate was 40%, and the 60-day mortality rate was 49%. In a study of 47 patients (38 patients on Impella 5.0 and nine patients on Impella 2.5), Lemaire et al[39] reported that the 30-day, 90-day, and 12-month mortality rates were 25%, 34%, and 36%, respectively. Complications occurred in 30% of the population and included device malfunction, high purge pressure, tube fracture, and groin hematoma. In a single-centre retrospective chart review, 29 patients on Impella devices [Impella 5.0 (n = 24) and Impella RD (n = 5)] were compared with 31 patients on ECMO. There was no significant difference in 30-day mortality rate between the Impella group and ECMO group (37.9% vs. 43.8%). However, blood transfusion, as indicated by the amount of blood products used, was significantly less frequent in patients supported by Impella devices than those supported by ECMO ($P < .001$).[38]

The literature search also identified a systematic review on percutaneous ventricular assist devices in cardiogenic shock.[40] Our review included the ISAR-SHOCK trial[15] as the single randomized controlled trial on Impella devices for cardiogenic shock. Given that the methodologic quality of the ISAR-SHOCK trial was assessed separately in our review, the quality of this published report[40] was not assessed and will not be discussed further in our review.

Table 13 summarizes the characteristics of the included studies on Impella percutaneous ventricular assist devices for cardiogenic shock.

Table 13: Characteristics of Studies on Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock

Author, Year	Sample Size, n	Study Design	Indication of Use	Additional Information
Comparison of Impella 2.5 With IABP				
Manzo-Silberman et al, 2013[36]	78 (35 on Impella 2.5, 43 on IABP)	Single-centre retrospective registry	Shock after cardiac arrest	• Impella group has significantly higher heart rate but lower left ventricular ejection factor than IABP group at baseline
Seyfarth et al, 2008[15] ISAR-SHOCK trial	25 (12 on Impella 2.5, 13 on IABP)	Two-centre prospective RCT	CS from acute MI with compromised hemodynamic state	• Initial sample size was 26. One patient died before Impella implantation
Noncomparative Observational Studies on Impella 2.5				
Casassus et al, 2015[33]	22	Single-centre retrospective chart review	Refractory CS from acute MI undergoing PCI	• Prior use of IABP
Lauten et al, 2013[32] Impella-EUROSHOCK registry	120	Multicentre retrospective registry	CS from acute MI	• Prior use of IABP • 8.4% required upgrading to other MCS with higher maximum pump flow (Impella 5.0, ECMO, or surgical LVAD)
O'Neill et al, 2014[31] USpella registry	154	Retrospective analysis of multicentre registry	CS from acute MI undergoing PCI	• Prior use of IABP • Funded by manufacturer
Noncomparative Observational Studies on Impella 5.0				
Engström et al, 2013[35]	46	Three-centre retrospective chart review	Postcardiotomy CS refractory to treatment	• Prior use of IABP
Griffith et al, 2013[34] RECOVER I study	16	Multicentre single-arm prospective study	Postcardiotomy CS refractory to treatment	

Abbreviations: CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; IABP, intra–aortic balloon pump; ISAR-SHOCK, Efficacy Study of Left Ventricular Assist Device to Treat Patients With Cardiogenic Shock; LVAD, left ventricular assist device; MCS, mechanical circulatory support; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

Methodologic Quality of the Included Studies
Complete results of the methodology checklist for included studies on cardiogenic shock are presented in Appendix 2. Seven studies were deemed directly applicable or partially applicable to the research question. The quality of the evidence was assessed as very low for hemodynamic stability and low for mortality, MACEs, bleeding complications, and vascular complications when Impella 2.5 was compared with IABP.

Results for Hemodynamic Stability
Table 14 presents findings for the outcome of hemodynamic stability. The included studies measured different clinical parameters before and after percutaneous ventricular support to quantify its effect on hemodynamic stability.

Table 14: Hemodynamic Stability

Author, Year	Hemodynamic Stability
Comparison of Impella 2.5 With IABP	
Seyfarth et al, 2008[15]	Change of cardiac index after 30 minutes of support
	Impella: 0.49 ± 0.46 L/min/m^2 IABP: 0.11 ± 0.31 L/min/m^2 P = .02
	Diastolic arterial pressure (after vs. before support)
	Impella: Increased by 9.2 ± 12.1 mmHg IABP: Decreased by 8.0 ± 13.1 mmHg P = .002
	Serum lactate
	Impella: 123 ± 87 hrs over mmol/L[a] IABP: 180 ± 147 hrs over mmol/L[a] P = .12
Noncomparative Observational Studies on Impella 2.5	
Casassus et al, 2015[33]	*Before vs. on support*
	Cardiac index: 2.2 ± 0.4 vs. 2.6 ± 0.7 L/min/m^2 (P = .047) Cardiac power index: 0.33 ± 0.1 vs. 0.49 ± 0.2 W/m^2 (P = .02) Systolic blood pressure: 88 ± 25 vs. 111 ± 22 mmHg (P = .003) Diastolic blood pressure: 55 ± 12 vs. 67 ± 10 mmHg (P = .009) Mean arterial pressure: 67 ± 15 vs. 82 ± 13 mmHg (P = .027) Mean pulmonary arterial pressure: 29 ± 10 vs. 21 ± 7 mmHg (P = .011) Pulmonary capillary arterial pressure: 24 ± 10 vs. 16 ± 7 mmHg (P = .027)
Lauten et al, 2013[32]	*Before vs. 48 hr after support*
	Plasma lactate: 5.8 ± 5.0 vs. 2.5 ± 2.6 mmol/L (P = .023)
O'Neill et al, 2014[31]	*Before vs. after support*
	Systolic blood pressure: 85.4 ± 25.6 vs. 126.7 ± 31.4 mmHg (P < .0001) Diastolic blood pressure: 50.8 ± 18.6 vs. 78.7 ± 21.1 mmHg (P < .0001) Mean arterial pressure: 62.7 ± 19.2 vs. 94.4 ± 23.1 mmHg (P < .0001) Pulmonary capillary wedge pressure: 31.9 ± 11.2 vs. 19.2 ± 9.7 mmHg (P < .0001) Cardiac output: 3.4 ± 1.3 vs. 5.3 ± 1.7 L/min (P < .0001) Cardiac index: 1.9 ± 0.7 vs. 2.7 ± 0.7 L/min/m^2 (P < .0001) Cardiac power input: 0.48 ± 0.17 vs. 1.06 ± 0.48 W (P < .0001)
Noncomparative Observational Studies on Impella 5.0	
Griffith et al, 2013[34]	*Before vs. after support*
	Cardiac index: 1.6 ± 0.4 vs. 2.5 ± 0.4 L/min/m^2 (P = .0001) Mean arterial pressure: 71.4 ± 12.5 vs. 83.1 ± 7.5 mmHg (P = .01) Pulmonary artery diastolic pressure: 28.0 ± 3.9 vs. 19.8 ± 3.2 mmHg (P < .0001)

Abbreviation: IABP, intra-aortic balloon pump.
[a]Results were area under the curve.

In the RCT by Seyfarth et al,[15] the primary outcome was the change in cardiac index. Patients randomized to receive Impella 2.5 had a significant increase in cardiac index after 30 minutes of support, compared with those randomized to receive IABP. However, there was no significant difference in serum lactate between groups (secondary outcome). The early time points (30

minutes) chosen for hemodynamic outcomes did not allow extrapolation to the effects of longer Impella 2.5 support.

All noncomparative observational studies showed that patients who received circulatory support from Impella 2.5 or Impella 5.0 have significantly improved hemodynamic parameters, including systolic and diastolic blood pressure, cardiac output, cardiac index, and pulmonary arterial pressure.[31-34]

The quality of evidence for hemodynamic stability was very low when Impella 2.5 was compared with IABP (Table 15).

Table 15: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock—Hemodynamic Stability

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations[d]	Undetected	None	⊕ Very Low
Noncomparative Observational Studies on Impella 2.5							
3 observational studies[31-33]	Serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 5.0							
1 observational study[34]	Serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Early time points for hemodynamic outcomes limited generalizability to effects of longer Impella 2.5 support.

[d]Wide confidence interval for difference in the change of cardiac index between Impella 2.5 and IABP (0.38 [0.07, 0.69] L/min/m^2).

[e]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Mortality
Table 16 presents findings for the outcome of mortality at various time points.

Table 16: Mortality

Author, Year	Mortality		
	30-Day	**6-Month**	**12-Month**
Comparison of Impella 2.5 With IABP			
Manzo-Silberman et al, 2013[36]	23% vs. 29.5% (P = .61)	NR	NR
Seyfarth et al, 2008[15]	46% vs. 46%	NR	NR
Noncomparative Observational Studies on Impella 2.5			
Casassus et al, 2015[33]	NR	40.9%	45.5%
Lauten et al, 2013[32]	64.2%	NR	71.7%[a]
O'Neill et al, 2014[31]	49.3%	NR	NR
Noncomparative Observational Studies on Impella 5.0			
Engström et al, 2013[35]	60.5%	NR	NR
Griffith et al, 2013[34]	6.3%	19%	25%

Abbreviations: IABP, intra-aortic balloon pump; NR, not reported.
[a]After 316 ± 526 days.

In the randomized controlled trial by Seyfarth et al,[15] the 30-day mortality rate was the same for both Impella 2.5 and IABP. Similarly, there was no statistically difference in 30-day mortality rate between Impella 2.5 and IABP in the observational study by Manzo-Silberman et al.[36]

The mortality rates at different time points in noncomparative observational studies on Impella 2.5 and Impella 5.0 largely varied, which could partially reflect the different degree of clinical severity of the patient populations.[31-35]

The quality of evidence for mortality was assessed as low when Impella 2.5 was compared with IABP (Table 17).

Table 17: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock—Mortality

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[c]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
3 observational studies[31-33]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 5.0							
1 observational study[34,35]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Imprecision due to small sample size.

[d]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Major Adverse Cardiac Events
Table 18 presents findings for the outcome of overall and individual rates of MACEs, including myocardial infarction, stroke, and revascularization. The included studies used different definitions for the composite outcome, making comparison across studies more difficult.

Table 18: Major Adverse Cardiac Events

| | Major Adverse Cardiac Events | | | |
| | In-Hospital | | 30-Day | |
Author, Year	Overall	Individual Events	Overall	Individual Events
Comparison of Impella 2.5 With IABP				
Manzo-Silberman et al, 2013[36]	NR	NR	NR	Stroke: 0% vs. 0%
Seyfarth et al, 2008[15]	NR	NR	No difference between groups in complex organ dysfunction scores (MODS and SOFA)	NR
Noncomparative Observational Studies on Impella 2.5				
Lauten et al, 2013[32]	NR	NR	15%[a]	MI: 6.7% Re-PCI: 10.8% CABG: 2.5% Stroke: 1.7%
O'Neill et al, 2014[31]	NR	Stroke: 1.9% Reinfarction: 0.9% RR: 2.6%	NR	NR
Noncomparative Observational Studies on Impella 5.0				
Griffith et al, 2013[34]	NR	NR	12.5%[b]	Stroke: 6.3%

Abbreviations: CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; MI, myocardial infarction, MODS, multiple organ dysfunction score; NR, not reported; PCI, percutaneous coronary intervention; RR, revascularization; SOFA, sepsis-related organ failure assessment.
[a]Major adverse cardiac event defined as recurrent myocardial infarction or cardiovascular intervention (PCI, CABG) or stroke.
[b]Major adverse cardiac event defined as death or stroke.

Seyfarth et al[15] used complex organ dysfunction scores at 30-day follow-up as safety outcomes and reported no significant differences in the multiple organ dysfunction score and sepsis-related organ failure assessment between Impella 2.5 and IABP. Manzo-Silberman et al[36] reported no stroke events in both Impella 2.5 and IABP groups.

The stroke rates of <2% were similar between the two noncomparative observational studies on Impella 2.5.[31,32] However, the rate of recurrent cardiovascular intervention was higher in the Impella-EUROSHOCK registry[32] than in the USpella registry.[31]

The quality of evidence for MACEs was assessed as low when Impella 2.5 was compared with IABP (Table 19).

Table 19: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock—Major Adverse Cardiac Events

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[c]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
2 observational studies[31,32]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 5.0							
1 observational study[34]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Imprecision due to small sample size.

[d]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Bleeding Complications
Table 20 presents findings for the outcome of bleeding complications, including access site hematoma, bleeding that required blood transfusion, bleeding that required surgery, and hemolysis.

Table 20: Bleeding Complications

	In-Hospital Bleeding Complications			
Author, Year	**Femoral Hematoma**	**Bleeding Requiring Blood Transfusion**	**Bleeding Requiring Surgery**	**Hemolysis**
Comparison of Impella 2.5 With IABP				
Manzo-Silberman et al, 2013[36]	NR	26% vs. 9% (*P* = .06)	NR	NR
Seyfarth et al, 2008[15]	NR	NR	NR	Significantly increased in the Impella group in first 24 hours[a]
Noncomparative Observational Studies on Impella 2.5				
Casassus et al, 2015[33]	10%	18.2%	NR	NR
Lauten et al, 2013[32]	NR	24.2%	4.2%	7.5%
O'Neill et al, 2014[31]	NR	17.5%	2.6%	10.3%
Noncomparative Observational Studies on Impella 5.0				
Griffith et al, 2013[34]	NR	NR	43.8%	6.3%

Abbreviations: IABP, intra-aortic balloon pump; NR, not reported.
[a]Results were presented in graphs.

In the RCT by Seyfarth et al,[15] there was a significantly higher rate of hemolysis among patients on Impella 2.5 support than those on IABP support, at various time points within the first 24 hours. Manzo-Silberman et al[36] also reported more patients in the Impella 2.5 group required blood transfusion from major bleeding than patients in the IABP group.

The absolute rates of bleeding that required blood transfusion, bleeding that required surgery, and hemolysis were similar among noncomparative observational studies on Impella 2.5.[31-33] However, the number of patients with bleeding that required surgery was substantially higher with Impella 5.0[34] than with Impella 2.5.[31,32]

The quality of evidence for bleeding complications was low when Impella 2.5 was compared with IABP (Table 21).

Table 21: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock—Bleeding Complications

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[c]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
3 observational studies[31-33]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 5.0							
1 observational study[34]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Imprecision due to small sample size.

[d]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Results for Vascular Complications

In the RCT by Seyfarth et al,[15] one case of acute limb ischemia required surgery after device explantation in the Impella group (8.3%). There were no vascular complications in the IABP group. Manzo-Silberman et al[36] reported no significant difference in vascular complication rate between Impella 2.5 and IABP (3% vs. 2%, *P* = .9).

Among noncomparative observational studies on Impella 2.5, Casassus et al[33] reported 10% of participants had limb ischemia and 5.6% had aortic insufficiency. From data in the USpella registry, O'Neill et al[31] reported 3.9% of participants had limb ischemia and 9.7% had vascular complications, defined as surgical intervention on a pseudo-aneurysm, arteriovenous fistula, vessel dissection/perforation, or access site thrombosis.

Griffith et al[34] reported one case of remote vascular injury (vein patch rupture), but no cases of limb ischemia or vascular perforation for patients who received Impella 5.0 support.

The quality of evidence for vascular complications was low when Impella 2.5 was compared with IABP (Table 22).

Table 22: GRADE Evidence Profile for Impella Percutaneous Ventricular Assist Devices in Cardiogenic Shock—Vascular Complications

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Comparison of Impella 2.5 With IABP							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[c]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 2.5							
2 observational studies[31,33]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Noncomparative Observational Studies on Impella 5.0							
1 observational study[34]	Serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Imprecision due to small sample size.

[d]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Limitations

- A single randomized controlled trial comparing Impella 2.5 and IABP in high-risk PCI was identified. This trial was terminated early for futility (i.e., inability to achieve its objective), leading to potential selection bias and insufficient statistical power.
- A single randomized controlled trial comparing Impella 2.5 and IABP in cardiogenic shock was identified. This trial was small (n = 16) and had imbalance of baseline characteristics. An early time point for primary hemodynamic outcomes did not allow extrapolating results to the effects of longer Impella support.
- Most included studies were noncomparative observational studies (i.e., registry or chart review), which have inherent limitations: no randomization, no blinding, no control group, potential imbalance of baseline characteristics, risk of missing data or inconsistent documentation in medical records, risk of reporting bias on adverse events, risk of selection bias on which patients were considered as high-risk for PCI or which devices patients were to receive, and different timing of implanting Impella devices in cardiogenic shock.

Conclusions

High-Risk PCI

Evidence from a single randomized controlled trial showed Impella 2.5 devices improved hemodynamic stability in high-risk PCI more than IABPs (GRADE low). There was no difference in 30-day mortality or MACEs between Impella 2.5 and IABP (GRADE low) (Table 23).

Cardiogenic Shock

Evidence from a single randomized controlled trial showed Impella 2.5 devices improved hemodynamic stability in cardiogenic shock more than IABPs (GRADE very low). There was no difference in 30-day mortality or MACEs between Impella 2.5 and IABP (GRADE low). However, Impella 2.5 devices were associated with a higher rate of hemolysis when compared with IABPs (GRADE low) (Table 23).

There was no comparative evidence available on Impella CP or Impella 5.0 in high-risk PCI and cardiogenic shock.

Table 23: Summary of Evidence on Impella Percutaneous Ventricular Assist Devices

Ventricular Assist Devices	Outcome	Results	GRADE
High-Risk PCI			
Impella 2.5 vs. IABP	Hemodynamic stability	Significantly improved hemodynamic stability comparing Impella 2.5 with IABP	Low
	Mortality	No significant difference between Impella 2.5 and IABP	Low
	Major adverse cardiac events		Low
	Bleeding complications		Very Low
	Vascular complications		Very Low
Noncomparative (Impella 2.5)	Hemodynamic stability	Free from hemodynamic instability with Impella 2.5 support	Low
	Mortality	Noncomparative results	Low
	Major adverse cardiac events		
	Bleeding complications		
	Vascular complications		
Cardiogenic Shock			
Impella 2.5 vs. IABP	Hemodynamic stability	Significantly improved hemodynamic stability comparing Impella 2.5 with IABPs	Very Low
	Mortality	No significant difference between Impella 2.5 and IABPs	Low
	Major adverse cardiac events		
	Bleeding complications	Significantly higher rate of hemolysis comparing Impella 2.5 with IABPs	Low
	Vascular complications	No significant difference between Impella 2.5 and IABPs	Low
Noncomparative (Impella 2.5)	Hemodynamic stability	Hemodynamic parameters improved significantly with Impella 2.5 support	Low
	Mortality	Noncomparative results	Low
	Major adverse cardiac events		
	Bleeding complications		
	Vascular complications		
Noncomparative (Impella 5.0)	Hemodynamic stability	Hemodynamic parameters improved significantly with Impella 5.0 support	Low
	Mortality	Noncomparative results	Low
	Major adverse cardiac events		
	Bleeding complications		
	Vascular complications		

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

ECONOMIC EVIDENCE REVIEW

Objective

The objective of this study was to review the published literature on the cost-effectiveness of the percutaneous ventricular assist devices Impella 2.5 and Impella LP (left peripheral) 5.0 compared with intra-aortic balloon pumps (IABPs) in high-risk hemodynamically unstable patients and in patients with cardiogenic shock.

Methods

Sources

We performed an economic literature search on December 10, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database and National Health Service (NHS) Economic Evaluation Database, for studies published from 1946 to December 10, 2015. We also extracted economic evaluation literature from the Canadian Agency for Drugs and Technologies in Health (CADTH), Institute of Health Economics (iHE), Institut national d'excellence en sante et en services (INESS), and McGill University Health Centre Health Technology Assessment Unit (MUHC–TAU). Finally, we reviewed reference lists of included economic literature for any additional relevant studies not identified through the systematic search. Appendix 1 provides details of the search strategy.

Literature Screening

We based our search terms on those used in the clinical evidence review of this report and applied economic filters to the search results. Study eligibility criteria for the literature search are listed below. A single reviewer reviewed titles and abstracts and, for those studies meeting the inclusion/exclusion criteria, we obtained full-text articles. For studies containing several comparators, only the results for the comparison of interest were extracted. The final search strategy was peer-reviewed using the PRESS Checklist.[16] See Appendix 1 for details, including all search terms.

Inclusion Criteria

- English-language full-text publications
- Studies published between 1946 and December 10, 2015
- Studies comparing Impella 2.5/5.0 with IABP
- Cost-effectiveness or cost-utility analysis, regardless of location
- Study follow-up time, or the time horizon of 1 year or greater in the economic evaluation

Exclusion Criteria

- Abstracts, letters, editorials, and unpublished studies

Outcomes of Interest

- Costs, cost per quality-adjusted life-years (QALYs), cost per clinical effect

Data Extraction

We extracted relevant data on the following:

- source (i.e., first authors' name, location, year)
- population and comparator
- interventions
- outcomes (i.e., health outcomes, costs, cost-effectiveness)

We contacted authors of the studies to provide unpublished data where required.

Limitations

The literature review was limited to a single reviewer.

Results

The database search yielded 119 citations between 1946 and December 10, 2015. We excluded a total of 110 articles on the basis of information in the title and abstract. We then obtained the full texts of nine potentially relevant articles for further assessment. Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

In reviewing the eight full-text articles and one health technology assessment, we found that two met the inclusion criteria. The two included articles were cost-utility analyses that directly compared Impella 2.5 with IABP: one study was from the United States,[41] the other from Germany.[42] Table 24 summarizes the two included studies. Excluded studies included one systematic review,[43] four costing studies,[28,44-46] and one budget impact analysis.[47] These studies were not cost-utility analyses. The health technology assessment[48] was a case-costing analysis and did not present a full economic evaluation.
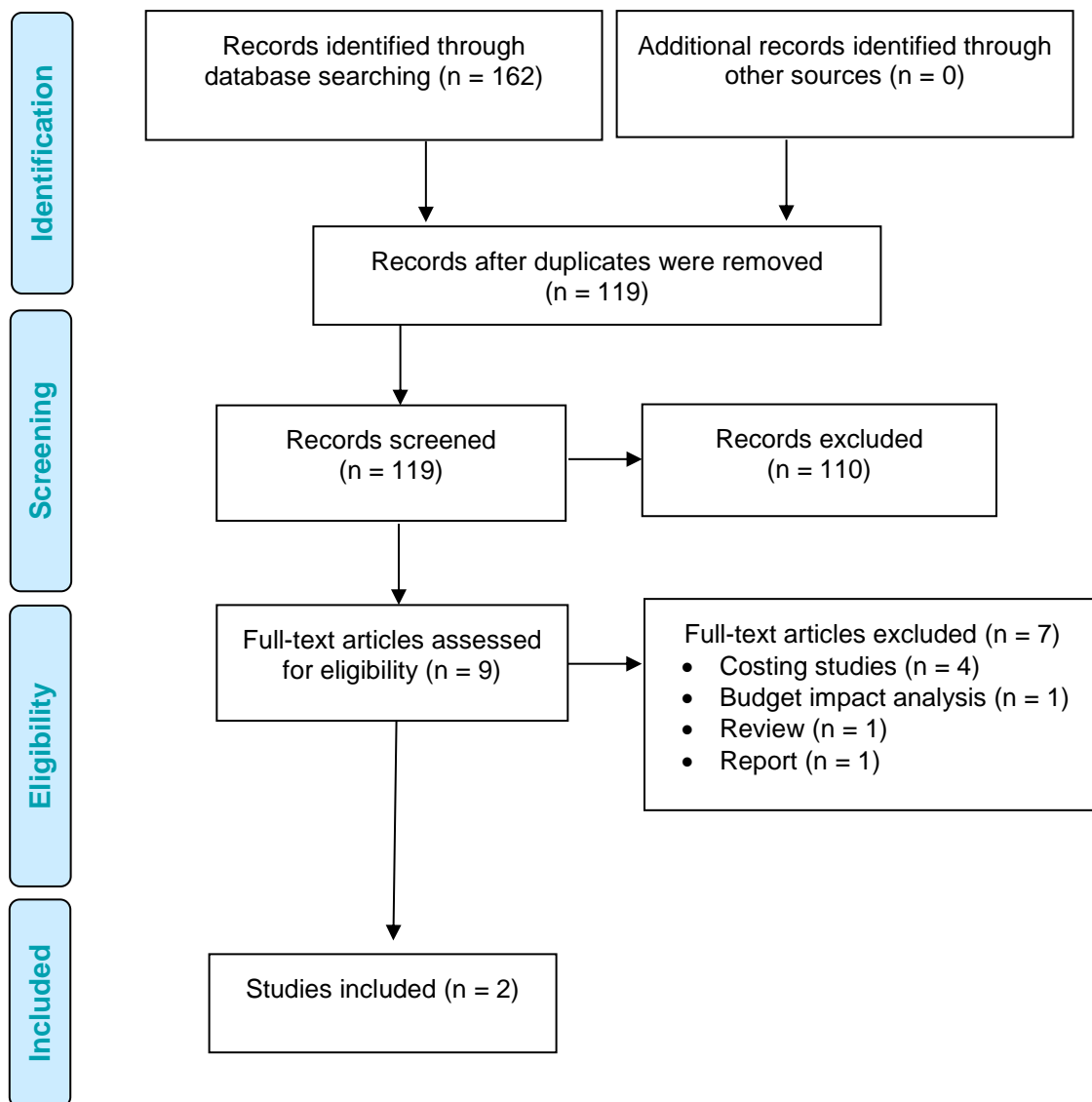
Figure 2: PRISMA Flow Diagram for Economic Evidence Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[18]

Table 24: Results of Economic Literature Review—Summary

Name, Year, Location	Study Design and Perspective	Population	Interventions/ Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Roos et al,[42] 2013, Germany	• Type of economic analysis: CUA • Study design: decision-analytic model • Perspective: European payer perspective • Time horizon: 10 years	High-risk hemodynamically unstable PCI patients	pVAD IABP	Total QALY IABP 3.84 and pVAD 4.06 (with Euro registry data) and QALY gained 0.22. Total QALY IABP 3.84 and pVAD 4.11 and QALY gained 0.27 (with US registry data) Annual discount rate: 3.5%	Currency: Euro Cost year 2011 Total cost IABP €27,792 and pVAD €36,169 (Euro registry) and IABP €27,792 and pVAD €36,391 (US registry). Incremental cost for pVAD was €8,377 (Euro registry) and €8,599 (US registry data) compared with IABP Annual discount rate: 3.5%	ICER: €38,069 (with Euroregistry data) and €31,727 (with US registry data) per QALY gained compared with IABP
Gregory et al,[41] 2013, United States	• Type of economic analysis: CUA • Study design: decision-analytical model • Perspective: US payer perspective • Time horizon: 10 years	High-risk hemodynamically unstable PCI patients	pVAD IABP	Total QALY IABP 2.22 and pVAD 2.48 and QALY gained 0.26 Annual discount rate: 3%	Currency: USD Cost year 2009 Incremental cost for pVAD was USD $10,241 compared with IABP. Total cost IABP $75,655 and pVAD $85,896 Annual discount rate: 3%	ICER: $39,389 per QALY gained compared with IABP

Abbreviations: CUA, cost-utility analysis; IABP, intra-aortic balloon pump; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; pVAD, percutaneous ventricular assist device; QALY, quality-adjusted life-year.

Discussion

Roos et al[42] evaluated the cost-effectiveness of percutaneous ventricular assist devices with IABPs. The authors developed a Markov model and used a time horizon of 10 years. The study was undertaken from the European payer perspective. Short-term effectiveness and safety data for percutaneous ventricular assist devices were obtained from two registries: Europella[49] and USpella.[50] Both are large multicentre studies of high-risk patient groups. The model estimated that percutaneous ventricular assist devices would generate more QALYs at a lower cost than IABPs. Given that the US registry encompassed all other various percutaneous devices, the clinical outcomes data from this study could not be directly applied to Impella 2.5.

Gregory et al[41] evaluated the cost-effectiveness of Impella 2.5 with IABP. The authors developed a Markov model and used a time horizon of 10 years. The study was undertaken from the US payer perspective. Short-term (i.e., 90 days) effectiveness data was based on a single randomized controlled trial. PROTECT II (Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention) was a head-to-head comparison study of Impella 2.5 versus IABP in high-risk percutaneous coronary intervention (PCI) patients.[19] The authors did not specify the source for mortality rates for patients who underwent PCI with Impella 2.5 or IABP. The model estimated that Impella 2.5 was more costly and more effective than IABP.

A recent retrospective analysis of Medicare data compared procedural costs and length of stay for percutaneous ventricular assist devices and IABPs for high-risk PCI. Management of high-risk PCI and cardiogenic shock patients with IABP was more cost-effective than routine use of percutaneous ventricular assist devices, including Impella 2.5.[28]

Finally, we did not find any economic evaluations of Impella 2.5/5.0 for cardiogenic shock patients.

While two economic evaluations showed percutaneous ventricular assist devices, including Impella 2.5, to be more cost-effective than IABP,[41,42] the studies had major limitations. Further, the recent US costing study indicated that percutaneous ventricular assist devices, including Impella 2.5, did not improve clinical outcomes or reduce rates of readmissions. We therefore decided to proceed with a primary economic evaluation.

PRIMARY ECONOMIC EVALUATION

Published economic evaluations identified in our literature review compared Impella 2.5 with intra-aortic balloon pump (IABP) for percutaneous coronary intervention (PCI) among high-risk hemodynamically unstable patients. Two economic evaluations showed percutaneous ventricular assist devices to be more cost-effective than IABPs.[41,42] However, one study favoured IABPs and indicated that percutaneous ventricular assist devices were not associated with improved clinical outcomes or reduced rates of readmission.[28] Given these mixed results, we decided to conduct an economic evaluation comparing Impella 2.5 with IABP.

Objective

The objective of this analysis was to assess the cost-effectiveness, from the perspective of the Ontario Ministry of Health and Long-Term Care, of Impella 2.5 versus IABP.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[51]

Analysis

Given the availability of utilities (measures of patients' preferences) related to treatments for PCI and the uncertainty of total QALYs associated with Impella 2.5 versus IABP, we developed a cost-utility analysis.

Target Population

The model population was high-risk hemodynamically unstable patients who underwent PCI with Impella 2.5 or IABP. The mean age of the target population was 67 years old, and about 80% were male.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We compared Impella 2.5 with IABP in high-risk PCI patients.

Discounting and Time Horizon

We applied an annual discount rate of 5% to both costs and QALYs. The time horizon for our base case analysis was 10 years. All costs are expressed in 2016 Canadian dollars.

Model Structure

We developed a Markov decision-analytic model to assess the cost-effectiveness of Impella 2.5 versus IABP (Figure 3). We adopted the Markov model structure from Roos et al.[42] Our model also assumed that all patients have a history of congestive heart failure.
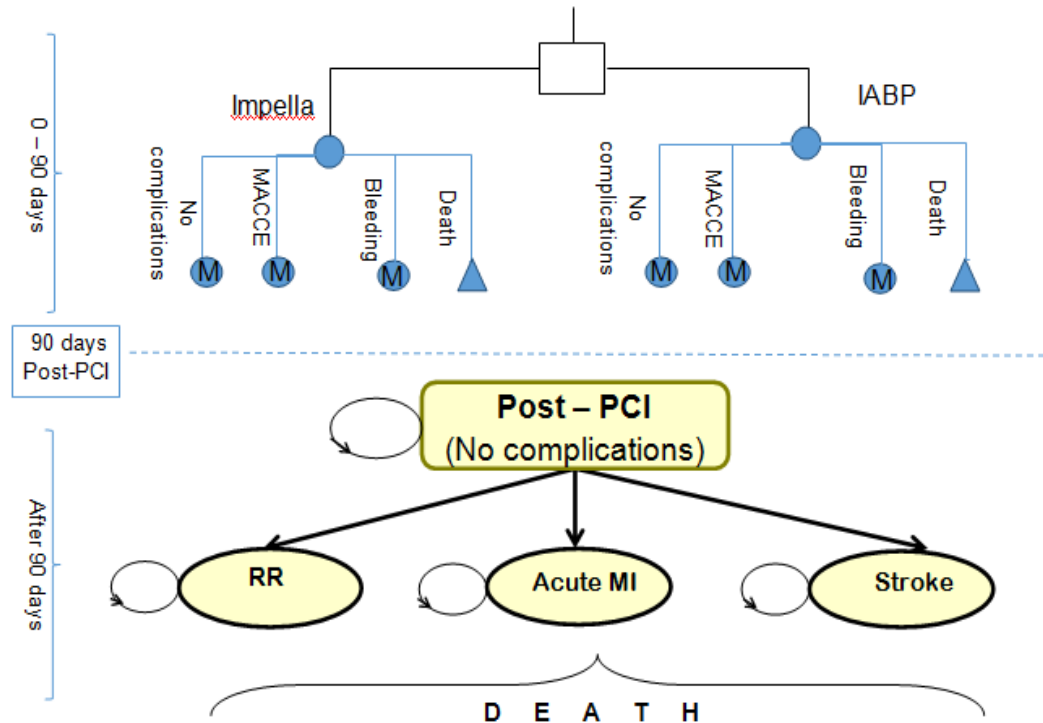
Figure 3: Impella 2.5 Versus IABP, Decision-Analytic Tree and Long-Term Markov Model

Abbreviations: IABP, intra-aortic balloon pump; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, repeat revascularization.
Patients from "No complications" and "Bleeding" chance nodes from the Decision Tree will move to the "Post-PCI" health state in the Markov model. "MACE" patients move directly to any of the four corresponding health states.

The decision tree in Figure 3 was used to follow patients for the first 90 days. It consists of four branches for each intervention (Impella 2.5 or IABP): 1) no complications; 2) MACEs;[2] 3) bleeding; and 4) death. The Markov model followed up patients who survive at 90 days post-PCI. There are five mutually exclusive Markov health states: 1) Post-PCI (no complications), followed by three MACE states; 2) repeat revascularization; 3) acute myocardial infarction; 4) stroke; and 5) death. We used monthly cycles in the model.

The model begins when a high-risk patient receives PCI by Impella 2.5 or IABP. Patients who survived PCI might have bleeding, have MACEs, have no complications, or die. Patients with no complications and with short-term adverse events (e.g., bleeding and complications other than acute myocardial infarction, stroke, and repeat revascularization) move to the Markov post-PCI

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[2]Many trials specified major adverse cardiac and cerebrovascular events (i.e., MACCE in the PROTECT II trial); we include this broader definition in the abbreviation MACE.

(no complications) state or might die. Patients at the Markov post-PCI state (no complication) might die or develop acute myocardial infarction, stroke, and repeat revascularization. They might also survive and stay in the same health state at the end of each monthly cycle.

The different health states in the model are described below.

Post-PCI (no complications): Patients in this state are free of short-term and long-term major adverse events. They could experience MACEs (including acute myocardial infarction, stroke, or repeat revascularization) down the road or die from any cause.

Repeat Revascularization: Patients who survive PCI sometimes have unplanned repeat PCI for restenosis at the lesion treated during the index PCI. These patients will incur the same cost and utility as patients who undergo PCI.

Acute Myocardial Infarction: Patients who have acute myocardial infarction will be hospitalized, and those who survive will receive ambulatory care.

Stroke: Patients who have a stroke will be hospitalized, and those who survive will receive ambulatory care. Quality of life in the acute stage will be lower than those in the chronic post-stroke stage.

Death: At any point during the model timeline, a patient might die from disease or natural causes. In addition to the disease-specific death state, all health states will be susceptible to death from natural causes; this will be the absorbing health state.

Model Parameters

We used several input parameters to populate the model. These inputs—clinical outcomes, utilities, and costs—are explained below.

Clinical Outcomes
Adverse Events

Probabilities of experiencing a treatment-related adverse event over time were extracted from studies identified in our clinical evidence review. Because all extracted data reflected a time frame greater than the cycle length of our model, we converted these data to monthly probabilities (Table 25[14-23]). We used short- and long-term transition probabilities in our model. Short-term (i.e., 30 and 90 days) transition probabilities and mortalities are from the PROTECT II trial.[19] Long-term (after 90 days) transition probabilities are similar for both arms and based on combined probabilities from 30 to 90 days in the PROTECT II trial. Because there is little reliable clinical evidence on high-risk patients who received Impella 2.5 or IABP after 90 days, we used clinical studies that reported long-term outcomes on similar patient populations. We used mortality data from these studies to populate our Markov model. Full calculations for our conversion of study data to monthly probabilities are presented in Appendix 3 (Table A13).

Table 25: Adverse Event Input Used in Economic Model

Model Parameters	Mean Monthly Probability	Min	Max	Author, Year
Short-term transition probabilities (30 and 90 days)				
IABP				
Bleeding at 30 days	0.1920	0.1715	0.2125	Perera et al, 2013[52]
Repeat revascularization at 30 days	0.0410	0.0358	0.0462	O'Neill et al, 2012[19]
Repeat revascularization at 60 and 90 days	0.0195	0.0170	0.0220	O'Neill et al, 2012[19]
Acute MI at 30 days	0.0680	0.0596	0.0764	O'Neill et al, 2012[19]
Acute MI at 60 and 90 days	0.0201	0.0174	0.0227	O'Neill et al, 2012[19]
Stroke at 30 days	0.0180	0.0157	0.0203	O'Neill et al, 2012[19]
Stroke at 60 and 90 days	0.0046	0.0021	0.0071	O'Neill et al, 2012[19]
Other MACE at 30 days	0.0960	0.0845	0.1075	O'Neill et al, 2012[19]
Other MACE at 60 and 90 days	0.0050	0.0043	0.0056	O'Neill et al, 2012[19]
Impella				
Bleeding at 30 days[a]	0.1266	0.1121	0.1411	Dixon et al, 2009[5]; Alasnag et al, 2011[53]; Boudoulas et al, 2012[54]; Iliodromitis et al, 2011[55]; Maini et al, 2012[50]; Sjauw et al, 2009[49]
Repeat revascularization at 30 days	0.0130	0.0113	0.0147	O'Neill et al, 2012[19]
Repeat revascularization at 60 and 90 days	0.0117	0.0102	0.0132	O'Neill et al, 2012[19]
Acute MI at 30 days	0.0580	0.0508	0.0652	Dangas et al, 2014[56]
Acute MI at 60 and 90 days	0	0	0	Dangas et al, 2014[56]
Stroke at 30 days	0	0	0	O'Neill et al, 2012[19]
Stroke at 60 and 90 days	0.0045	0.0030	0.0060	O'Neill et al, 2012[19]
Other MACE at 30 days	0.0750	0.0659	0.0841	O'Neill et al, 2012[19]
Other MACE at 60 and 90 days	0.0022	0.0019	0.0024	O'Neill et al, 2012[19]
Long-term transition probabilities (after 90 days) of combined cohort				
Repeat revascularization, combined cohort	0.0030	0.0010	0.0050	Roe et al, 2013[57]
Acute MI, combined cohort	0.0096	0.0087	0.0106	O'Neill et al, 2012[19]
Stroke, combined cohort	0.0048	0.0044	0.0053	O'Neill et al, 2012[19]
Mortality				
At 30 days when using IABP	0.0590	0.0516	0.0664	O'Neill et al, 2012[19]
At 60 and 90 days when using IABP	0.0150	0.0130	0.0169	O'Neill et al, 2012[19]
At 30 days when using Impella device	0.0760	0.0668	0.0852	O'Neill et al, 2012[19]
At 60 and 90 days when using Impella device	0.0247	0.0215	0.0278	O'Neill et al, 2012[19]
Repeat revascularization	0.0031	0.0010	0.0040	Littnerova et al, 2015[58]
Acute MI	0.0073	0.0072	0.0074	Roe et al, 2013[57]
Stroke	0.0067	0.0064	0.0071	Lakshminarayan et al, 2014[59]

Other MACE (short-term)	0.0072	0.0070	0.0073	Banach et al, 2011[60]
Post-PCI state (no complications)	0.0031	0.0010	0.0050	Littnerova et al, 2015[58]

Abbreviations: IABP, intra-aortic balloon pump; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Other MACEs grouped together because of their short-term (30 to 90 days) effects including need for cardiac or vascular operation, cardiopulmonary resuscitation/ventricular arrhythmia, angiographic failure, and acute renal dysfunction.

aWeighted average of 6 studies with 450 patients in total.

Health Utilities

Utility values for post-PCI (no complications) and post-stroke health states were obtained from a study that examined health utility in the Canadian population (n = 17,626) obtained from the National Population Health Survey.[61] Patients who undergo PCI at the first month cycle have a utility decrement of 0.06,[62] and an additional decrement of 0.04 if they also have a bleeding complication.[63] In our model, we assumed that, after recovery from either post-PCI or post–repeat revascularization, utilities in these patients would be similar, regardless of the intervention received. Utility values for acute myocardial infarction and post–myocardial infarction health states were obtained from a UK study that relied on the EQ-5D (a descriptive system of health-related quality-of-life states consisting of five dimensions) to elicit preferences in patients (n = 1,810) with myocardial infarction.[64] Other MACEs reported in the PROTECT II trial were mainly related to short-term cardiovascular disorders (e.g., cardiac or vascular operation, cardiopulmonary resuscitation/ventricular arrhythmia, angiographic failure, and acute renal dysfunction). Utility values for heart failure were obtained from an Italian study that used the time trade-off method to elicit preferences from patients (n = 234) with heart failure.[65] Utility values for a major stroke were obtained from US patients (n = 621) via time trade-off techniques.[66] We used short-term utility decrement and utilities in acute (event) states. We used utilities obtained from various sources in the post-event states. Table 26 shows the utility values incorporated in the model.

Table 26: Utilities Used in Economic Model

Health State	Mean Utility (Standard Error)	Author, Year
Post-PCI (no complication), reference case	0.8 (0.002)	Mittmann et al, 1999[61]
Utility decrement due to bleeding (first month)	0.04	Cohen et al, 1994[63]
Utility decrement at post-PCI health state first month	0.06	Garg et al, 2008[62]
Other MACE	0.6 (0.0007)	Capomolla et al, 2002[65]
RR (first month)	0.74 (0.0006)	Cohen et al, 1994[63]; Mittmann et al, 1999[61]
Post-RR	0.8 (0.0022)	Mittmann et al, 1999[61]
Acute MI (first month)	0.59 (0.001)	Kim et al, 2005[64]
Post-acute MI	0.68 (0.0018)	Kim et al, 2005[64]
Utility at stroke (first month) health state	0.3 (0.0036)	Mittmann et al, 1999[61]
Utility at post-stroke health state	0.68 (0.002)	Mittmann et al, 1999[61]

Abbreviations: MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, repeat revascularization.

Costs

All costs included in our study originated from the Ontario Schedule of Benefits for Physician Services,[67] the Ontario Case Costing Initiative (OCCI),[68] and Cardiac Care Network[69] of Ontario registry. The number of high-risk and cardiogenic shock patients who received PCI was identified through the Cardiac Care Network database. Treatment-related adverse events were identified through inpatient hospital care databases from OCCI. Physician fee codes used to search the administrative data and schedule of benefits are presented in Appendix 3, Table A14.

Initial PCI Treatment
Costs for the initial PCI treatment include short-term cost of hospitalization, physician services fee, and cost of technologies (Impella 2.5 and IABP). Cost mean and ranges for hospitalization for PCI were obtained from the Cardiac Care Network and inflated to 2016 dollars. We assumed there would be a 2-day reduction in length of hospital stay for patients who receive Impella 2.5 instead of IABP. This assumption was based on economic studies that assessed cost implications of percutaneous ventricular assist devices using the US registry.[41,47]

Physician services include fees of the interventional cardiologist, most responsible physician, and surgeon.[67] Details of physician fees are provided in Appendix 3, Table A14. Costs of Impella 2.5 devices and IABPs were obtained from one study that reported the price of both technologies,[28] thus making the cost comparable. All costs were converted to 2016 Canadian dollars.

Post-PCI Complications, or MACEs
Costs from post-PCI complications were based on the mean inpatient and outpatient hospital length of stay and ambulatory visits in the OCCI data.[68] Short-term costs include those from hospital stay and physician services. Long-term costs include ambulatory cost and physician follow-up cost calculated by multiplying the mean number of visits per month by the cost per physician service. In our analysis, we assumed that all physician visits were to a family physician. Table 27[28,67-72] presents the treatment used in the base case analysis.

Table 27: Treatment Costs Used in Economic Model

Cost of Treatment for Single Case	Mean Cost ($)	Minimum Cost ($)	Maximum Cost ($)	Author, Year
Device				
Impella 2.5	30,739	15,000	37,000	Shah et al, 2015[28]
Impella 5.0	36,400	20,000	45,000	Written communication with manufacturer (M. Ford, May 2016)
IABP	1,086	600	1,500	Shah et al, 2015[28]
Short-term (hospitalization)				
IABP hospitalization + OHIP physician billing (first month)	26,481	668	47,338	CCN[a], and MOHLTC, 2015[67]
Impella 2.5 hospitalization (saving 2 days) + OHIP physician billing (first month)	24,959	20,000	30,000	WHO, 2016,[72] estimates of unit cost
RR hospitalization + OHIP physician billing (first month)	26,481	668	47,338	OCCI[b,68] and MOHLTC, 2015[67]
Same as Impella 2.5 for PCI above	24,959	20,000	30,000	WHO estimates of unit cost[72]
Other MACE (heart failure hospitalization) + OHIP physician billing (first month)	14,266	830	279,800	OCCI[b,68] and MOHLTC, 2015[67]
Acute MI hospitalization + OHIP physician billing (first month)	11,664	688	212,284	OCCI[b,68] and MOHLTC, 2015[67]
Stroke hospitalization + OHIP physician billing (first month)	8,924	76	196,120	OCCI[b,68] and MOHLTC, 2015[67]
Long-term (ambulatory) care				
PCI ambulatory care + OHIP physician billing	150	100	200	Expert opinion, personal communication
RR ambulatory care + OHIP physician billing	150	100	200	Expert opinion, personal communication
Heart failure ambulatory care + OHIP physician billing	281	200	350	OCCI[b,68] and MOHLTC, 2015[67]
Acute MI ambulatory care + OHIP physician billing	350	233	466	Singh et al, 2013[73]
Stroke ambulatory care + OHIP physician billing	721	74	1,218	Wijeysundera et al, 2013[71]

Abbreviations: CCN, Cardiac Care Network; IABP, intra-aortic balloon pump; MACE, major adverse cardiac event; MOHLTC, Ministry of Health and Long-Term Care; MI, myocardial infarction; OCCI, Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Plan; PCI, percutaneous coronary intervention; RR, repeat revascularization; WHO, World Health Organization.
[a]Data from Cardiac Care Network, 2013.
[b]Data from Ontario Case Costing Initiative, 2011.

Analysis

In the base case analysis, we applied actual values or mean values as model inputs. This method provides the best estimate of cost-effectiveness of the Impella 2.5 intervention, but it does not consider the uncertainty of various inputs to the model or the possibility of other clinical

scenarios. We present the results as the incremental costs (the difference in costs) and incremental QALYs of Impella 2.5 versus IABP.

While the base case analysis provided the best estimates of cost-effectiveness for Impella 2.5 devices, we performed sensitivity analyses to address the uncertainty of model inputs and clinical scenarios. We assessed variability and uncertainty in the model through one-way and probabilistic sensitivity analyses. To determine how simultaneously varying numerous variables affects the assigned distributions, we conducted a probabilistic sensitivity analysis by running 1,000 simulations of the model. Results of the probabilistic sensitivity analysis are presented on a cost-effectiveness plane and, if necessary, a cost-effectiveness acceptability curve. We assigned a beta distribution for probability and utility values. For cost inputs where standard deviation or confidence intervals were presented, a gamma distribution was assigned. We conducted one-way sensitivity analyses by varying specific model variables and examining the effect on results. Variables and ranges are presented in Table 28.[19,28,58,61,63,67,68,74]

Table 28: Variables in One-Way Sensitivity Analyses

Variable	Range		Author, Year
	High	**Low**	
Discount rate	7%	3%	CADTH, 2006[74]
Cost of hospitalization for PCI treated with IABP	$668	$47,338	OCCI[a],[68] and MOHLTC, 2015[67]
Cost of hospitalization for PCI treated with Impella	$20,000	$30,000	Assumption
IABP device cost	$600	$1,500	Shah et al, 2015[28]
Impella 2.5 device cost	$15,000	$37,000	Shah et al, 2015[28]
Utility at post-PCI (no complication)	0.99	0.61	Mittmann et al, 1999[61]
Utility at RR (first month)	0.80	0.70	Cohen et al, 1994[63]
Mortality at 30 days using IABP	0.0664	0.0516	O'Neill et al, 2012[19]
Mortality at 30 days using Impella	0.0852	0.0668	O'Neill et al, 2012[19]
Mortality at 60 and 90 days using Impella	0.0278	0.0215	O'Neill et al, 2012[19]
Monthly mortality at post-PCI state	0.0050	0.0010	Littnerova et al, 2015[58]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; IABP, intra-aortic balloon pump; MOHLTC, Ministry of Health and Long-Term Care; OCCI, Ontario Case Costing Initiative; PCI, percutaneous coronary intervention; RR, repeat revascularization.
[a]Data from Ontario Case Costing Initiative, 2011.

Main Assumptions

The major assumptions for this model are:

- High-risk PCI patients treated with either Impella or IABP have similar probabilities of major adverse events after 90 days
- PCI patients have no multiple adverse events in the long term
- Inpatients will see a physician daily during hospitalization; outpatients will see a physician monthly
- Two days in "hotel cost" would be saved during readmissions when using Impella 2.5. Hotel cost includes only patient accommodation (indirect medical cost)
- There is no difference in either short- or long-term medication use among patients treated with Impella 2.5 or IABP

- "Other MACE" parameters (Table 27) would be short-term (not more than 90 days) and related to heart problems, and these will be assigned with corresponding costs of heart failure and associated utilities
- In "repeat revascularization," only costs of hospitalization and physician fees were included. Costs of devices were excluded for IABP and Impella

Generalizability

Our findings from this economic analysis cannot be generalized to all patients with high-risk PCI. They can, however, be used to guide decisions about the specific patient populations addressed in studies investigated by Health Quality Ontario.

Expert Consultation

Throughout development of this model, we solicited expert consultation from specialists in cardiology. The role of expert advisors was to review the structure and inputs of the economic model to confirm that information we used reasonably reflects the clinical setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Base Case Analysis

The base case results for our analysis are presented in Table 29. In the model, Impella 2.5 cost more and produced fewer QALYs than IABP.

Table 29: Base Case Analysis

Strategy	Average Total Costs, $	Incremental Cost, $	Average Total QALYs	Incremental QALYs	ICER
Impella 2.5	80,316		4.048		
IABP	56,055	24,260[a]	4.156	−0.109[b]	Impella 2.5 was dominated by IABP

Abbreviations: IABP, intra-aortic balloon pump; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]Incremental costs = average costs of Impella 2.5 – average costs of IABP.
[b]Incremental effects = average effects of Impella 2.5 − average effects of IABP.

Sensitivity Analysis

The incremental cost and incremental QALYs calculated for each simulation of the probabilistic sensitivity analysis are illustrated in Figure 4. In the comparison of Impella 2.5 and IABP, incremental costs ranged from $7,516 to $56,304, while incremental QALYs ranged from −0.57 to 0.53. We did not develop cost-effectiveness acceptability curves because almost all simulations in the probabilistic sensitivity analysis resulted in a dominant situation for IABP (lower incremental cost and higher incremental QALYs). Results of the one-way sensitivity analysis are presented in Table 30. As shown, when parameters were varied in a plausible range, IABP dominated in every situation. Model results are most sensitive to the following parameters: mortality at 30 days for both interventions, utility at post-PCI (no complication) health state, cost of the Impella 2.5 device, and hospitalization. Model results are less sensitive to utility and probabilities of MACE, cost of IABP device, and discount rate.

Table 30: One-Way Sensitivity Analysis Results for Impella 2.5 Versus IABP

Scenario	Incremental Cost Range, $[a]	Incremental Effect[b] Range	Result
Discount rate	23,826–24,710	−0.119 to −0.099	IABP dominates
Cost of hospitalization for PCI treated with IABP	4,400–48,848	−0.109	IABP dominates
Cost of hospitalization for PCI treated with Impella 2.5	19,542–29,066	−0.109	IABP dominates
IABP device cost	23,869–24,727	−0.109	IABP dominates
Impella 2.5 device cost	9,275–30,228	−0.109	IABP dominates
Utility at post-PCI (no complication)	24,264	−0.146 to −0.072	IABP dominates
Utility at RR (first month)	24,264	−0.121 to −0.100	IABP dominates
Mortality at 30 days using IABP	24,049–24,479	−0.142 to −0.076	IABP dominates
Mortality at 30 days using Impella 2.5	24,008–24,521	−0.149 to −0.068	IABP dominates
Mortality at 60 and 90 days using Impella 2.5	24,128–24,401	−0.087 to −0.130	IABP dominates
Monthly mortality at post-PCI state	24,173–24,378	−0.091 to −0.123	IABP dominates

Abbreviations: IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RR, repeat revascularization.
[a]Incremental costs = average costs of Impella 2.5 − average costs of IABP.
[b]Incremental effects = average effects of Impella 2.5 − average effects of IABP.
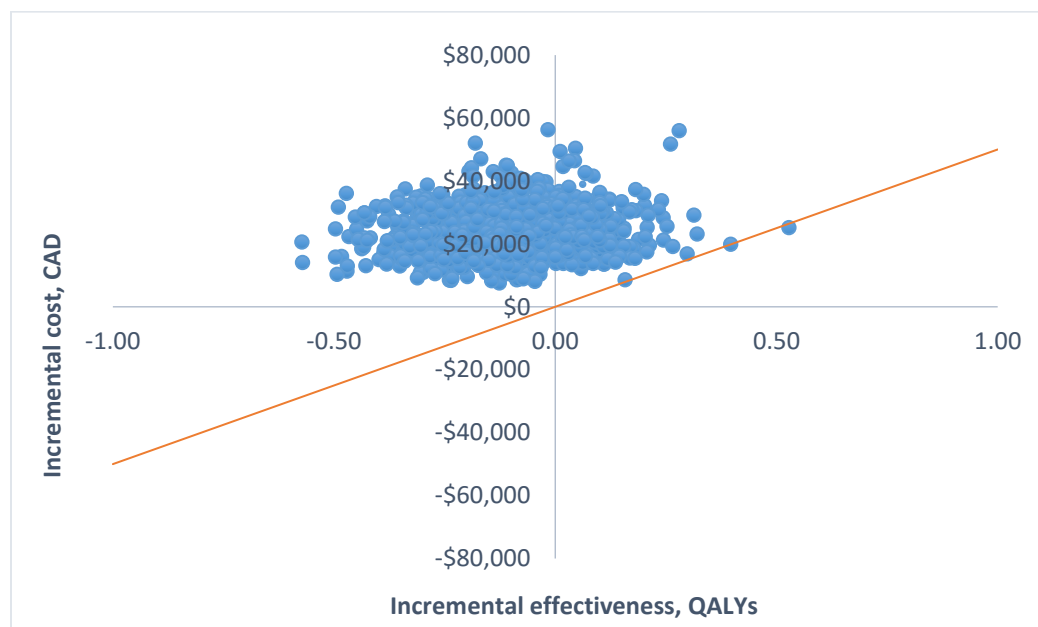
Figure 4: Incremental Cost and QALYs of Impella 2.5 Versus IABP

Abbreviations: CAD, Canadian dollars; IABP, intra-aortic balloon pump; QALY, quality-adjusted life-year.

We also performed two-way sensitivity analyses to examine the effects of simultaneously varying the values from two parameters of our model. The two parameters that underwent two-way sensitivity analyses were mortality rates of Impella 2.5 and IABP. These two variables were the predominant drivers that influenced the base case results. As shown in Figure 5, under extreme values of increasing the mortality rate for IABP by 50% and decreasing the Impella mortality rate by 50%, the ICER was $137,341/QALY.

		IABP										
		50%	60%	70%	80%	90%	100%	110%	120%	130%	140%	150%
		0.0295	0.0354	0.0413	0.0472	0.0531	0.0590	0.0649	0.0708	0.0767	0.0826	0.0885
50%	0.038	-336210	-530733	-1235793	3984792	771265	429562	298920	229930	187283	158309	137341
60%	0.0456	-228171	-305518	-458898	-908791	-27389490	987426	488360	325883	245352	197258	165289
70%	0.0532	-171942	-213383	-279884	-404036	-718151	-3077944	1373629	566089	358304	263051	208393
80%	0.0608	-137464	-163274	-200355	-258154	-360765	-593293	-1628145	2260610	673646	398026	283570
90%	0.0684	-114161	-131776	-155412	-188791	-239498	-325764	-505179	-1105674	6418058	832280	447829
100%	0.0760	-97357	-110146	-126524	-148251	-178456	-223308	-296868	-439670	-836410	-7595878	1089699
110%	0.0836	-84667	-94373	-106391	-121659	-141699	-169166	-209125	-272609	-389056	-672186	-2380794
120%	0.0912	-74744	-82363	-91557	-102873	-117139	-135683	-160768	-196597	-251952	-348776	-561571
130%	0.0988	-66773	-72912	-80174	-88896	-99569	-112929	-130139	-153141	-185451	-234152	-315957
140%	0.1064	-60229	-65282	-71162	-78091	-86377	-96460	-108999	-125014	-146183	-175470	-218654
150%	0.1140	-54760	-58992	-63851	-69488	-76107	-83988	-93530	-105322	-120262	-139809	-166480

(Impella 2.5 is the row axis label)

Legend: + ICER (orange); - ICER (blue); Mortality rate (yellow); Base case (pink)

Figure 5: Two-Way Sensitivity Analysis: Mortality Rate[a] of Two Treatments in First Month

Abbreviations: IABP, intra-aortic balloon pump; ICER, incremental cost–effectiveness ratio.

[a]Mortality rates are presented as a percentage. Base case ICER is highlighted in the pink box.

We examined several scenarios that would favour Impella 2.5 over IABP (Table 31). Examples include using the same mortality rate in patients receiving either Impella 2.5 devices or IABPs, switching mortality rate between two devices, and using data on probabilities for nonfatal events (acute myocardial infarction and stroke) from randomized controlled trials after 90 days.[75-77] Even when we used transition probabilities for MACEs after 90 days from long-term clinical trials instead of combined probabilities from the PROTECT II trial (our base case), Impella 2.5 was still associated with higher cost and lower QALYs (Scenario 1). The results from other scenarios that favoured Impella (Scenarios 2–4) over IABP are presented in Table 31 below.

Table 31: Scenario Analysis Results, Impella 2.5 Versus IABP

Scenario	Incremental Cost $	Incremental Effect[a]	Results
Scenario 1: PROTECT II data from 0–90 days. After 90 days, data from RCTs[75-77] were used for probability of nonfatal events (MI and stroke)	23,896	−0.088	IABP dominates
Scenario 2: Equal mortality for both treatment arms	25,166	0.034	$739,793/QALY
Scenario 3: Equal mortality for both treatment arms at 90 days. After 90 days, data from RCTs[75-77] were used for probability of nonfatal events (MI and stroke)	24,613	0.065	$377,367/QALY
Scenario 4: Mortality rate switch between arms. After 90 days, data from RCTs[75-77] for probability of nonfatal events (MI and stroke) were used	25,319	0.209	$120,943/QALY

Abbreviations: IABP, intra-aortic balloon pump; MI, myocardial infarction; PROTECT, Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention; QALY, quality-adjusted life-year; RCT, randomized controlled trial.
[a]Long-term clinical data from Roos et al, 2013.[42]

Discussion

In our primary economic evaluation comparing Impella 2.5 with IABP in treatment of high-risk PCI patients, we observed that Impella 2.5 was more costly and had lower QALYs (i.e., Impella 2.5 was dominated by IABP). This observation remained consistent in the one-way sensitivity analyses for all parameter ranges used in the model. Model parameters were most sensitive to mortality for both interventions, utility at post-PCI health state, and the cost of Impella 2.5 device. Model results are less sensitive to utilities and probabilities of MACEs and the cost of IABP devices. The probabilistic sensitivity analysis confirmed that the overall results remained consistent (higher cost and lower QALYs for Impella 2.5), even when uncertainty in the model inputs was considered. Compared with Impella 2.5, IABP was less costly and had higher QALYs, and this was consistently observed in more than 99% of all simulation results in the sensitivity analyses. Even in scenarios that favoured the intervention, Impella 2.5 was not more cost-effective than IABP in treatment of high-risk PCI patients at the commonly used threshold of $50,000/QALY. Mortality rate in the first month after PCI was shown to be the most sensitive parameter to affect base case results. When this variable underwent two-way sensitivity analysis (50% increase and 50% decrease) for both Impella and IABP, results remained the same: compared with IABP, Impella 2.5 was still not cost-effective.

In the largest randomized controlled trial on hemodynamic support for Impella 2.5 versus IABP among patients undergoing high-risk PCI, the follow-up time was only 90 days.[19] The preferred time horizon for economic evaluation of chronic conditions is a lifetime, however. To compensate for the many uncertainties about long-term outcomes of both treatment strategies and patients with worse prognoses, we selected a time horizon of 10 years.

Our study results were consistent with a recent US study that compared all randomized controlled trials of percutaneous ventricular assist devices (Impella and TandemHeart) versus IABP for high-risk PCI patients.[28] This retrospective cost analysis compared procedural cost and

hospital lengths of stay on the basis of 2010 and 2011 MEDPAR (Medicare Provider Analysis and Review). Results showed that management of high-risk PCI and cardiogenic shock patients with IABP was more cost-effective than routine use of percutaneous ventricular assist devices. However, results of Roos et al[41,42] and Gregory et al[1] were in stark contrast.[41,42] Results of these two studies showed that Impella 2.5, when compared with IABP, was cost-effective at the commonly used threshold of $50,000/QALY. It should be noted that the studies by Roos et al[42] and Gregory et al[41] were funded by the manufacturer. Factors could have caused differences in the results are first model parameters and second model structure and data sources.

In terms of the model parameters, mortality was a major driver in the model. Roos et al[42] used probability data from 30-day mortality for IABP (0.0896), which was almost twice as high as percutaneous ventricular assist devices from the European registry (0.0559) and from the US registry (0.0449) (Appendix 3, Table A15). Using lower mortality rates would significantly favour percutaneous ventricular assist devices. This contradicts outcomes reported in the PROTECT II trial. Gregory et al[41] used all nonfatal MACEs from the PROTECT II trial, but used mortality from a different source (not cited in the original study), and judged rates to be equal for Impella 2.5 and IABP. In this study, we used mortality rates from a head-to-head randomized controlled trial (PROTECT II)[19] that compared Impella 2.5 and IABP. The 90-day mortality rate from the PROTECT II trial was lower in the IABP arm (8.7%) than in the Impella arm (12.1%).

In the model by Gregory et al,[41] long-term transition probabilities from PCI health state to MACE states (among patients with no complications) were significantly higher for IABPs than for Impella 2.5 (Appendix 3, Table A16). Long-term trials of head-to-head comparisons with those two devices are unavailable. Short-term (30 days) transition probabilities are compared in Appendix 3 (Table A17).

Roos et al[42] and Gregory et al[41] included the cost of the device in figures for initial treatment or hospitalization (admission). This inclusion makes it difficult to identify the real procurement value of the device and its impact on economic evaluation results. The difference in the purchasing price of Impella 2.5 and IABP is quite significant (Impella 2.5 costs about 30 times more than IABP), and our sensitivity results indicated that the cost of the device was an important reason Impella 2.5 was dominated by IABP. In addition, the 2-day reduction in the length of hospital stay (because of the lower readmission rate) was not directly proportional to the reduction in hospital cost, as Gregory et al[41] showed—even though the authors used cost data from the administrative database. Because most hospitalization costs are incurred in the first few days, shorter stays usually reduce overall hospitalization cost only marginally ("hotel" cost includes nursing and capital costs).[78] Consequently only the "hotel" cost would be reduced; costs of all procedures and physician fees would remain the same. Recent retrospective cost analysis of Medicare data compared procedural costs and length of stay for percutaneous ventricular assist devices and IABP for high-risk PCI. This analysis showed that percutaneous ventricular assist devices, including Impella 2.5, did not shorten hospital stays.[28]

Our model excluded heart failure as a health state because the PROTECT II trial[19] on which our model was based, did not report acute heart failure events. Roos et al relied on data from the US and European registries. The US registry did not specify various types of percutaneous ventricular assist devices: Impella 2.5 and all other percutaneous devices would have been included.

Our analysis has numerous strengths. Our model more precisely reflected real-life clinical consequences because it consisted of both a decision tree and a Markov model. The decision tree modelled short-term events and the Markov model modelled long-term events in patients

with high-risk PCI. Unlike previous economic evaluations[42] that relied on observational data,[49,50] we incorporated higher-quality data from a randomized controlled trial (PROTECT II) into our model. We used monthly cycles to capture changes with Impella 2.5 and IABP, as well as rates of PCI-related adverse events that were similar to changes experienced by patients. Probabilities of treatment-related adverse events included in our model were based on an extensive clinical review of published literature.[5,19,20,23-25,52,54,57-60,79] We also used Ontario-specific data on costing. Where model inputs were unavailable from published studies, we used Ontario administrative data to minimize the number of assumptions in the model.

There were also several limitations in our analysis. First, we lack evidence on long-term (after 90 days) clinical outcomes for both Impella 2.5 and IABP. We used combined (or similar) probabilities for MACE and mortality from the PROTECT II trial to model the effects of short-term outcomes in our analysis. Second, high-risk patients who survive after PCI might have more than one MACE during their lifetime. In reality, repeat revascularization or stroke might happen after an acute myocardial infarction. This sequela might provide some benefit for Impella 2.5, which has lower rates of nonfatal MACE than IABP. Our model did not consider this possibility. Third, we applied health state utility scores obtained from various instruments. Different instruments (direct vs. indirect) can provide different utilities for the same health state. Fourth, it was challenging estimate the incremental cost of Impella 2.5 versus IABP precisely. Our estimate was based largely on data from the Cardiac Care Network that included other patients in addition to the PCI patients, and the data could have significant standard deviation from the mean.

We concluded that Impella 2.5 is more costly and has lower QALY outcomes than IABP. These observations were consistent even when uncertainty in model inputs and parameters was considered.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden over the next 4 years of funding Impella 2.5 and Impella 5.0 for high-risk percutaneous coronary intervention (PCI) and cardiogenic shock patients. All costs are reported in 2016 Canadian dollars.

Objective

The objective of this study was to assess the budget impact, from the perspective of the Ontario Ministry of Health and Long-Term Care, of publicly funding the Impella 2.5 and Impella 5.0 devices versus intra-aortic balloon pumps (IABPs) for high-risk PCI and cardiogenic shock.

Methods

Total Volume and Proportion of Impella Devices and IABPs Implanted in Ontario

Two distinct hypothetical populations were incorporated into this analysis. The first group consists of high-risk hemodynamically unstable PCI patients. The second group consists of cardiogenic shock patients. High-risk PCI is defined as any PCI requiring an IABP or an Impella 2.5/5.0 device, and cardiogenic shock is defined as having cardiogenic shock or assigned a Killip Class score of 4.[69] Based on data provided from the Cardiac Care Network Registry, we estimated the number of new cases each year by extrapolating the volume of new cases of high-risk PCI and cardiogenic shock between fiscal years 2011/12 and 2015/16.[69] Figure 6 shows the total volume of Impella 2.5/5/0 devices and IABPs implanted in Ontario during the period between fiscal years 2011/12 and 2015/16.
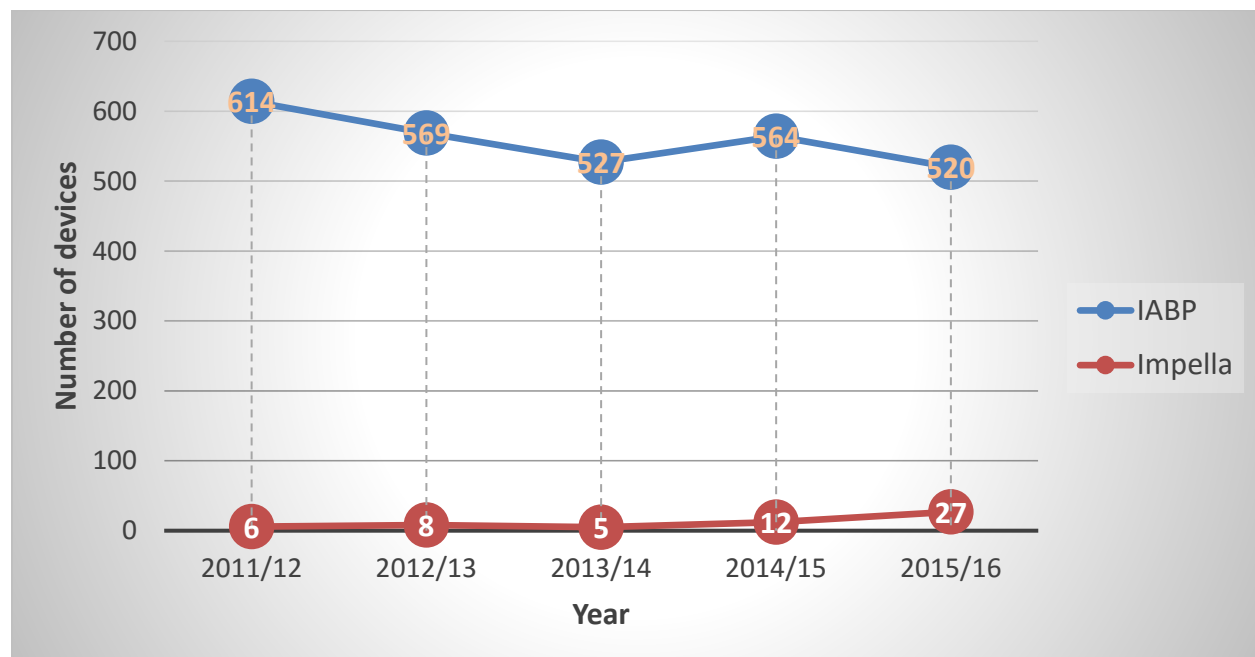
Figure 6. Total Volume of Impella Devices and IABPs Implanted in Ontario

Abbreviation: IABP, intra-aortic balloon pump.
Source: Cardiac Care Network (CCN) Registry.[69]

As shown in Figure 6, in fiscal year 2015/16, a total of 547 patients received either IABP (n = 520) or Impella 2.5/5.0 (n = 27). The proportion of Impella in Ontario, currently 4.9% (27/547), could increase if public funding becomes available (expert consultation, Dr. Harindra Wijeysundera, Interventional Cardiologist, Sunnybrook Health Sciences Centre, May 2016).

Figure 7 shows the proportion of Impella 2.5/5.0 devices and IABPs implanted by the various indications: high-risk PCI, catheterization, cardiogenic shock, and coronary artery bypass graft in Ontario.
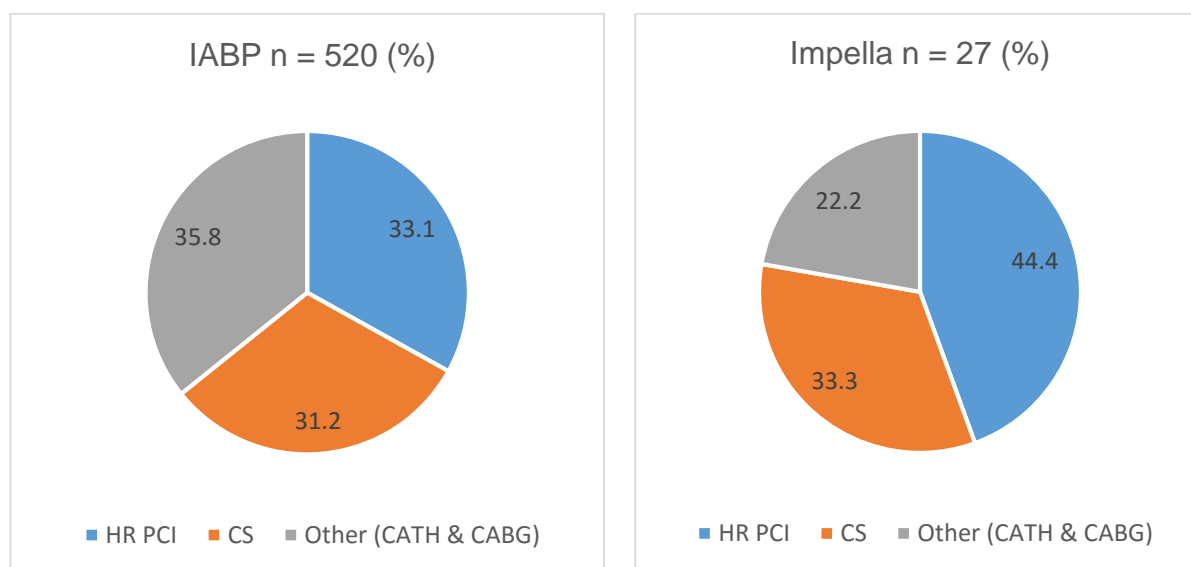
Figure 7. Indications for Implantation of Impella Devices and IABPs in Ontario, Fiscal Year 2015/16

Abbreviations: CABG, coronary artery bypass graft; CATH, catheterization; CS, cardiogenic shock; HR PCI, high-risk percutaneous coronary intervention; IABP, intra-aortic balloon pump.
Source: Cardiac Care Network.[69]

Target Population

In fiscal year 2015/16, IABPs were used in 172 (52%) high-risk PCI and 162 (48%) cardiogenic shock patients, while Impella devices were used in 12 (57%) high-risk PCI and 9 (43%) cardiogenic shock patients. Of the 355 patients, 184 had high-risk PCI and 171 had cardiogenic shock. Because the proportion of the implanted devices does not differ between high-risk PCI and cardiogenic shock patients,[69] we used the conservative assumption of 50% of high-risk PCI patients and 50% of cardiogenic shock patients in our budget impact analysis. We assumed that cardiogenic shock patients would receive Impella 5.0 and patients with high-risk PCI would receive Impella 2.5.

Resource and Costs

Costs of Impella 2.5 ($30,739) and IABP ($1,086) were obtained from Shah et al.[28] Cost of Impella 5.0 ($36,400) was obtained from the manufacturer (written communication, Mandy Ford, Abiomed Inc., May 2016). All costs were converted to 2016 Canadian dollars.

Analysis

For high-risk PCI, the total cost of treatment was obtained by multiplying the unit cost of Impella 2.5 by the estimated number of patients in this cohort. For cardiogenic shock, the total cost of

treatment was obtained by multiplying the unit cost of Impella 5.0 by the estimated number of patients in this group. We assumed no annual increase in the number of patients with either high-risk PCI or cardiogenic shock.

The cost of Impella 2.5 is currently approximately 30 times greater than the cost of an IABP. We analyzed a scenario consisting of various price reductions of Impella 2.5/5.0 and of an annual uptake rate increased by 25%. We multiplied the proportion of high-risk PCI and cardiogenic shock patients by the corresponding uptake rate and the cost of device. The difference between Impella 2.5/5.0 and IABP yielded the net budget impact assessment of percutaneous ventricular assisted devices in the current target population of 355 high-risk PCI and cardiogenic shock patients.

Results

Table 32 shows the net budget impact of the various device cost scenarios with an uptake rate increased by 25%.

Table 32: Device Cost Scenarios (Annual 25% Uptake Increase)

	Device Cost, $ Million			
Year	Use of Impella 2.5 and 5.0, %	Current Manufacturer Price (Base Case)	Reduced by 25%	Reduced by 50%
High-Risk PCI				
2017	25	1.3	1.0	0.6
2018	50	2.6	2.0	1.3
2019	75	4.0	2.9	1.9
2020	100	5.3	3.9	2.5
Cardiogenic Shock				
2017	25	1.6	1.2	0.8
2018	50	3.1	2.3	1.5
2019	75	4.7	3.5	2.3
2020	100	6.3	4.7	3.0
Total				
2017	25	**2.9**	2.1	1.4
2018	50	**5.8**	4.3	2.8
2019	75	**8.7**	6.4	4.2
2020	100	**11.5**	8.6	5.6

Abbreviation: PCI, percutaneous coronary intervention.

Discussion

This budget impact analysis revealed that, in the first 4 years, publicly funding Impella 2.5 and Impella 5.0 could result in incremental spending for high-risk PCI ($1.3–$5.3 million per year) and cardiogenic shock ($1.6–$6.3 million per year), depending on the uptake rate. In total, incremental public spending on both devices would vary from $2.9 to $11.5 million per year. Budget spending would be expected to increase over time, as uptake of treatment rises. This trend would likely stabilize at Year 5, when most of the target population would already be receiving percutaneous ventricular assist devices.

We analyzed a scenario in which the cost of Impella 2.5 was reduced by 25% and Impella 5.0 by 50%. We estimated incremental spending of $2.1 to $8.6 million per year if the cost of Impella 2.5/5.0 were reduced by 25%, and of $1.4 to $5.6 million per year if the cost were reduced by 50%.

To our knowledge, this is the first budget impact analysis on Impella 2.5/5.0 for high-risk PCI and cardiogenic shock undertaken from the Canadian health care perspective. Currently, only two published studies assess the budget impact of high-risk PCI patients treated with percutaneous ventricular assist devices.[28,47] Both studies were conducted from the US payer perspective. Shah et al[28] reported an incremental budget impact of $34 million to hospitals and up to $109 million to public payers if percutaneous ventricular assist devices were introduced for high-risk PCI and cardiogenic shock. In contrast, Gregory et al[41] reported net savings that ranged from approximately $2.2 million to $3.7 million when assuming that percutaneous ventricular assist device migration would range from 30% to 50% for both indications. The difference in the results could be attributed to the type of model applied and various data inputs.

Our analysis had two important limitations that merit emphasis. First, our estimates of cohort size were based on volumes of procedures from administrative data. Because of limitations in reporting, the cohort sizes used in our calculations could have been underestimated. At present, the actual volumes in Ontario might be under-reported because IABPs inserted in intensive care areas and at non-advanced cardiac hospitals are not reflected in the Cardiac Care Network registry. The second, and arguably most important, limitation was the uncertainty surrounding the hospitalization cost and resource utilization savings for Impella 2.5/5.0 versus IABP. We addressed this uncertainty of the budget impact by focusing primarily on the cost of devices.

We concluded that, if the Impella 2.5/5.0 were publicly funded as an alternative to IABPs in high-risk PCI and cardiogenic shock, the additional cost would be $2.9 to $11.5 million per year.

PATIENT AND PUBLIC ENGAGEMENT

We informally assessed the value of undertaking patient and public engagement for this technology. We considered how the illness affects patients, the nature of the technology, degree of controversy around its use, and whether any particular factors made patient engagement likely to produce information that would substantially increase the value of our review of the published evidence. Considering this assessment, and also the scarcity of resources to conduct patient engagement, this health technology was not prioritized for patient engagement.

ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
ECMO	Extracorporeal membrane oxygenation
EQ-5D	Descriptive system of health-related quality of life states consisting of five dimensions
FDA	United States Food and Drug Administration
GRADE	Grading of recommendations assessment, development, and evaluation
IABP	Intra-aortic balloon pump
ICER	Incremental cost-effectiveness ratio
iHE	Institute of Health Economics
Impella LP	Impella Left Peripheral device
INESS	Institut national d'excellence en sante et en services
ISAR-SHOCK	Efficacy study of left ventricular assist device to treat patients with cardiogenic shock
MeSH	Medical subject headings
MUHC-TAU	McGill University Health Centre Health Technology Assessment Unit
NHS	National Health Service
OCCI	Ontario Case Costing Initiative
PCI	Percutaneous coronary intervention
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROTECT	Prospective randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention
QALY	Quality-adjusted life-year

GLOSSARY

Adverse event	Any unexpected problem that happens during treatment, regardless of the cause or severity
Area under the curve	The area composed of positive numbers (numbers above the x-axis) that fall below the probability curve (the curve formed by the equation or plotted numbers that make up the graph)
Cardiogenic shock	A dangerous condition resulting from low blood flow caused by interruptions in the operation of the heart. Often caused by a heart attack or an obstruction in the heart.
Case report	A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Also known as a case study.
Case series	A group or series of case reports involving patients who were given similar treatment.
Extracorporeal membrane oxygenation	A technique to provide respiratory support. The blood is circulated through an artificial lung consisting of two compartments, with the blood on one side and

	oxygen on the other. A filter between the two compartments is designed to allow oxygen, but not blood, to flow from one side to the other.
Hemodynamic stability	A treatment goal for patients with unstable blood pressure, who have either hypertension or hypotension (high or low blood pressure, respectively).
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Incremental cost-effectiveness ratio (ICER)	Determines "a unit of benefit" for an intervention by dividing the incremental cost by the effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as additional years of life or as "quality-adjusted life years."
Intra-aortic balloon pump	A technology using a balloon inserted into the aorta that expands and contracts at a specified rate to help push blood through the aorta and relieve stress on the heart. The IABP is typically used for a short time (less than 10 days) after a cardiac event.
Left ventricular assist device	A mechanical pump that supports weakened hearts by taking blood from the lower chamber of the heart and pumping it out to the arteries and vital organs.
Major adverse cardiac events	A summary of all significant unexpected problems related to the heart. This summary is usually compiled at the end of a research study. Because there is no agreed-upon standard for what constitutes a significant problem, the summary is of limited value.
Percutaneous coronary intervention	A procedure to open up a blood vessel that has been dangerously narrowed by plaque buildup (atherosclerosis). In this procedure, a thin flexible tube known as a catheter is used to insert a stent into the affected blood vessel. The stent is a small structure that forces the narrow vessel open to allow a more normal blood flow.
Percutaneous ventricular assist device	A small pump connected to the heart, but worn outside the body, that gives short-term support (less than 2 weeks) to the heart while it recovers from some trauma, such as a heart attack or heart surgery.
Quality-adjusted life-year	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). One QALY is expressed as a number between zero (no benefit) and one (perfect health). The QALY is commonly used as an outcome measure in cost–utility analyses.
Sensitivity analysis	Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.
Utility	The perceived benefit (value) placed on a treatment by a person or society.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Literature Search

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <4th Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 49>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:
----
1   exp Percutaneous Coronary Intervention/ (114629)
2   ((percutaneous adj coronary adj2 (intervention* or revasculari*)) or PCI or Percutaneous transluminal coronary angioplast* or PTCA or Percutaneous transluminal angioplast* or (Coronary adj (angioplast* or stent*)) or balloon angioplast*).tw. (145240)
3   exp Angioplasty/ (133372)
4   (angioplast* or endoluminal repair*).tw. (94075)
5   Shock, Cardiogenic/ (19837)
6   (cardiogenic* adj shock*).tw. (20752)
7   or/1-6 (263855)
8   Heart-Assist Devices/ (16818)
9   (((heart or ventric* or vascular* or percutaneous) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or mechanical circulatory support).tw. (23913)
10   Impella*.tw. (885)
11   or/8-10 (30354)
12   7 and 11 (3806)
13   exp Animals/ not (exp Animals/ and Humans/) (9444121)
14   12 not 13 (3486)
15   limit 14 to english language [Limit not valid in CDSR,DARE; records were retained] (3167)
16   15 use pmoz,cctr,coch,dare,clhta,cleed (1324)
17   exp percutaneous coronary intervention/ (114629)
18   ((percutaneous adj coronary adj2 (intervention* or revasculari*)) or PCI or Percutaneous transluminal coronary angioplast* or PTCA or Percutaneous transluminal angioplast* or (Coronary adj (angioplast* or stent*)) or balloon angioplast*).tw. (145240)
19   exp angioplasty/ (133372)
20   (angioplast* or endoluminal repair*).tw. (94075)
21   cardiogenic shock/ (23132)
22   (cardiogenic* adj shock*).tw. (20752)
23   or/17-22 (264658)
24   heart assist device/ (17167)
25   (((heart or ventric* or vascular* or percutaneous) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or mechanical circulatory support).tw. (23913)

26   Impella*.tw. (885)
27   or/24-26 (30467)
28   23 and 27 (3889)
29   (exp animal/ or nonhuman/) not exp human/ (9571754)
30   MI not 29 (3764)
31   limit 30 to english language [Limit not valid in CDSR, DARE; records were retained] (3440)
32   31 use emez (2116)
33   16 or 32 (3440)
34   33 use pmoz (1265)
35   33 use emez (2116)
36   33 use cctr (37)
37   33 use coch (6)
38   33 use dare (7)
39   33 use clhta (4)
40   33 use cleed (5)
41   remove duplicates from 33 (2420)

Economic Literature Search

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <4th Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 49>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

#	Searches	Results
1	exp Percutaneous Coronary Intervention/	114635
2	((percutaneous adj coronary adj2 (intervention* or revasculari*)) or PCI or Percutaneous transluminal coronary angioplast* or PTCA or Percutaneous transluminal angioplast* or (Coronary adj (angioplast* or stent*)) or balloon angioplast*).tw.	145334
3	exp Angioplasty/	133373
4	(angioplast* or endoluminal repair*).tw.	94094
5	Shock, Cardiogenic/	19837
6	(cardiogenic* adj shock*).tw.	20758
7	or/1-6	263961
8	Heart-Assist Devices/	16818

9	(((heart or ventric* or vascular* or percutaneous) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or mechanical circulatory support).tw.	23932
10	Impella*.tw.	886
11	or/8-10	30373
12	7 and 11	3810
13	economics/	250500
14	economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/	713726
15	economics.fs.	376433
16	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw.	657991
17	exp "costs and cost analysis"/	496547
18	cost*.ti.	225872
19	cost effective*.tw.	237233
20	(cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab.	148440
21	models, economic/	131282
22	markov chains/ or monte carlo method/	116010
23	(decision adj1 (tree* or analy* or model*)).tw.	32190
24	(markov or markow or monte carlo).tw.	95647
25	quality-adjusted life years/	25355
26	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw.	47106
27	((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw.	92053
28	or/13-27	2208035
29	12 and 28	189
30	29 use pmoz,cctr,coch,dare,clhta	68
31	12 use cleed	5
32	or/30-31	73
33	limit 32 to english language [Limit not valid in CDSR,DARE; records were retained]	67
34	exp percutaneous coronary intervention/	114635
35	((percutaneous adj coronary adj2 (intervention* or revasculari*)) or PCI or Percutaneous transluminal coronary angioplast* or PTCA or Percutaneous transluminal angioplast* or (Coronary adj (angioplast* or stent*)) or balloon angioplast*).tw.	145334
36	exp angioplasty/	133373
37	(angioplast* or endoluminal repair*).tw.	94094
38	cardiogenic shock/	23132
39	(cardiogenic* adj shock*).tw.	20758
40	or/34-39	264764

41	heart assist device/	17167
42	(((heart or ventric* or vascular* or percutaneous) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or mechanical circulatory support).tw.	23932
43	Impella*.tw.	886
44	or/41-43	30486
45	40 and 44	3893
46	Economics/	250500
47	Health Economics/ or exp Pharmacoeconomics/	211902
48	Economic Aspect/ or exp Economic Evaluation/	383821
49	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw.	657991
50	exp "Cost"/	496547
51	cost*.ti.	225872
52	cost effective*.tw.	237233
53	(cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab.	148440
54	Monte Carlo Method/	49219
55	(decision adj1 (tree* or analy* or model*)).tw.	32190
56	(markov or markow or monte carlo).tw.	95647
57	Quality-Adjusted Life Years/	25355
58	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw.	47106
59	((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw.	92053
60	or/46-59	1809293
61	45 and 60	172
62	61 use emez	105
63	limit 62 to english language [Limit not valid in CDSR,DARE; records were retained]	95
64	33 or 63	162
65	64 use pmoz	47
66	64 use emez	95
67	64 use cctr	7
68	64 use coch	6
69	64 use dare	2
70	64 use clhta	0
71	64 use cleed	5
72	remove duplicates from 64	123

Appendix 2: Evidence Quality Assessment

Our first consideration was study design; we started with the assumption that randomized controlled trials are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that can raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[17] For more detailed information, please refer to the latest series of GRADE articles.[17]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High   High confidence in the effect estimate—the true effect lies close to the estimate of the effect

Moderate   Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different

Low   Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect

Very Low   Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Table A1: GRADE Evidence Profile for Comparison of Impella 2.5 With IABP in High-Risk PCI

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Hemodynamic Stability							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
Mortality							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
1 observational study[11]	Serious limitations (−1)	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Major Adverse Cardiac Events							
1 RCT[19]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
Bleeding Complications							
1 observational study[11]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Vascular Complications							
1 observational study[11]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.
[a]Optimal sample size not met. The trial was terminated early for futility reason; at risk of selection bias.
[b]Insufficient statistical power.
[c]Boudoulas et al[11]: significant difference in disease severity at baseline between Impella 2.5 and IABP groups.

Table A2: Risk of Bias Among Randomized Controlled Trials Comparing Impella 2.5 With IABP in High-Risk PCI

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
O'Neill et al, 2011[19]	No limitations	No limitations[a]	No limitations	No limitations	Limitations[b,c]

Abbreviations: IABP; intra-aortic balloon pump; PCI, percutaneous coronary intervention.
[a]Impossible to blind because of different radiographic appearance. Attending physicians treated patients randomized to receive Impella 2.5 more frequently and more vigorously with rotational atherectomy, resulting in fewer revascularizations, but higher rate of periprocedural myocardial infarction. In a high-risk PCI, it was assumed that attending physicians would prepare lesions aggressively with balloon predilation for patients randomized to receive IABP.
[b]Optimal sample size not met. Trial was terminated early for futility reasons; at risk of selection bias.
[c]Insufficient statistical power.

Table A3: Risk of Bias Among Observational Studies Comparing Impella 2.5 With IABP in High-Risk PCI

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Boudoulas et al, 2012[11]	No limitations	No limitations	No limitations	Limitations[a]	Limitations[b]

Abbreviations: IABP; intra-aortic balloon pump; PCI, percutaneous coronary intervention.
[a]Significant difference in disease severity at baseline between Impella and IABP groups.
[b]No explanation of the 22.7% loss to follow-up at 1 year.

Table A4: GRADE Evidence Profile for Noncomparative Observational Studies of Impella 2.5 in High-Risk PCI

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Hemodynamic Stability							
4 observational studies[5,22-24]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Mortality							
8 observational studies[5,8,20,22-26]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Major Adverse Cardiac Events							
8 observational studies[5,8,20,22-26]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Bleeding Complications							
9 observational studies[5,8,20-26]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Vascular Complications							
6 observational studies[8,20,22-25]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCI, percutaneous coronary intervention.
[a]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which patients were considered as high risk, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Table A5: Risk of Bias Among Noncomparative Observational Studies of Impella 2.5 in High-Risk PCI

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Alasnag et al, 2011[20]	Limitations[a]	No limitations	Limitations[b]	No limitations	No limitations
Anusionwu et al, 2012[21]	Limitations[a]	No limitations	Limitations[b]	No limitations	No limitations
Cohen et al, 2015[22]	Limitations[a]	No limitations	Limitations[c]	No limitations	No limitations
Dixon et al, 2009[5]	Limitations[a]	No limitations	Limitations[c]	No limitations	No limitations
Iliodromitis et al, 2011[23]	Limitations[a]	No limitations	No limitations	No limitations	Limitations[d]
Kovacic et al, 2013[8]	Limitations[a]	No limitations	No limitations	No limitations	No limitations
Maini et al, 2012[24]	Limitations[a]	No limitations	Limitations[c]	No limitations	No limitations
Schwartz et al, 2011[26]	Limitations[a]	No limitations	No limitations	No limitations	Limitations[e]
Sjauw et al, 2009[25]	Limitations[a]	No limitations	Limitations[c]	No limitations	No limitations

Abbreviation: PCI, percutaneous coronary intervention.
[a]Potential selection bias: which patients were considered as high risk for PCI was determined by clinical judgment of attending physicians.
[b]Risk of missing data from medical records.
[c]Risk of inconsistent documentation in registry.
[d]8% of patients lost to follow-up at 30 days.
[e]54% of patients lost to follow-up at 30 days.

Table A6: GRADE Evidence Profile for Comparison of Impella 2.5 With IABP in Cardiogenic Shock

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Hemodynamic Stability							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations[d]	Undetected	None	⊕ Very Low
Mortality							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[e]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Major Adverse Cardiac Events							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[e]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Bleeding Complications							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[e]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Vascular Complications							
1 RCT[15]	Very serious limitations (−2)[a,b]	No serious limitations	No serious limitations	Serious limitations[e]	Undetected	None	⊕⊕ Low
1 observational study[36]	Serious limitations[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

[a]Small sample size (n = 16); imbalance in baseline characteristics.

[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).

[c]Early time points for hemodynamic outcomes limited generalizability to effects of longer Impella 2.5 support.

[d]Wide confidence interval for the difference in change of cardiac index between Impella 2.5 and IABP (0.38 [0.07, 0.69] L/min/m^2).

[e]Imprecision due to small sample size.

[f]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Table A7: Risk of Bias Among Randomized Controlled Trials Comparing Impella 2.5 With IABP in Cardiogenic Shock

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Seyfarth et al, 2008[15]	No limitations	No limitations	No limitations	No limitations	Limitations[a,b,c,d]

Abbreviation: IABP, intra-aortic balloon pump.
[a]Small sample size (n = 16); imbalance in baseline characteristics.
[b]Risk of model misclassification because of small sample size, as data distribution could be skewed (which could under- or over-estimate the effect estimate if analyses were based on normal distribution).
[c]Early time points for hemodynamic outcomes limited generalizability to effects of longer Impella 2.5 support.
[d]Wide confidence interval for difference in change of cardiac index between Impella 2.5 and IABP (0.38 [0.07, 0.69] L/min/m^2).

Table A8: Risk of Bias Among Observational Studies Comparing Impella 2.5 With IABP in Cardiogenic Shock

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Manzo-Silberman et al, 2013[36]	No limitations	No limitations	No limitations	Limitations[a,b]	No limitations

Abbreviation: IABP, intra-aortic balloon pump.
[a]Significant difference in heart rate and left ventricular ejection factor between Impella and IABP groups at baseline.
[b]Potential treatment bias: timing of Impella insertion and all adjunctive therapies was at discretion of attending physicians.

Table A9: GRADE Evidence Profile for Noncomparative Observational Studies of Impella 2.5 in Cardiogenic Shock

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Hemodynamic Stability							
3 observational studies[31-33]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Mortality							
3 observational studies[31-33]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Major Adverse Cardiac Events							
2 observational studies[31,32]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Bleeding Complications							
3 observational studies[31-33]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Vascular Complications							
2 observational studies[31,33]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Table A10: Risk of Bias Among Noncomparative Observational Studies of Impella 2.5 in Cardiogenic Shock

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Casassus et al, 2015[33]	Limitations[a]	No limitations	Limitations[b]	Limitations[c]	No limitations
Lauten et al, 2013[32]	Limitations[a]	No limitations	Limitations[b]	Limitations[c]	No limitations
O'Neill et al, 2014[31]	Limitations[a]	No limitations	Limitations[b]	Limitations[c]	Limitations[d]

[a]Potential selection bias on modality of mechanical support based on patients' conditions.
[b]Risk of missing data in medical records.
[c]Potential treatment bias: timing of Impella insertion and all adjunctive therapies was at discretion of attending physicians.
[d]Follow-up data unavailable.

Table A11: GRADE Evidence Profile for Noncomparative Observational Studies of Impella 5.0 in Cardiogenic Shock

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Hemodynamic Stability							
1 observational study[34]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Mortality							
2 observational studies[34,35]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Major Adverse Cardiac Events							
1 observational study[34]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Bleeding Complications							
1 observational study[34]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Vascular Complications							
1 observational study[34]	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Observational studies started with low level of GRADE because of inherent limitations in study design, e.g., lack of randomization, lack of blinding, risk of selection bias on which devices patients were to receive, risk of missing data from chart review or inconsistent documentation from prospective study, and loss to follow-up. No further downgrade of GRADE unless there were more substantial limitations of the study conduct.

Table A12: Risk of Bias Among Noncomparative Observational Studies of Impella 2.5 in Cardiogenic Shock

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Engström et al, 2013[35]	Limitations[a]	No limitations	Limitations[b]	Limitations[c]	No limitations
Griffith et al, 2013[34]	Limitations[a]	No limitations	No limitations	Limitations[c]	No limitations

[a]Potential selection bias on modality of mechanical support based on patients' conditions.
[b]Risk of missing data in medical records.
[c]Potential treatment bias: timing of Impella insertion and all adjunctive therapies was at discretion of attending physicians.

Appendix 3: Full Economic Model Inputs

Table A13: Clinical Outcomes Used in Economic Model

Model Parameters	Probability Reported	Converted Monthly Rate	Monthly Probability	Author, Year
Short-term transition probabilities (30 and 90 days)				
IABP				
Bleeding at 30 days	0.1920	0.2132	0.1920	Perera et al, 2013[52]
Repeat revascularization at 30 days	0.0410	0.0419	0.0410	O'Neill et al, 2012[19]
Repeat revascularization at 60 and 90 days[a]	0.0780	0.0197	0.0195	O'Neill et al, 2012[19]
Acute MI at 30 days	0.0680	0.0704	0.0680	O'Neill et al, 2012[19]
Acute MI at 60 and 90 days[a]	0.1050	0.0203	0.0201	O'Neill et al, 2012[19]
Stroke at 30 days	0.0180	0.0182	0.0180	O'Neill et al, 2012[19]
Stroke at 60 and 90 days[a]	0.0270	0.0046	0.0046	O'Neill et al, 2012[19]
Other MACE at 30 days	0.0960	0.1009	0.0960	O'Neill et al, 2012[19]
Other MACE at 60 and 90 days[a]	0.1050	0.0050	0.0050	O'Neill et al, 2012[19]
Impella				
Bleeding at 30 days[a]	0.1266	0.1354	0.1266	Dixon et al, 2009[5]; Alasnag et al, 2011[53]; Boudoulas et al, 2012[54]; Iliodromitis et al, 2011[55]; Maini et al, 2012[50]; Sjauw et al, 2009[49]
Repeat revascularization at 30 days	0.0130	0.0131	0.0130	O'Neill et al, 2012[19]
Repeat revascularization at 60 and 90 days[a]	0.0360	0.0118	0.0117	O'Neill et al, 2012[19]
Acute MI at 30 days	0.0580	0	0.0580	Dangas et al, 2014[56]
Acute MI at 60 and 90 days[a]	0	0	0	Dangas et al, 2014[56]
Stroke at 30 days	0	0	0	O'Neill et al, 2012[19]
Stroke at 60 and 90 days[a]	0.0090	0.0045	0.0046	O'Neill et al, 2012[19]
Other MACE at 30 days	0.0750	0.0780	0.0750	O'Neill et al, 2012[19]
Other MACE at 60 and 90 days[a]	0.0790	0.0022	0.0022	O'Neill et al, 2012[19]
Long-term transition probabilities (after 90 days) of combined cohort				
Repeat revascularization, combined cohort	0.167 (5 years)	0.0030	0.0030	Roe et al, 2013[57]
Acute MI, combined cohort	0.0192	0.0097	0.0096	O'Neill et al, 2012[19]
Stroke, combined cohort	0.0096	0.0048	0.0048	O'Neill et al, 2012[19]

Model Parameters	Probability Reported	Converted Monthly Rate	Monthly Probability	Author, Year
Mortality				
At 30 days when using IABP	0.0590	0.0608	0.0590	O'Neill et al, 2012[19]
At 60 and 90 days when using IABP[a]	0.0870	0.0151	0.0150	O'Neill et al, 2012[19]
At 30 days when using Impella device	0.0760	0.0790	0.0760	O'Neill et al, 2012[19]
At 60 and 90 days when using Impella device[a]	0.1210	0.0250	0.0247	O'Neill et al, 2012[19]
Repeat revascularization	0.1060 (3 years)	0.0031	0.0031	Littnerova et al, 2015[58]
Acute MI	0.3550 (5 years)	0.0073	0.0073	Roe et al, 2013[57]
Stroke	0.555 (10 years)	0.0067	0.0067	Lakshminarayan et al, 2014[59]
Other MACE (short-term)	0.350 (5 years)	0.0072	0.0072	Banach et al, 2011[60]
Post-PCI state (no complications)	0.1060 (3 years)	0.0031	0.0031	Littnerova et al, 2015[58]

Abbreviations: IABP, intra-aortic balloon pump; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a]Probability for 60 and 90 days calculated as conditional from cumulative probability at 90 days

Table A14: Physician Fees from Ontario Schedule of Benefit for Physician Services

Code	Service	Cost per Service	Source	Comments
Hospital admission				
A605	Cardiology consultation	$157	A46	Applied to all health states
E082	Admission assessment by MRP	add 30%	GP27	MRP
Total (hospital admission)		$204.10		
Inpatient (during hospital stay)				
First day				
C122	Subsequent visit by MRP	58.8	A9	Day following hospital admission assessment (Day 1)
E083	Subsequent visit by MRP	add 30%	GP32	
Total (first day)		$76.44		
Third day				
C123	Visit by MRP	58.8	A9	Second day following hospital assessment
E083	Subsequent visit by MRP	add 30%	GP32	
Total (third day)		$76.44		
Subsequent visits				
C602	Subsequent visits	$31.00	A48	Subsequent visits during first 5 weeks
Total physician fee in hospital		$418.98		Assume patients stay 5 days (all health states)
Outpatient				
A601	Complex medical specific re-assessment	$70.90	A47	Monthly ambulatory visit physician fee
PCI				
Z442	Selective coronary catheterization	$289.55	J9	Both arteries; angiogram at 50%
Z434	One or more sites on single major vessel	$471.60	J9	PCI at 100%
Z440	Retrograde aortic	210.55	J8	at 50%
G297	Angiography	118.7	J9	at 50%
G 400	Critical care	223.1		
Total PCI physician fee		$1,004.10		

Abbreviations: MRP, most responsible physician; PCI, percutaneous coronary intervention.

Note: Codes suggested by Dr. Harindra Wijeysundera, Interventional Cardiologist, Sunnybrook Health Sciences Centre (written communication, May 2016).

Table A15: Mortality Parameters Used in Various Impella Models

	PROTECT II	Roos et al[2]	Gregory et al[1]
PCI intervention			
IABP at 30 days	0.059	0.0896	0.036
Impella at 30 days	0.076	0.0559	0.036
MACE (monthly)			
Acute MI	0.0073	0.0160	RR = 5
Stroke	0.0067	0.0199	RR = 3.8
PCI	0.0030	0.0017	

Abbreviations: IABP, intra-aortic balloon pump; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PROTECT, Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention; RR, repeat revascularization.

Table A16: Long-Term Transition Probabilities: Impella 2.5 Versus IABP

Adverse Event	PROTECT II	Roos et al[2]	Gregory et al[1]	
RR	0.003		IABP	0.0032
			Impella 2.5	0.0021
Acute MI	0.0096	0.0028	IABP	0.0064
			Impella 2.5	0.004
Stroke	0.005	0.0018	IABP	0.0042
			Impella 2.5	0.0024

Abbreviations: IABP, intra-aortic balloon pump; MI, myocardial infarction; PROTECT, Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention; RR, repeat revascularization.

Table A17: Short-Term Transition Probabilities: Impella 2.5 Versus IABP

Treatment	PROTECT II	Roos et al[2]	Gregory et al[1]
Repeat revascularization			
IABP at 30 days	0.041		0.0432
Impella at 30 days	0.013		0.0208
Acute MI			
IABP at 30 days	0.068		0.0432
Impella at 30 days	0.058		0.0356
Stroke			
IABP at 30 days	0.018	0.0319	0.0081
Impella at 30 days	0	0.007	0.0047

Abbreviations: IABP, intra-aortic balloon pump; MI, myocardial infarction; PROTECT, Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention.

REFERENCES

(1)   Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapur NK, et al. 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care (Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology - Association Canadienne de Cardiologie d'intervention). J Card Fail. 2015;21(6):499-518.

(2)   Kar B, Basra SS, Shah NR, Loyalka P. Percutaneous circulatory support in cardiogenic shock: interventional bridge to recovery. Circulation. 2012;125(14):1809-17.

(3)   Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA. 2005;294(4):448-54.

(4)   Goldberg RJ, Samad NA, Yarzebski J, Gurwitz J, Bigelow C, Gore JM. Temporal trends in cardiogenic shock complicating acute myocardial infarction. N Engl J Med. 1999;340(15):1162-8.

(5)   Dixon SR, Henriques JP, Mauri L, Sjauw K, Civitello A, Kar B, et al. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (the PROTECT I trial): initial U.S. experience. JACC Cardiovasc Interv. 2009;2(2):91-6.

(6)   Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The percutaneous ventricular assist device in severe refractory cardiogenic shock. J Am Coll Cardiol. 2011;57(6):688-96.

(7)   Makdisi G, Wang IW. Extra corporeal membrane oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis. 2015;7(7):E166-76.

(8)   Kovacic JC, Nguyen HT, Karajgikar R, Sharma SK, Kini AS. The Impella Recover 2.5 and TandemHeart ventricular assist devices are safe and associated with equivalent clinical outcomes in patients undergoing high-risk percutaneous coronary intervention. Catheter Cardiovasc Interv. 2013;82(1):E28-37.

(9)   Valgimigli M, Steendijk P, Sianos G, Onderwater E, Serruys PW. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. Catheter Cardiovasc Interv. 2005;65(2):263-7.

(10)   Remmelink M, Sjauw KD, Henriques JPS, De Winter RJ, Koch KT, Van Der Schaaf RJ, et al. Effects of left ventricular unloading by Impella Recover LP 2.5 on coronary hemodynamics. Catheter Cardiovasc Interv. 2007;70(4):532-7.

(11)   Boudoulas KD, Pederzolli A, Saini U, Gumina RJ, Mazzaferri EL Jr, Davis M, et al. Comparison of Impella and intra-aortic balloon pump in high-risk percutaneous coronary intervention: vascular complications and incidence of bleeding. Acute Card Care. 2012;14(4):120-4.

(12)   U.S. Food and Drug Administration. Impella 2.5 system - P140003 [Internet]. Silver Spring (MD): U.S. Department of Health and Human Resources; 2015 [cited 2016 May 26]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p140003

(13)   U.S. Food and Drug Administration. Premarket approval [Internet]. Silver Spring (MD): U.S. Department of Health and Human Services; 2016 [cited 2016 June 7]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140003S005

(14)   Technology Assessment Unit of the McGill University Health Centre. The Impella®
       percutaneous ventricular assist device [Internet]. Montreal (QC): McGill University; 2009
       [cited 2015 Oct 13]. Available from:
       https://www.mcgill.ca/tau/files/tau/IMPELLA_FINAL_JUNE_2009.pdf

(15)   Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, 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):1584-8.

(16)   McGowan J, Sampson M, Salzwedel D, Cogo E, Foerster V, Lefebvre C. PRESS peer
       review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol.
       2016;75:40-6.

(17)   Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines:
       a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol.
       2011;64(4):380-2.

(18)   Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for
       systematic reviews and meta-analyses: the PRISMA statement. PLoS Med.
       2009;6(7):e1000097.

(19)   O'Neill WW, Kleiman NS, Moses J, Henriques JP, Dixon S, Massaro 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):1717-27.

(20)   Alasnag MA, Gardi DO, Elder M, Kannam H, Ali F, Petrina M, et al. Use of the Impella
       2.5 for prophylactic circulatory support during elective high-risk percutaneous coronary
       intervention. Cardiovasc Revasc Med. 2011;12(5):299-303.

(21)   Anusionwu O, Fischman D, Cheriyath P. The duration of Impella 2.5 circulatory support
       and length of hospital stay of patients undergoing high-risk percutaneous coronary
       interventions. Cardiol Res. 2012;3(4):154-7.

(22)   Cohen MG, Matthews R, Maini B, Dixon S, Vetrovec G, Wohns D, et al. Percutaneous
       left ventricular assist device for high-risk percutaneous coronary interventions: real-world
       versus clinical trial experience. Am Heart J. 2015;170(5):872-9.

(23)   Iliodromitis KE, Kahlert P, Plicht B, Hoffmann AC, Eggebrecht H, Erbel R, et al. High-risk
       PCI in acute coronary syndromes with Impella LP 2.5 device support. Int J Cardiol.
       2011;153(1):59-63.

(24)   Maini B, Naidu SS, Mulukutla S, Kleiman N, Schreiber T, Wohns D, et al. Real-world use
       of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary
       intervention: the USpella Registry. Catheter Cardiovasc Interv. 2012;80(5):717-25.

(25)   Sjauw KD, Konorza T, Erbel R, Danna PL, Viecca M, Minden HH, et al. Supported high-
       risk percutaneous coronary intervention with the Impella 2.5 device. The Europella
       registry. J Am Coll Cardiol. 2009;54(25):2430-4.

(26)   Schwartz BG, Ludeman DJ, Mayeda GS, Kloner RA, Economides C, Burstein S. High-
       risk percutaneous coronary intervention with the TandemHeart and Impella devices: a
       single-center experience. J Invasive Cardiol. 2011;23(10):417-24.

(27)   Venugopal V, Spiro J, Zaphiriou A, Khan S, Townend JN, Ludman PF, et al.
       Percutaneous mechanical ventricular support in acute cardiac care: a UK quaternary
       centre experience using 2.5L, 3.8L and 5.0L Impella catheters. Cardiol Ther.
       2015;4(1):47-58.

(28)   Shah AP, Retzer EM, Nathan S, Paul JD, Friant J, Dill KE, et al. Clinical and economic
       effectiveness of percutaneous ventricular assist devices for high-risk patients undergoing
       percutaneous coronary intervention. J Invasive Cardiol. 2015;27(3):148-54.

(29)   Lee JM, Park J, Kang J, Jeon KH, Jung JH, Lee SE, et al. The efficacy and safety of
       mechanical hemodynamic support in patients undergoing high-risk percutaneous

coronary intervention with or without cardiogenic shock: Bayesian approach network meta-analysis of 13 randomized controlled trials. Int J Cardiol. 2015;184(1):36-46.

(30)   Cohen MG, Ghatak A, Kleiman NS, Naidu SS, Massaro JM, Kirtane AJ, et al. Optimizing rotational atherectomy in high-risk percutaneous coronary interventions: insights from the PROTECT II study. Catheter Cardiovasc Interv. 2014;83(7):1057-64.

(31)   O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, et al. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. J Interv Cardiol. 2014;27(1):1-11.

(32)   Lauten A, Engström AE, Jung C, Empen K, Erne P, Cook S, et al. Percutaneous left-ventricular support with the Impella-2.5-assist device in acute cardiogenic shock: results of the Impella-EUROSHOCK-Registry. Circ Heart Fail. 2013;6(1):23-30.

(33)   Casassus F, Corre J, Leroux L, Chevalereau P, Fresselinat A, Seguy B, et al. The use of Impella 2.5 in severe refractory cardiogenic shock complicating an acute myocardial infarction. J Interv Cardiol. 2015;28(1):41-50.

(34)   Griffith BP, Anderson MB, Samuels LE, Pae WE Jr, Naka Y, Frazier OH. The RECOVER I: a multicenter prospective study of Impella 5.0/LD for postcardiotomy circulatory support. J Thorac Cardiovasc Surg. 2013;145(2):548-54.

(35)   Engström AE, Granfeldt H, Seybold-Epting W, Dahm M, Cocchieri R, Driessen AHG, et al. Mechanical circulatory support with the Impella 5.0 device for postcardiotomy cardiogenic shock: a three-center experience. Minerva Cardioangiol. 2013;61(5):539-46.

(36)   Manzo-Silberman S, Fichet J, Mathonnet A, Varenne O, Ricome S, Chaib A, et al. Percutaneous left ventricular assistance in post cardiac arrest shock: comparison of intra aortic blood pump and Impella Recover LP 2.5. Resuscitation. 2013;84(5):609-15.

(37)   Higgins J, Lamarche Y, Kaan A, Stevens LM, Cheung A. Microaxial devices for ventricular failure: a multicentre, population-based experience. Can J Cardiol. 2011;27(6):725-30.

(38)   Lamarche Y, Cheung A, Ignaszewski A, Higgins J, Kaan A, Griesdale DEG, et al. Comparative outcomes in cardiogenic shock patients managed with Impella microaxial pump or extracorporeal life support. J Thorac Cardiovasc Surg. 2011;142(1):60-5.

(39)   Lemaire A, Anderson MB, Lee LY, Scholz P, Prendergast T, Goodman A, et al. The Impella device for acute mechanical circulatory support in patients in cardiogenic shock. Ann Thorac Surg. 2014;97(1):133-8.

(40)   Cheng JM, Den Uil CA, Hoeks SE, Van Der Ent M, Jewbali LSD, Van Domburg RT, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J. 2009;30(17):2102-8.

(41)   Gregory D, Scotti DJ, de Lissovoy G, Palacios I, Dixon S, Maini B, et al. A value-based analysis of hemodynamic support strategies for high-risk heart failure patients undergoing a percutaneous coronary intervention. Am Health Drug Benefits. 2013;6(2):88-99.

(42)   Roos JB, Doshi SN, Konorza T, Palacios I, Schreiber T, Borisenko OV, et al. The cost-effectiveness of a new percutaneous ventricular assist device for high-risk PCI patients: Mid-stage evaluation from the European perspective. J Med Econ. 2013;16(3):381-90.

(43)   Maini B, Scotti DJ, Gregory D. Health economics of percutaneous hemodynamic support in the treatment of high-risk cardiac patients: A systematic appraisal of the literature. Expert Review of Pharmacoeconomics and Outcomes Research. 2014;14(3):403-16.

(44)   Borisenko O, Wylie G, Payne J, Bjessmo S, Smith J, Firmin R, et al. The cost impact of short-term ventricular assist devices and extracorporeal life support systems therapies on the National Health Service in the UK. Interact Cardiovasc Thorac Surg. 2014;19(1):41-8.

(45)   Scotti DJ, Gregory DA, Schreiber TL, Shroff A, Buck DR. Operational implications of
       utilizing 2 advanced technologies for rendering short-term hemodynamic support to
       patients presenting with cardiogenic shock: a view through the lens of hospital
       readmissions. Managed care (Langhorne, Pa). 2015;24(5):38-44, 6.

(46)   Wohns D, Muthusamy P, Davis AT, Khan M, Postma JK, Williams EE, et al. Economic
       and operational implications of a standardized approach to hemodynamic support
       therapy using percutaneous cardiac assist devices. Innovations (Phila). 2014;9(1):38-42.

(47)   Gregory D, Scotti DJ. A Budget impact model to estimate the cost dynamics of treating
       high-risk heart failure patients with advanced percutaneous cardiac assist devices: The
       payer perspective. Journal of Managed Care Medicine. 2013;16(1):61-9.

(48)   Esfandiari S, Erickson L, McGregor M. The Impella percutaneous ventricular assist
       device. Montreal (QC): McGill University; 2009.

(49)   Sjauw KD, Konorza T, Erbel R, Danna PL, Viecca M, Minden HH, et al. Supported high-
       risk percutaneous coronary intervention with the Impella 2.5 device the Europella
       registry. J Am Coll Cardiol. 2009;54(25):2430-4.

(50)   Maini B, Naidu SS, Mulukutla S, Kleiman N, Schreiber T, Wohns D, et al. Real-world use
       of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary
       intervention: the USpella Registry. Catheter Cardiovasc Interv. 2012;80(5):717-25.

(51)   Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al.
       Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.
       Value Health. 2013;16(2):e1-5.

(52)   Perera D, Stables R, Clayton T, De Silva K, Lumley M, Clack L, et al. Long-term
       mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a
       randomized, controlled trial of elective balloon counterpulsation during high-risk
       percutaneous coronary intervention. Circulation. 2013;127(2):207-12.

(53)   Alasnag MA, Gardi DO, Elder M, Kannam H, Ali F, Petrina M, et al. Use of the Impella
       2.5 for prophylactic circulatory support during elective high-risk percutaneous coronary
       intervention. Cardiovasc Revasc Med. 2011;12(5):299-303.

(54)   Boudoulas KD, Pederzolli A, Saini U, Gumina RJ, Mazzaferri EL, Jr., Davis M, et al.
       Comparison of Impella and intra-aortic balloon pump in high-risk percutaneous coronary
       intervention: vascular complications and incidence of bleeding. Acute Card Care.
       2012;14(4):120-4.

(55)   Iliodromitis KE, Kahlert P, Plicht B, Hoffmann AC, Eggebrecht H, Erbel R, et al. High-risk
       PCI in acute coronary syndromes with Impella LP 2.5 device support. Int J Cardiol.
       2011;153(1):59-63.

(56)   Dangas GD, Kini AS, Sharma SK, Henriques JP, Claessen BE, Dixon SR, et al. Impact
       of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump on
       prognostically important clinical outcomes in patients undergoing high-risk percutaneous
       coronary intervention (from the PROTECT II randomized trial). Am J Cardiol.
       2014;113(2):222-8.

(57)   Roe MT, Li S, Thomas L, Wang TY, Alexander KP, Ohman EM, et al. Long-term
       outcomes after invasive management for older patients with non-ST-segment elevation
       myocardial infarction. Circ Cardiovasc Qual Outcomes. 2013;6(3):323-32.

(58)   Littnerova S, Kala P, Jarkovsky J, Kubkova L, Prymusova K, Kubena P, et al. GRACE
       score among six risk scoring systems (CADILLAC, PAMI, TIMI, Dynamic TIMI, Zwolle)
       demonstrated the best predictive value for prediction of long-term mortality in patients
       with ST-elevation myocardial infarction. PLoS One. 2015;10(4):e0123215.

(59)   Lakshminarayan K, Berger AK, Fuller CC, Jacobs DR, Jr., Anderson DC, Steffen LM, et
       al. Trends in 10-year survival of patients with stroke hospitalized between 1980 and
       2000: the Minnesota stroke survey. Stroke. 2014;45(9):2575-81.

(60)   Banach M, Bhatia V, Feller MA, Mujib M, Desai RV, Ahmed MI, et al. Relation of baseline systolic blood pressure and long-term outcomes in ambulatory patients with chronic mild to moderate heart failure. Am J Cardiol. 2011;107(8):1208-14.

(61)   Mittmann N, Trakas K, Risebrough N, Liu BA. Utility scores for chronic conditions in a community-dwelling population. Pharmacoeconomics. 1999;15(4):369-76.

(62)   Garg P, Cohen DJ, Gaziano T, Mauri L. Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents: results of a decision analytic model. J Am Coll Cardiol. 2008;51(19):1844-53.

(63)   Cohen DJ, Breall JA, Ho KK, Kuntz RE, Goldman L, Baim DS, et al. Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease. Use of a decision-analytic model. Circulation. 1994;89(4):1859-74.

(64)   Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KA, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). J Am Coll Cardiol. 2005;45(2):221-8.

(65)   Capomolla S, Febo O, Ceresa M, Caporotondi A, Guazzotti G, La Rovere M, et al. Cost/utility ratio in chronic heart failure: comparison between heart failure management program delivered by day-hospital and usual care. J Am Coll Cardiol. 2002;40(7):1259-66.

(66)   Samsa GP, Matchar DB, Goldstein L, Bonito A, Duncan PW, Lipscomb J, et al. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. Am Heart J. 1998;136(4 Pt 1):703-13.

(67)   Ministry of Health and Long Term Care. Schedule of benefits physician services [Internet]. Toronto (ON): The Ministry; 2015 [cited 2016 Jun 9]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/sob_master11 062015.pdf

(68)   Ontario Case Costing Initiative [Internet]. Toronto (ON): Ministry of Health and Long-Term Care. 2016 [cited 2016 Jun 9]. Available from: https://hsimi.ca/occp/occpreports/

(69)   Cardiac Care Network. About us [Internet]. Toronto (ON): The Network; 2016 [cited 2016 Jun 9]. Available from: http://www.ccn.on.ca/ccn_public/FormsAboutCCN/about.aspx

(70)   Singh SM, Micieli A, Wijeysundera HC. Economic evaluation of percutaneous left atrial appendage occlusion, dabigatran, and warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. Circulation. 2013;127(24):2414-23.

(71)   Wijeysundera HC, Tomlinson G, Ko DT, Dzavik V, Krahn MD. Medical therapy v. PCI in stable coronary artery disease: a cost-effectiveness analysis. Med Decis Making. 2013;33(7):891-905.

(72)   World Health Organization. Country-specific unit costs [Internet]. Geneva, Switzerland: The Organization; 2016 [cited 2016 Jun 9]. Available from: http://www.who.int/choice/country/country_specific/en/

(73)   Singh V, Patel SV, Savani C, Patel NJ, Patel N, Arora S, et al. Mechanical Circulatory Support Devices and Transcatheter Aortic Valve Implantation (from the National Inpatient Sample). Am J Cardiol. 2015;116(10):1574-80.

(74)   Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies. 3rd ed. Ottawa (ON): Agency; 2006.

(75)   Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol. 2009;53(1):13-20.

(76)   Witt BJ, Ballman KV, Brown RD, Jr., Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. Am J Med. 2006;119(4):354 e1-9.

(77)   Fokkema ML, van der Vleuten PA, Vlaar PJ, Svilaas T, Zijlstra F. Incidence, predictors, and outcome of reinfarction and stent thrombosis within one year after primary percutaneous coronary intervention for ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2009;73(5):627-34.

(78)   Drummond MF, Sculpher MJ, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes 3rd ed. Oxford, UK: Oxford University Press; 2005.

(79)   Dangas GD, Kini AS, Sharma SK, Henriques JPS, Claessen BE, Dixon SR, et al. Impact of hemodynamic support with impella 2.5 versus intra-aortic balloon pump on prognostically important clinical outcomes in patients undergoing high-risk percutaneous coronary intervention (from the PROTECT II randomized trial). Am J Cardiol. 2014;113(2):222-8.

About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

About the Ontario Health Technology Advisory Committee (OHTAC)

About OHTAS

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