High-risk percutaneous coronary intervention in patients with reduced left ventricular ejection fraction deemed not suitable for surgical revascularisation. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) in collaboration with the ESC Working Group on Cardiovascular Surgery

Andreas Schäfer[1], MD; Mirvat Alasnag[2], MD; Daniele Giacoppo[3-6], MD, MSc, PhD; Carlos Collet[7], MD, PhD; Tanja K. Rudolph[8], MD; Ariel Roguin[9], MD, PhD; Piotr P. Buszman[10], MD, PhD; Roisin Colleran[11], MB, BCh; Giulio Stefanini[12,13], MD, PhD; Thierry Lefèvre[14], MD; Nicolas Van Mieghem[15], MD, PhD; Guillaume Cayla[16], MD, PhD; Christoph Naber[17], MD; Andreas Baumbach[18,19], MD; Adam Witkowski[20], MD; Francesco Burzotta[21], MD, PhD; Davide Capodanno[22], MD, PhD; Dariusz Dudek[23], MD, PhD; Rasha Al-Lamee[24], MD; Adrian Banning[25], MD; Philip MacCarthy[26], MD; Roman Gottardi[27], MD; Florian S. Schoenhoff[28], MD; Martin Czerny[29,30], MD; Matthias Thielmann[31], MD; Nikos Werner[32], MD; Giuseppe Tarantini[4*], MD

A. Schäfer, M. Alasnag, N. Werner, and G. Tarantini contributed equally to the manuscript.

GUEST EDITOR: Franz-Josef Neumann, MD, PhD; *Department of Cardiology and Angiology, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany*

Corresponding author: Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Via Giustiniani 2, 35128, Padua, Italy. E-mail: giuseppe.tarantini.1@gmail.com

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ABSTRACT

This clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions was developed in association with the European Society of Cardiology Working Group on Cardiovascular Surgery. It aims to define procedural and contemporary technical requirements that may improve the efficacy and safety of percutaneous coronary intervention (PCI), both in the acute phase and at long-term follow-up, in a high-risk cohort of patients on optimal medical therapy when clinical and anatomical high-risk criteria are present that entail unacceptable surgical risks, precluding the feasibility of coronary artery bypass grafting (CABG). This document pertains to patients with surgical contraindication according to the Heart Team, in whom medical therapy has failed (e.g., residual symptoms), and for whom the Heart Team estimates that revascularisation may have a prognostic benefit (e.g., left main, last remaining vessel, multivessel disease with large areas of ischaemia); however, there is a lack of data regarding the size of this patient population. This document aims to guide interventional cardiologists on how to proceed with PCI in such high-risk patients with reduced left ventricular ejection fraction after the decision of the Heart Team is made that CABG – which overall is the guideline-recommended option for revascularisation in these patients – is not an option and that PCI may be beneficial for the patient. Importantly, when a high-risk PCI is planned, a multidisciplinary decision by interventional cardiologists, cardiac surgeons, anaesthetists and non-invasive physicians with expertise in heart failure management and intensive care should be agreed upon after careful consideration of the possible undesirable consequences of PCI, including futility, similar to the approach for structural interventions.

The incidences of complex coronary artery disease (CAD) and heart failure (HF) are growing in view of ageing populations and an increasing comorbidity burden[1]. Approximately 1-2% of hospitalisations in Europe and the United States are due to HF, and the treatment of patients suffering from CAD and reduced left ventricular ejection fraction (LVEF) represents a major clinical and public health challenge[2,3]. The European Society of Cardiology (ESC) 2018 guidelines on myocardial revascularisation recommend a coronary artery bypass graft (CABG) as the primary revascularisation strategy for patients with CAD and reduced LVEF. This recommendation is based on studies in a patient population with low or intermediate surgical risk and chronic coronary syndrome. In clinical practice, there are an increasing number of patients with depressed LVEF and high-risk features of CAD, including stabilised acute coronary syndromes (ACS), for whom the Heart Team votes against CABG due to high, or even prohibitive, surgical risk. Data from real-world practice indicate that percutaneous coronary intervention (PCI) is preferred over CABG in approximately 50% of patients due to high surgical risk or excessive frailty features[4-6]. In addition, an unknown number of patients decide against CABG due to a personal decision-making process after careful informed consent. Currently, given the absence of randomised controlled trials (RCTs), recommendations – weighing the efficacy and safety of PCI and CABG in the setting of left ventricular (LV) dysfunction in high-risk patients – are based on registries and secondary analyses of RCTs performed in the setting of stable CAD[4,7-9]. The results of these studies are prone to multiple confounders and selection bias, whereas reality leads to frequent performance of PCI in very high to prohibitive surgical risk patients, for whom medical management is believed not to be a viable option[5,10]. This clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) was developed in association with the European Society of Cardiology (ESC) Working Group on Cardiovascular Surgery; it aims to define procedural and contemporary technical requirements that may improve the efficacy and safety of PCI, both in the acute phase and at long-term follow-up, in this high-risk cohort of patients on optimal medical therapy (OMT) when clinical and anatomical high-risk criteria are present that entail unacceptable surgical risks, precluding the feasibility of CABG **(Figure 1)**.

This document pertains to patients in whom CABG, which is the overall guideline-recommended option for revascularisation in patients with complex CAD and reduced LVEF, is not an option according to the Heart Team, in whom medical therapy has failed (e.g., residual symptoms), and for whom the Heart Team estimates that revascularisation may have a prognostic benefit (e.g., left main, last remaining vessel, multivessel disease with large areas of ischaemia).

A multidisciplinary decision-making process by interventional cardiologists, cardiac surgeons, anaesthetists and non-invasive physicians with expertise in HF management and intensive care will be discussed within the consensus statement to evaluate the pros and cons of high-risk PCI. This is of high importance, since data are limited or non-existing on (1) any patient benefit from revascularisation, (2) patient benefit from additional mechanical circulatory support (MCS) during revascularisation, and (3) post-PCI care of this high-risk cohort.

We provide a consensus for an interdisciplinary, case-by-case decision-making process for patients with significantly impaired LVEF and complex CAD with high-risk features for whom the Heart Team has voted to carry out a high-risk PCI procedure due to risk of surgical futility (surgical turndown patients) or when the patient has decided against CABG **(Central illustration)**.
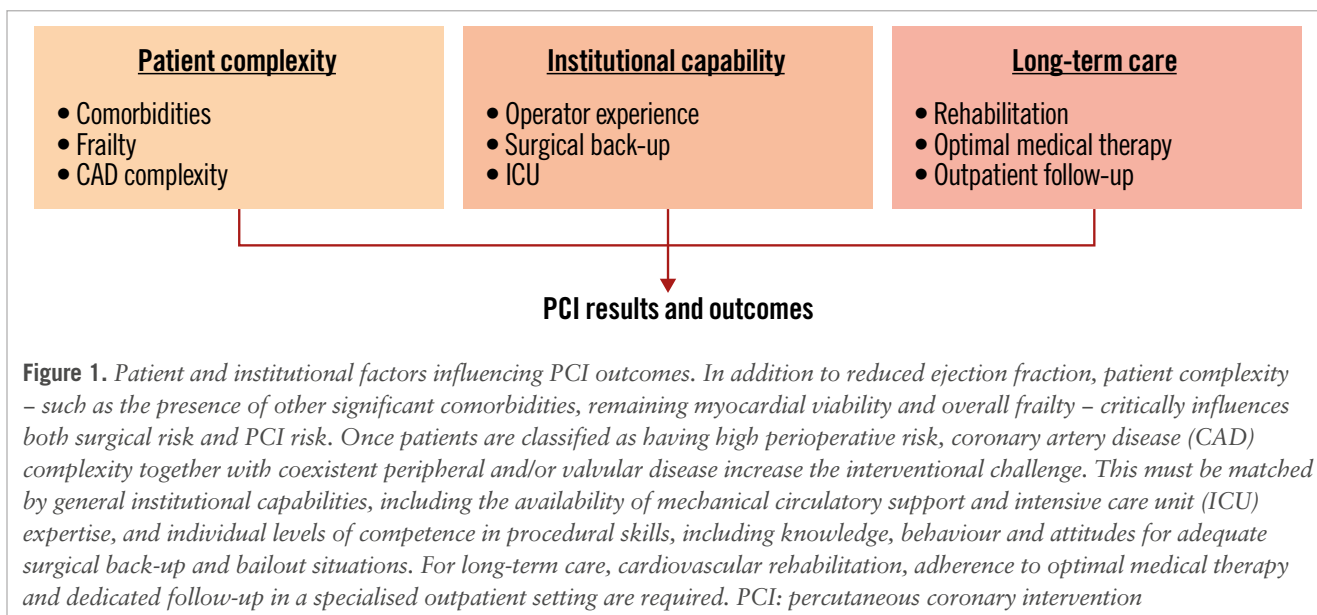
Revascularisation strategies in patients with severe LV dysfunction

Patients presenting with low LVEF and complex CAD potentially requiring revascularisation are discussed in the Heart Team with a comprehensive, multidisciplinary evaluation of risks and benefits including, but not limited to, anaesthesia, cross-clamping of the aorta, coronary artery disease pattern, concomitant valve disease or aortic dilatation, and degree of LV dysfunction[4,11]. Regarding the evidence for revascularisation from RCTs for this patient cohort, the extended observation, up to 10 years, of the Surgical Treatment for Ischemic Heart Failure (STICH) trial revealed that many patients with severely impaired LVEF can benefit from coronary revascularisation with CABG compared to OMT alone[9,12], thereby driving the guideline recommendations for CABG in this patient cohort[4].

Comparisons between PCI and CABG are primarily limited to analyses of RCTs enrolling patients suitable for both CABG and PCI, in which the average LV function was normal in the majority of patients[7,13-15]. The eligibility criteria of these available RCTs led to the exclusion of most patients with very complex clinical and anatomical conditions as well as patients who would not accept a surgical option. While this may have excluded patients with higher probability of benefits by CABG, it also excluded inoperable patients potentially amenable to PCI[15].

Abbreviations

CABG	coronary artery bypass graft	**IABP**	intra-aortic balloon pump
CAD	coronary artery disease	**LV**	left ventricular
CTO	chronic total occlusion	**LVEF**	left ventricular ejection fraction
EACTS	European Association for Cardio-Thoracic Surgery	**MCS**	mechanical circulatory support
EAPCI	European Association of Percutaneous Cardiovascular Interventions	**OMT**	optimal medical therapy
ESC	European Society of Cardiology	**PCI**	percutaneous coronary intervention
HF	heart failure	**RCT**	randomised controlled trial

Figure 1. *Patient and institutional factors influencing PCI outcomes. In addition to reduced ejection fraction, patient complexity – such as the presence of other significant comorbidities, remaining myocardial viability and overall frailty – critically influences both surgical risk and PCI risk. Once patients are classified as having high perioperative risk, coronary artery disease (CAD) complexity together with coexistent peripheral and/or valvular disease increase the interventional challenge. This must be matched by general institutional capabilities, including the availability of mechanical circulatory support and intensive care unit (ICU) expertise, and individual levels of competence in procedural skills, including knowledge, behaviour and attitudes for adequate surgical back-up and bailout situations. For long-term care, cardiovascular rehabilitation, adherence to optimal medical therapy and dedicated follow-up in a specialised outpatient setting are required. PCI: percutaneous coronary intervention*

Regarding the comparison between PCI and OMT, the recent REvascularisation for Ischemic VEntricular Dysfunction-BCIS2 (REVIVED-BCIS2) trial investigated whether PCI in combination with OMT reduces mortality and HF hospitalisation compared to OMT alone. Most of these patients did not have angina or severe HF symptoms (New York Heart Association Class I-II). As such, the population included in the REVIVED-BCIS2 trial may not be representative of patients with ischaemic symptoms and impaired LVEF requiring recurrent HF hospitalisations. A significant proportion of patients in the REVIVED-BCIS2 trial had intermediate-complexity coronary artery disease with only half of the patients having either 3-vessel or left main CAD. The trial was powered for 700 patients with an expected overall event rate of 43%. Over a median of 41 months, the trial did not provide evidence of benefit of PCI over OMT[16]. The overall event rate was lower than anticipated, and many HF events occurred in patients who died during the follow-up period[16]. To observe a clinically relevant improvement in LV function and HF events in otherwise asymptomatic patients, one would assume the presence of rather extensive CAD causing the compromised LV function. **Table 1** provides an overview of current data.

Observational studies have demonstrated the feasibility of PCI in patients with severe LV dysfunction with acceptable rates of in-hospital and long-term mortality[17-21]. In the absence of RCTs, registry data suggest that PCI using modern drug-eluting stents (DES) may be an acceptable alternative to CABG in patients with multivessel disease and impaired LVEF when complete revascularisation can be achieved[22]. However, observational data indicate a benefit of CABG over PCI in patients with impaired LVEF[23-25]. As such, a comprehensive assessment of patients is advocated, and reduced LVEF needs to be considered along with other major comorbid conditions.

CONSENSUS STATEMENT
OMT forms the foundation of all revascularisation strategies. In cases where patients meet the criteria observed in STICH patients, the Heart Team must reassess surgical strategies. For patients who have been declined surgical intervention and for those who refuse surgical options, PCI-based treatment strategies may present a viable alternative, despite the absence of randomised data.

Revascularisation based on the anatomical pattern of CAD
HF with reduced LVEF is associated with worse outcomes, both periprocedurally and long term, in patients treated with PCI[26]. However, robust prospective data with respect to the mode of revascularisation in patients with HF and reduced LVEF are still lacking[16,27,28].

Regarding coronary anatomy, a thoughtful evaluation between safety and efficacy is of paramount importance, especially in a high-risk population of patients with a higher propensity for complications. If intraprocedural vessel occlusion or flow-limiting dissection occurs in patients with an impaired LVEF, further severe haemodynamic deterioration can ensue, with the potential to rapidly lead to shock or arrest. Several angiographic scoring systems that validly estimate plaque burden and coronary anatomy complexity are available, but they do not account for the reduced LVEF[29]. The SYNTAX score II includes LVEF as a variable, but patients with significantly impaired LVEF were significantly underrepresented in the score development cohort, accounting for only 2%.

Therefore, rather than relying on these scores, the anatomical complexity of high-risk PCI can be more pragmatically described by patterns that are encountered in clinical practice. These include the last remaining vessel, chronic total occlusions (CTOs), left main disease, and diffuse 3-vessel CAD. Treatment of these high-risk patients should be limited to experienced operators with technical expertise and routine performance of such complex procedures. Similar cautioning applies to patients with severely depressed LVEF shortly after a myocardial infarction.

Multiple clinical studies and guidelines have addressed infrastructural and technical aspects of complex coronary

EuroIntervention — Central Illustration

Revascularisation in patients with complex CAD and reduced LVEF.

FIRST STEP
Initial evaluation

1. Assess patient quality of life and symptoms
2. Check for optimal medical therapy
3. Evaluation of CAD characteristics and complexity

If revascularisation is deemed possible and useful

SECOND STEP
Heart Team evaluation

1. Assess surgical risk
2. Evaluate site-specific preferences and expertise
3. Evaluate myocardial viability and patient's comorbidities

If CABG is not an option due to high surgical risk or patient refusal

THIRD STEP
Preprocedural planning

1. Risk stratification for high-risk PCI (*based on anatomy – left main disease, multivessel CAD, chronic total occlusions – and functional impact – severely reduced LVEF, risk of haemodynamic instability*)
2. **Evaluate the need for MCS based on high-risk factors**
3. Revascularisation strategy goal: complete or nearly complete revascularisation (*using advanced treatment strategies, such as intravascular imaging and advanced PCI techniques and devices*)

After discharge

FOURTH STEP
Follow-up

1. Guideline-directed optimal medical therapy
2. Long-term outpatient follow-up
3. Cardiac rehabilitation

CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention

interventions. This includes position statements on decision-making within the Heart Team for complex coronary anatomy[30], strategies on bifurcation intervention including left main PCI[31], the use of left ventricular assist devices in patients with an indication for complex PCI and reduced LVEF[32], the use of intravascular imaging[33,34], lesion preparation including rotational atherectomy[35], and strategies to deal with revascularisation failure[36]. In addition, a vast number of publications address treatment options in specific coronary anatomical challenges, e.g., ostial and long lesions, CTOs, calcified lesions, in-stent stenosis, bypass graft interventions and others, which are extensively reviewed and discussed in The PCR-EAPCI Textbook of Percutaneous Interventional Cardiovascular Medicine (www.pcronline.com/eurointervention/textbook/pcr-textbook/table-of-contents/).

Complex anatomy often necessitates intracoronary imaging guidance during PCI, but the additive information obtained by intravascular ultrasound and optical coherence tomography should be weighed against the increased ischaemic and procedural times and amount of contrast media. Nevertheless, in complex CAD, it reduces the risk of postprocedural cardiovascular events[37,38]. When intravascular imaging is not feasible or the expected information is not relevant, stenting optimisation can be adequately assessed by stent enhancement using subtraction imaging algorithms[39]. Fractional flow reserve or instantaneous wave-free ratio, in principle, are other options to confirm acute PCI success[40]; however, these measurements are affected by intra-aortic balloon pump (IABP) use and are not clearly validated on LV support[41-43]. It remains unclear whether either anatomical or physiological lesion selection is beneficial to guide PCI in patients with LV dysfunction or those on MCS devices.

CONSENSUS STATEMENT
State-of-the-art functional and imaging studies, along with advanced revascularisation techniques, are essential for complex PCI procedures. Intracoronary imaging has demonstrated its ability to enhance outcomes and is emerging as a necessary standard in high-risk, complex PCI procedures. In high-risk PCI, its use should be weighed against the increased ischaemic and procedural times and amount of contrast media.

Completeness of myocardial revascularisation

The strong relationship between the extent of ischaemia and clinical endpoints suggests that complete revascularisation is preferable in order to improve outcomes and quality of life. A residual SYNTAX score indicative of incomplete revascularisation portends a higher risk of mortality and major adverse cardiac events (MACE), irrespective of whether an anatomical or score-based definition of incomplete revascularisation is employed[44]. The degree of risk correlates with the degree of incomplete revascularisation. In 2018, the ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularisation stated that the ability to achieve complete revascularisation should be considered when choosing between revascularisation modalities[4]. This was re-emphasised in the 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes[11]. Nevertheless, since the decision on

Table 1. Characteristics of STICH and REVIVED-BCIS2 trials.

Parameter	STICH[12,13]	REVIVED-BCIS2[17]
Patients enrolled	610 (CABG)/602 (OMT)	347 (PCI)/353 (OMT)
Inclusion criteria	LVEF ≤35%, extensive CAD	LVEF ≤35%, extensive CAD, myocardial viability
Mean age, years	60/59	70/69
Mean LVEF, %	27/28	27/27
Mean BMI, kg/m^2	27/27	28/29
Diabetes	39/40	39/43
NYHA III-IV	37/37	23/29
Angina CCS III-IV	5/4	2/2
Previous MI	76/78	50/56
Previous PCI/CABG	17/14	22/28
Left main CAD	3/2	14/13
3-vessel CAD	62/59	38/42
Primary endpoint	All-cause death	Death or HF
Result	CABG: 218 (36) OMT: 244 (41) HR 0.86 (95% CI: 0.72-1.04)	PCI: 129 (37.2) OMT: 134 (38.0) HR 0.99 (95% CI: 0.78-1.27)
Secondary endpoint	Death or HF	All-cause death
Result	CABG: 290 (48) OMT: 324 (54) HR 0.84 (95% CI: 0.71-0.98)	PCI: 110 (31.7) OMT: 115 (32.6) HR 0.98 (95% CI: 0.75-1.27)
Median follow-up, months	56 (IQR 48-68)	41 (IQR 28-60)
Conclusions	There was no significant difference between medical therapy alone and medical therapy plus CABG with respect to all-cause death. Lower rates of death from cardiovascular causes and of death from any cause or hospitalisation for cardiovascular causes were noted in those undergoing CABG plus OMT.	PCI in addition to OMT in patients with severe LV dysfunction & coronary artery disease with viable myocardium did not significantly improve overall mortality or rates of heart failure hospitalisation. PCI with OMT was not superior to OMT alone in improving LV systolic function, NYHA Functional Class, or quality of life.
Limitations	Younger cohort with a mean age 60 years; effect of CABG on all-cause mortality diminished with increasing age (p-interaction=0.062).	Older population not revascularised by CABG, introducing selection bias early on in patients with few symptoms of angina or HF.

Data are given as % or n (%), unless stated otherwise. Baseline characteristics and outcome parameters of the Surgical Treatment for Ischemic Heart Failure (STICH)[12] and the Revascularisation for Ischaemic Ventricular Dysfunction-British Cardiovascular Intervention Society-2 (REVIVED-BCIS2)[16] trials. BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; CI: confidence interval; HF: heart failure; HR: hazard ratio; IQR: interquartile range; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; OMT: optimal medical therapy; PCI: percutaneous coronary intervention

revascularisation in ischaemic cardiomyopathy is complex (anatomical and/or functional incomplete/complete/extensive revascularisation), decision-making cannot be based solely on guidelines.

A few non-randomised studies have evaluated completeness of revascularisation in high-risk PCI patients treated with MCS devices. These registries have shown that the extent of revascularisation in symptomatic patients with complex coronary anatomies, often unsuitable for surgical treatment, demonstrates improvement in LVEF (in segments correlating with severity of revascularisation scores) and outcomes[18,20,45,46]. The European best practice consortium suggests that decision-making on revascularisation with MCS-facilitated PCI should be based on the capability to achieve complete and extensive revascularisation[47]. However, at present, the choice between the two types of intervention and the completeness of treatment is left to the clinician following an in-depth evaluation of patient comorbidities. Individualised therapy may include staged complete revascularisation supported by LV unloading.

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When undertaking revascularisation via PCI in critically ill patients with severe LV dysfunction and no surgical options, the procedure should strive for nearly complete revascularisation whenever feasible. Moreover, in situations where MCS is utilised to facilitate high-risk PCI, the stabilised haemodynamic environment should be leveraged to achieve as comprehensive a revascularisation as possible. This approach may enable the undertaking of more complex interventions, particularly in the left main or in patients with compromised LV function following recent myocardial infarction. In instances where the potential target lesion involves a CTO, a specialised CTO operator should have assessed the patient's angiogram beforehand and be readily available for that aspect of the procedure if warranted.

Extent of myocardial ischaemia and residual myocardial viability
The presence and extent of myocardial ischaemia has been strongly associated with poor patient prognosis and

adverse events, especially in patients with HF and reduced LVEF. Several studies have demonstrated that significant myocardial ischaemia, as detected by perfusion imaging tests, is associated with unfavourable clinical outcomes at long-term follow-up[48-50]. Furthermore, residual ischaemia after treatment has been similarly associated with long-term mortality[51]. Consistently, a more complete revascularisation by a surgical approach has been shown to improve survival in stable patients with ischaemic HF and reduced LVEF, compared with OMT alone[9].

A controversial point is the evaluation of residual myocardial viability and, most importantly, its impact on clinical outcomes. Viability testing in revascularisation trials, including examples such as STICH or COURAGE, was not a determinant of outcomes and hence limits the clinical importance of myocardial ischaemia assessment in influencing the decision-making for revascularisation. Of note, myocardial viability was a part of the protocol design in REVIVED-BCIS2, in order to unequivocally confirm a diagnosis of ischaemic cardiomyopathy. Previous registries have demonstrated favourable associations between myocardial viability, coronary revascularisation, and clinical outcomes[52-55]. On the contrary, a *post hoc* analysis of the randomised STICH trial failed to find an impact of viability on all-cause mortality, regardless of revascularisation. Of note, the vast majority of the patients had evidence of myocardial viability on single-photon emission computed tomography/echo-dobutamine tests only but not on other validated modalities, such as cardiac magnetic resonance. Notwithstanding, myocardial viability was associated with a significant improvement in LVEF. Interestingly, a trend towards a significant interaction between the presence of myocardial viability and the treatment arm was shown for long-term cardiovascular mortality, suggesting a possible beneficial role of revascularisation of viable myocardium. Accordingly, current ESC/EACTS guidelines on myocardial revascularisation support the assessment of myocardial viability in patients with CAD and HF before revascularisation[4]. The recently published REVIVED-BCIS2 trial did not show improvement in LV function in patients with low LVEF and CAD treated with PCI on top of OMT despite viable myocardium[16]. No data were provided on the anatomical location and extent of CAD nor the rate of appropriate complete revascularisation, as suggested before[56]. Patients with functional incomplete revascularisation had a significantly higher rate of MACE compared with those with functional complete revascularisation. A combined anatomical and physiological scoring system after PCI demonstrated a higher discriminatory value for risk prediction[57].

Currently, no subanalysis argues for a PCI strategy in patients with similar characteristics of the REVIVED-BCIS2 cohort. A strategy of initial OMT and postponing additional revascularisation therapies may help in the decision-making process.

The latest guidelines give a Class I recommendation for CABG in patients with an LVEF of 30% with multivessel disease and no diabetes[4]. Since severely reduced LV function remains a leading reason for surgical turndown, a first-line strategy of OMT seems appropriate, bringing the patient to a different risk class which may then argue for revascularisation.

The ongoing PROTECT IV Trial (ClinicalTrials.gov: NCT04763200; described in more detail below) will provide new evidence in this field with a prespecified analysis on the association between myocardial viability and post-revascularisation outcomes in high-risk PCI patients.

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Patients classified as having low to intermediate surgical risk with complex CAD are considered suitable candidates for CABG, irrespective of their LVEF, per current guideline recommendations. Conversely, patients with high to prohibitive risk with complex CAD derive benefits from OMT, regardless of their LVEF. However, there is a lack of randomised trial data providing guidance on revascularisation strategies for this patient cohort, particularly in cases of surgical turndown or high-risk patients declining CABG. For PCI, achieving functional complete revascularisation of all haemodynamically flow-limiting lesions, allowing for anatomically "incomplete" revascularisation of physiologically non-significant lesions and vessels, is the preferred approach, whereas anatomically complete revascularisation after CABG is the current standard of care[58]. It is anticipated that symptom improvement will occur in this group, although the debate on LVEF improvement persists, as demonstrated by REVIVED-BCIS2. In instances where LVEF improvement is observed, positive effects on outcomes may be expected. A clear correlation between myocardial ischaemia and coronary artery stenosis in large and prognostically relevant coronaries, preferably measured with fractional flow reserve, serves as a treatment indication.

Expected benefit balanced with procedural risk

High-risk PCI aims primarily to improve symptoms and quality of life in patients with advanced CAD and reduced LVEF, whether in chronic or acute coronary syndromes. The potential benefits in quality of life have to be balanced against procedural risks such as target vessel failure, vascular complications, bleeding, renal impairment due to higher contrast volume, and potential ischaemia-related haemodynamic instability during or after the procedure.

If the Heart Team decides to use MCS to prevent haemodynamic instability, the increased risks of vascular complications and bleeding associated with MCS have to be weighed against the potential benefit of more successful and/or more complete revascularisation. This balance is crucial when discussing the use of MCS in high-risk PCI patients. Even in cardiogenic shock, this issue remains unresolved: MCS use is linked to more complications and, in some analyses, higher mortality rates, though these patients were generally sicker[59]. The Heart Team needs to evaluate whether the potential revascularisation benefit justifies the use of large-bore access to stabilise the patient for procedural success. Lessons learned from MCS use in shock indicate that improved outcomes can be achieved despite bleeding and vascular complications[60], highlighting the importance of thorough preprocedural planning. This includes selecting the appropriate MCS device and optimising vascular access,

similar to structural interventions, where complications have been reduced over time.

The following section covers the available data and provides the consensus. For detailed guidance on planning and procedure to minimise risk and improve success, please refer to **Supplementary Appendix 1-Supplementary Appendix 3**.

MCS in high-risk PCI

The use of MCS devices is an option in high-risk PCI patients with severely depressed LV function but should not be assumed as the default treatment strategy. There are three categories of MCS: IABP, microaxial flow pumps, and venoarterial extracorporeal membrane oxygenation (VA-ECMO)[61,62]. While traditionally used in patients with cardiogenic shock[60,63,64], their use in high-risk PCI has increased, particularly in elderly patients with multiple comorbidities[65,66]. However, there are limited supportive outcome data, compared to OMT alone, and no clear evidence on the superiority of one device over another or their cost-effectiveness in high-risk PCI[67-70].

Regarding RCTs in this field, two larger studies have been conducted but have provided limited supportive data:
1. Balloon Pump Assisted Coronary Intervention Study (BCIS-1) investigated elective IABP support in patients with LVEF <30% and severe CAD. The trial did not show a reduction in composite endpoints (death, acute myocardial infarction, cerebrovascular event, or revascularisation) at discharge, suggesting no benefit for routine IABP placement before PCI in severe LV dysfunction[71,72]. However, an extended assessment indicated a 33% reduction in all-cause mortality with IABP support during high-risk PCI, though this trial was not designed to address mortality outcomes specifically[73].
2. PROTECT II Trial evaluated the Impella 2.5 (Abiomed) in high-risk PCI patients with impaired LVEF ≤35% and severe CAD. The trial was halted early due to assumed futility, and the primary endpoint (composite of all-cause death, myocardial infarction, stroke or transient ischaemic attack, any repeat revascularisation by PCI or CABG, need for a cardiac or vascular operation, acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency and angiographic failure of PCI) was not significantly reduced[19]. Although exploratory analyses suggested symptom reduction and improved LVEF at 90 days, there was no significant reduction in the composite endpoint (death, myocardial infarction, stroke). Real-world data indicate a sicker patient cohort undergoing PCI with microaxial flow pump support compared to the trial population[21,74].

Current use and future research

Despite a lack of prospective data showing clinical improvement, the prophylactic use of MCS, especially microaxial flow pumps, has increased. The ongoing PROTECT IV Trial aims to determine if PCI with a microaxial flow pump is superior to PCI without it in reducing composite rates of adverse outcomes at 3-year follow-up in high-risk patients with complex CAD and reduced LVEF ≤40%.

In summary, the interventional community faces neutral or inconclusive trial results, yet MCS devices, particularly

microaxial flow pumps, continue to be used broadly in complex PCI procedures[75]. While some experts question their cost-effectiveness, others favour their use due to anticipated haemodynamic benefits during complex PCI. The existing lack of definitive evidence underscores the need for further trials, although conducting such trials is challenging because of the perceived high risk in standard-care groups.

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The pathophysiological effects of MCS devices can bring safety to the procedure and reduce the consequences of complications during complex PCI. However, severe complications, particularly related to access site, may impact outcomes, and recent studies have not clearly established a morbidity or mortality benefit. Until the randomised PROTECT IV study is published, careful patient selection, personal preference, and active prevention and surveillance of vascular complications are essential for safe MCS device use.

Therefore, MCS should not be used as the default strategy for high-risk PCI in patients with severely depressed LVEF. The potential benefit of haemodynamic stability must be weighed against the risks of bleeding, vascular complications and increased contrast exposure. The selected MCS device should represent the least invasive yet haemodynamically adequate device. Retrospective analyses suggest that VA-ECMO is extremely invasive, while IABP may not provide sufficient haemodynamic stability in some cases, making microaxial pumps a suitable choice in most situations. MCS devices should be used for the shortest time necessary. For most patients, the duration is purely periprocedural, with explantation and access closure performed in the cath lab. However, in some cases, extended MCS use for several hours post-procedure will be required, necessitating intensive care unit capabilities familiar with managing MCS patients.

Postprocedural management
ANTITHROMBOTIC THERAPY
Periprocedural intravenous anticoagulation and antiplatelet therapy should, in general, follow the current ESC/EACTS guidelines[4]. While PCI is possible in patients on oral anticoagulants in principle, in high-risk PCI, an interruption of these is commonly required based on the individual risk, use of large-bore access, and intensive intravenous anticoagulation during PCI[76]. Dual antiplatelet therapy is loaded before elective stenting[4] and, after high-risk PCI, is prescribed for the usually recommended duration[77]. Patients with substantial individual ischaemic risk, particularly after extensive stent implantation, may benefit from more intense and/or prolonged antithrombotic strategies[11].

OPTIMAL MEDICAL THERAPY
Optimal medical therapy of CAD is important for symptom control and prevention of associated events[11]. This comprises antianginal medications, if indicated, and secondary prevention pharmacotherapy in accordance with clinical practice guidelines[11,78]. Medication adherence is paramount to ensure maximal efficacy. HF therapy should be optimised according to guideline recommendations, ideally in consultation with an HF specialist[79]. The aim is to reduce mortality; improve clinical status, functional capacity and quality of life; and prevent

hospitalisation[79]. Unless contraindicated or not tolerated, the use of inhibitors of the renin-angiotensin-aldosterone system, beta blockers, mineralocorticoid-receptor antagonists and sodium glucose transporter 2-inhibitors are indicated in all patients with HF and reduced LVEF, with additional pharmacological and/or implantable device therapies when indicated[79]. Since medical therapy is continuously developing, not all drugs considered to be part of optimal medical therapy today were used in the revascularisation and device trials mentioned before.

Follow-up and heart failure specialist consultation

OMT and lifestyle modification, with smoking cessation and dietary adaptations, are paramount for risk reduction and prevention of future cardiovascular events[78]. HF is the most common reason for hospital readmission after PCI[46,80]. Cardiac rehabilitation is recommended by current ESC guidelines for all patients after PCI for acute infarction[4]. However, patients with reduced LVEF deemed ineligible for surgery who have undergone high-risk PCI are more likely to present with coexisting conditions, such as severe lung disease, liver dysfunction, chronic kidney disease, peripheral vascular disease, and cerebrovascular disease. In these circumstances, rehabilitation may need to be realistically adapted to meet individual needs[5]. Careful discharge planning is essential, with planned early review. Despite a successful procedure, impaired LVEF is likely to persist in this high-risk patient group and HF therapy should be adapted[79]. Long-term follow-up requires cardiac services with referral to specialist teams, such as HF services and cardiac device specialists.

Training and protocols

To optimise patient care, multidisciplinary and interprofessional institutional protocols for patients with reduced LVEF undergoing invasive cardiac procedures and/or requiring MCS support should be established, as has been described for cardiogenic shock in the acute setting[81-83]. Similar to the 2020 EAPCI Core Curriculum for Percutaneous Cardiovascular Interventions, we suggest a defined minimum qualification for operators performing high-risk PCI with or without MCS support, which requires a higher level of competence in several techniques. Operators should be experienced in techniques such as radial access in general; femoral access with devices ≥10 Fr; rescue pericardiocentesis; right and left haemodynamic assessment; PCI in all cases of ACS including multivessel disease, bypass grafts, bifurcation lesions and left main disease; lesion preparation including rotational, laser and orbital atherectomy, as well as shockwave lithotripsy; invasive physiology and intracoronary imaging; strategies to manage revascularisation failure or complications; and, in particular, the use of percutaneous MCS devices[84].

Gaps in knowledge

The proportion of high-risk procedures in elderly populations with complex disease, reduced LVEF causing HF, and comorbidities precluding surgical revascularisation is steadily growing. The prognostic impact of high-risk PCI in this setting of patients still warrants high-quality data. Generally, the evidence on MCS devices for elective procedures in patients with impaired LV function is controversial, with underpowered trials assessing a wide spectrum of patients[19]. While registries support the idea of MCS support in certain disease constellations[20,46,85], it still remains unknown whether interventional, surgical or medical treatment is the best modality. In case of circulatory support, it remains unclear whether the different types of MCS used in HF patients with high surgical risk are equivalent in terms of cardioprotection or do themselves impose negative effects. Last but not least, we do not know whether extensive revascularisation improves outcomes regarding mortality or quality of life in these patients. Based on this lack of prospective data, current ESC guidelines on myocardial revascularisation and heart failure do not provide any recommendations regarding the use of MCS when discussing revascularisation in heart failure patients[4,79].

Conclusions

High-risk PCI in patients with reduced LVEF deemed unsuitable for surgical revascularisation is growing. Percutaneous options often entail complex revascularisation strategies requiring plaque debulking, multistent procedures, and circulatory support during extended revascularisation procedures. It is critical for an early Heart Team discussion to take place during risk stratification and management planning that extends beyond the PCI and includes optimising guideline-directed medical therapy and treating concomitant valvular heart disease. As such, establishing a more comprehensive treatment plan – assessing individual risk, identifying viable myocardium, offering complete revascularisation, determining the need for circulatory support and providing cardiac rehabilitation – is necessary for these patients **(Table 2, Figure 2)**. Discussion by two experienced operators suggesting alternative treatment options might be helpful early in the patient assessment.
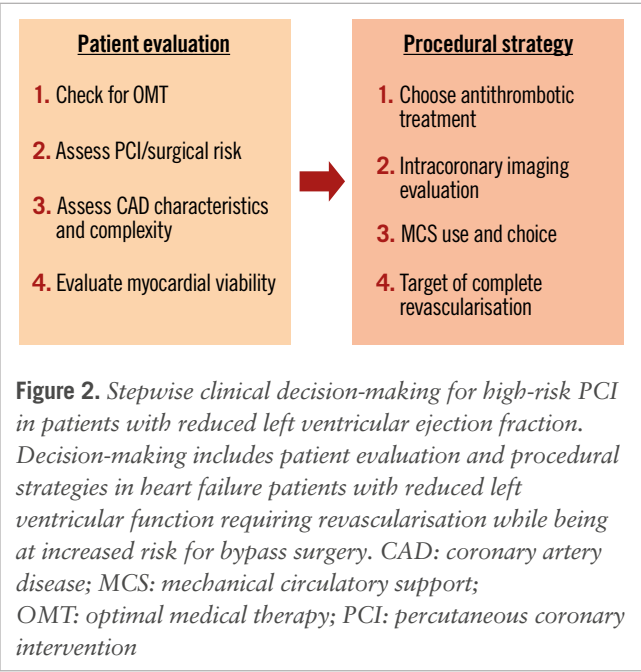
Randomised trials have often excluded these patients, making real-world registries important in capturing short-term outcomes. In the future, developing predictive risk scores will permit a more tailored and individualised patient-centred approach.

Authors' affiliations

1. Cardiac Arrest Center, Department of Cardiology and Angiology, Hannover Medical School, Hanover, Germany; 2. Cardiac Center, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia; 3. Department of Cardiology, Alto Vicentino Hospital, Santorso, Italy; 4. Department of Cardiac-Thoracic-Vascular Sciences, University of Padua, Padua, Italy; 5. Cardiovascular Research Institute Dublin, Royal College of Surgeons in Ireland, Dublin, Ireland; 6. ISA Research, German Heart Center, Munich, Germany; 7. Department of Cardiology, Cardiovascular Center Aalst, Aalst, Belgium; 8. Department of Cardiology, Heart and Diabetes Center NRW, Ruhr-University, Bad Oeynhausen, Germany; 9. Department of Cardiology, Hillel Yaffe Medical Center, Hadera, Israel; 10. Department of Cardiology, Andrzej Frycz Modrzewski Kraków University, Krakow, Poland and Center for Cardiology and Cardiac Surgery of American Heart of Poland, Bielsko-Biała, Poland; 11. Department of Cardiology, Mater Private Hospital, Dublin, Ireland; 12. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy; 13. IRCCS Humanitas Research Hospital,

Table 2. Appropriate approach to the patient and consensus on the management plan.

Logistics prior to high-risk PCI in patients with severely compromised LV function not suitable for surgery
Obtain proper patient consent after ensuring that the patient is fully informed about the substantial risk and probable benefit of the procedure
Offer a second opinion
Preload the patient with acetylsalicylic acid and a P2Y$_{12}$ inhibitor prior to PCI
Assess kidney function and hydrate as much as possible
Assess access site with ultrasound
Assess the potential need for MCS and, if necessary, decide on timing (upfront or as bailout) and type of MCS (IABP, ECMO or microaxial flow pump)
Ensure availability of ICU bed in case of need for postprocedural circulatory support
Formally assess bleeding and ischaemic risks
Provide a stepwise plan for the intervention including bailout procedures

Logistics to be resolved prior to high-risk PCI in patients with severely compromised LV function who are not suitable for surgery. ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; LV: left ventricular; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention

Figure 2. *Stepwise clinical decision-making for high-risk PCI in patients with reduced left ventricular ejection fraction. Decision-making includes patient evaluation and procedural strategies in heart failure patients with reduced left ventricular function requiring revascularisation while being at increased risk for bypass surgery. CAD: coronary artery disease; MCS: mechanical circulatory support; OMT: optimal medical therapy; PCI: percutaneous coronary intervention*

Rozzano, Italy; 14. Hôpital privé Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France; 15. Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 16. Department of Cardiology, University Hospital Nîmes, University of Montpellier, Nîmes, France; 17. Department of Cardiology and Internal Intensive Care, Wilhelmshaven Hospital, Wilhelmshaven, Germany; 18. Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom; 19. Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom; 20. Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warsaw, Poland; 21. Department of Cardiovascular Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 22. Division of Cardiology, AOU Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy; 23. Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland; 24. Imperial College London, Imperial College Healthcare NHS Trust, London, United Kingdom; 25. Department of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom; 26. King's College Hospital, London, United Kingdom; 27. Department of Cardiovascular Surgery, Heart Center Lahr, Lahr, Germany; 28. Department of Cardiac Surgery, University Hospital Bern, Bern, Switzerland; 29. Department of Cardiovascular Surgery, University Heart Center Freiburg – Bad Krozingen, Bad Krozingen, Germany; 30. Faculty of Medicine, Albert Ludwig University Freiburg, Freiburg, Germany; 31. Department of Thoracic and Cardiovascular Surgery, West-German Heart & Vascular Center Essen at University Duisburg-Essen, Essen, Germany; 32. Department of Cardiology, Heart Center Trier, Krankenhaus der Barmherzigen Brüder, Trier, Germany

Guest Editor

Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. Periprocedural aspects on the use of MCS in high-risk PCI.
Supplementary Appendix 2. MCS periprocedural aspects.
Supplementary Appendix 3. Postprocedural management.

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Supplementary data

Supplementary Appendix 1. Periprocedural aspects on the use of MCS in high-risk PCI.

High-risk PCI aims primarily to improve symptoms and quality of life in patients with advanced CAD and reduced LVEF in the context of either chronic or acute coronary syndromes. Therefore, the potential benefit in quality of life has to balance with the potential procedural risk including target vessel failure, vascular complications, bleeding, renal impairment due to higher contrast volume, and potential ischaemia-related haemodynamic instability during or after the procedure.

When -during the planning phase for the procedure- it is decided to perform PCI facilitated by the use of MCS in order to prevent hemodynamic instability, the increased risk for vascular complications and bleeding owing to MCS has to be counterbalanced with the potential benefit assumed of more successful and/or more complete revascularisation prior to the procedure when the Heart Team decides about the case. Balancing potential outcome benefits to increased rates of vascular complications and bleeding is the crucial point when discussing the use of MCS in patients undergoing high-risk PCI. Even in the context of cardiogenic shock, this issue is still unresolved: the use of MCS devices is associated with more complications, in some recent analyses mortality was even higher, but patients on MCS were sicker[59]. Therefore, the Heart Team needs to decide whether the potential benefit in revascularisation is so large that it justifies potential large bore access, if required to stabilise the patient for safe procedural success. The lessons learned from MCS use in shock potentially improving outcome despite bleeding and vascular complications[60] underline the importance of adequate pre-procedural planning including selection from the different devices for MCS support and optimised vascular access like in structural interventions, where complications have been dramatically reduced over time by such an approach. The following section of this manuscript is intended to provide step-by-step guidance through the planning process in order to minimize risk exposure and improve procedural success.

Supplementary Appendix 2. MCS periprocedural aspects.

The use of MCS devices is an option in high-risk PCI patients with severely depressed LV function but should not be taken for granted when discussing treatment strategies. Currently three categories of MCS are available: IABP, microaxial flow pumps, and va-ECMO[61,62]. IABP requires forward blood-flow and an LV capable of increasing stroke volume upon minor afterload reduction along with increased coronary perfusion. Its efficacy is limited by tachycardia and arrhythmia, and IABP is inefficient in circulatory arrest, when it occurs during high-risk PCI. Microaxial flow pumps require sufficient LV filling to avoid suction, and have limitations when LV preload is decreased or LV cavity size is small (e.g. due to hypertrophy, septum shift or compression). va-ECMO requires sufficient venous filling and volume return to avoid suction, and increases LV afterload. Both microaxial flow pumps and va-ECMO can provide sufficient support in cases of transient loss of pulsatility during high-risk PCI[81], however, extracorporeal devices such as Tandem Heart and va-ECMO are mostly reserved for cardiogenic shock.

MCS devices have conventionally been used in the setting of cardiogenic shock[60,63,64]. However, over the course of the last decade, there has been increased uptake for PCI in high-risk elderly populations with multiple comorbidities[65,66]. Despite the expanding use of MCS, there is paucity of supportive outcomes data compared to OMT alone, comparative data determining superiority of one device over the other, or the cost efficiency of such devices particularly in the setting of high-risk PCI[67-70]. Each device is unique in terms of profile, level of support and potential complications[86]. Such factors influence device selection in addition to availability, expertise and cost. Commonly used devices for high-risk PCI include IABP and microaxial systems.

In patients with severe LVEF reduction, MCS can provide haemodynamic stability in procedural settings that would otherwise rapidly lead to haemodynamic deterioration in those patients such as the treatment of the left main and major bifurcations, atherectomy techniques employment, and coronary artery stenting optimisation by using intracoronary imaging, in particular when PCI in severely reduced LVEF is performed on the last patent vessel or in patients with already critically elevated left-ventricular end-diastolic pressure[87]. Whether proper conductance of these interventions under MCS in patients with severe LVEF reduction translates into clinical benefit, however, has not yet been sufficiently demonstrated.

The first trial investigating a potential benefit of MCS was the Balloon Pump–Assisted Coronary Intervention Study (BCIS)-1 trial investigating whether elective IABP support in 301 patients with LVEF <30% and severe CAD (defined by a BCIS-1 jeopardy score ≥8)

undergoing PCI reduces the composite endpoint of death, acute myocardial infarction, cerebrovascular event, or further revascularisation at hospital discharge (within 28 days). Elective IABP insertion did not reduce this endpoint, thereby not supporting a strategy of routine IABP placement before PCI in patients with severe LV dysfunction[71]. While the primary study design included an exploratory 6-months mortality analysis[72], which showed no significant effect, an extended assessment indicated that all-cause mortality was significantly reduced by 33% in patients supported with IABP during high-risk PCI. However, the trial was not prospectively designed to address all-cause mortality[73]. Nevertheless, the trial's mortality data generated the hypothesis of a potential long-term benefit of circulatory support in high-risk PCI procedures.

The trial that was meant to investigate a potential benefit of Impella® 2.5 in patients with impaired LV function was the PROTECT II trial. The PROTECT II study investigated non-emergent PCI in high-risk adult patients (defined by LVEF ≤35% undergoing PCI on an unprotected left main or last patent coronary vessel, or LVEF ≤30% undergoing multivessel PCI in patients with 3-vessel disease). The trial had been designed and powered for 654 patients, but the data safety monitoring board stopped the trial prematurely because of futility when only 448 patients had been randomised. The primary end-point (composite of all-cause death, myocardial infarction, stroke or transient ischaemic attack, any repeat revascularisation by PCI or CABG, need for a cardiac or vascular operation, acute renal insufficiency, severe intra-procedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency and angiographic failure of PCI) at 30 days was not significantly reduced. Therefore, the trial did not provide evidence for routine use of microaxial flow pumps in high-risk PCI in patients with impaired LVEF. An exploratory per-protocol analysis suggested that at 90 days use of microaxial flow pumps was associated with a reduction of symptoms and improved LVEF, however, there was no indication that a hard composite end-point consisting of death, myocardial infarction and stroke was significantly reduced[19]. The incidence of acute kidney injury in those undergoing microaxial flow pump-supported high-risk PCI was lowered[88]. Real-life data, e.g. from Europe, indicate a quite different and much sicker patient cohort undergoing high-risk PCI on microaxial flow pump support compared to those initially investigated in the Protect-II trial[21,74].

In summary, the interventional community is confronted with an overall neutral randomised-controlled and prematurely halted trial that showed no benefit of microaxial flow pump-

assisted PCI, but based on selective post-hoc analyses generated the hypothesis of potential functional improvement and reduced demand for repeat revascularisations in high-risk patients with protected-PCI[19]. Despite the lack of prospective data showing improvement, in real life the prophylactic use of MCS in patients partly not even fitting the BCIS-1 or PROTECT II studies inclusion criteria increased over time[75]. The ongoing PROTECT-IV trial investigates whether PCI with a microaxial flow pump is superior to PCI without it in reducing the composite rate of all-cause death, stroke, durable LVAD implant or heart transplant, myocardial infarction or hospitalisation for cardiovascular causes at 3-year follow-up in high-risk patients with complex CAD and reduced LVEF. The trial will randomize 1252 patients to Impella® CP or 2.5 compared to standard treatment with or without IABP. Patients must have impaired LVEF ≤40% when undergoing complex PCI including complex multi-vessel, last-vessel or left-main disease. The still existing lack of evidence raises a quest for new trials in the field, but conducting them is made difficult by the perceived high risk in the standard care group in case of elective procedures. Despite the fact that clinical data concerning MCS devices did not show an advantage in terms of clinical endpoints, MCS devices and especially microaxial flow pumps are broadly used during complex PCI procedures. While some experts call a microaxial flow pump the most expensive device, which is not supported by evidence from RCTs, others favour its use due to the anticipated positive effects on haemodynamics during complex PCI.

Planning of high-risk PCI procedures gets more complicated and challenging once there is accompanying severe aortic stenosis also requiring an intervention (e.g. TAVR). At present, a combined approach including both CAD and valvular disease treatment may be reasonable in patients with impaired LVEF, particularly in the presence of proximal and/or severely symptomatic CAD. Complexity is added by these accompanying disease as those patients are less tolerant to haemodynamic compromise but also provide limitations in case of considered MCS use. Anecdotal reports have described MCS use as a technically feasible option to reduce procedural and peri-procedural haemodynamic instability[89]. The use of an MCS is possible in the presence of aortic stenosis, but may require balloon aortic valvuloplasty in case of a microaxial flow pump or delicate programming in case of va-ECMO, which further increases procedural complexity[90,91]. With borderline CAD and concomitant valvular heart disease, invasive functional tests may be helpful to clarify relevance of CAD, although a standardised approach in this setting has not been established yet[92].

Vascular complications and bleeding are the major downsides of routine MCS use. Computed tomography or invasive angiography identifies whether vasculature diameters and paths are

sufficient for placement, while ultrasound alone can reduce the risk of bleeding and visualise the optimal point of anterior puncture, but may be insufficient for a complete assessment of the vasculature[93].

While va-ECMO requires extensive vascular access including large-bore venous, large-bore arterial and eventually antegrade arterial perfusion in addition to the usual sheath for PCI, microaxial flow pumps allow single-access insertion of a guiding catheter through the MCS sheath[94]. Vessel diameters >5 mm are suitable for support[95]. Technical aspects should be tailored according to the case-specific clinical presentation and, alternative access sites availability (e.g., subclavian, axillary, etc.)[95,96]. Pre-closure with a suture device limits vascular complications and a 4F sheath dilator can be safely introduced via the remaining wire for micro-angiography to exclude vascular access complications. Pre-closure devices are highly effective and large experience has accrued. Large bore post-closure devices are emerging technical options that have generally shown initial favourable results[97], but a recent RCT in patients with transcatheter aortic valve replacement showed a higher rate of access-related vascular complications with post- compared to pre-procedural devices[98]. We highly discourage to routinely use manual compression to achieve haemostasis after sheath removal for large-bore access sites.

Systematic assessment for peripheral artery disease is advisable before elective high-risk PCI as placement of long-sheaths able to cross diseased vessel segments and/or arterial lumen preparation by plain balloon and/or intravascular lithotripsy may be required[99-102]. When feasible, percutaneous insertion and early sheath removal should be pursued. Systematic post-PCI arterial angiography helps to rapidly recognise and manage vascular complications, especially in case of large bore access.

Consensus statement:

The pathophysiological effects of MCS devices are capable of bringing safety to the procedure. However, severe complications especially associated with access site may influence outcomes, and a morbidity and mortality benefit has not been clearly established by recent studies. Until the randomised PROTECT IV study will have been published, personal preference, careful patient selection, and active prevention and surveillance of vascular complications is needed to ensure a safe procedure using MCS devices.

Supplementary Appendix 3. Postprocedural management.

MCS-devices

In case of high-risk PCI, MCS intended to provide haemodynamic stability during the procedure is usually only required peri-interventional and, therefore, mainly limited to the catheterisation laboratory. However, haemodynamic instability may persist in patients with severely impaired LVEF and it is sometimes necessary to transfer patients on MCS to an Intensive Care Unit (ICU). It is advisable that non-interventional physicians and nurses on ICU are trained in the management of MCS-supported patients. ICU staff has to ensure proper positioning of the MCS system and optimise device settings for haemodynamic support and weaning[81,103].

Handling of MCS in the ICU requires certain standards of operation. Anticoagulation to avoid clotting during device function and dual anti-platelet therapy following extensive or complex PCI procedures are required. However, this unavoidably increases the risk of bleeding. In case of microaxial flow pumps, local sutures around the access channel are helpful to reduce bleeding alongside the channel[70]. Ipsilateral extremity perfusion remains an often disregarded issue and selective lower limb perfusion is preferred in all cases where MCS is needed beyond the index procedure and limits antegrade perfusion. While this is often considered as mandatory in case of va-ECMO due to almost complete occlusion of the femoral artery by the arterial ECMO cannula, this is not so obvious in case of femoral microaxial flow pumps. If a 14F device is inserted and used along the 9F replacement sheath, the smaller diameter may allow for adequate and sustained lower leg perfusion in most cases. Nevertheless, once a microaxial flow pump remains in place for longer durations than the original PCI procedure, adequate antegrade leg perfusion needs to be monitored. Commonly used approaches are Doppler-ultrasound measurements or near-infrared spectroscopy to monitor distal oxygen supply.

Peri-procedural intravenous anticoagulation and antiplatelet therapy should follow the current ESC/EACTS guidelines in general[4]. While PCI is possible in patients on oral anticoagulants in principle, although an interruption in high-risk PCI is commonly required based on the individual risk, use of large-bore access, and intensive intravenous anticoagulation when using MCS[76]. High-risk PCI on MCS requires sufficient anticoagulation with an activated clotting time >160 seconds[81].