Review of current evidence and assessment of potential implications for future clinical practice

PCI in the management of chronic coronary syndromes after the ISCHEMIA Study

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Summary

The role of percutaneous coronary intervention (PCI) in the management of chronic coronary syndromes (CCS) has long been a subject of debate. Numerous clinical trials have demonstrated limited benefit from revascularisation on hard clinical endpoints among patients with CCS. The latest of these studies, the International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA) trial, found no significant reduction in mortality or myocardial infarction from revascularisation in patients with CCS when compared with optimal medical therapy (OMT) alone. At face value, these results suggest that patients with significant ischaemia on stress testing no longer need to be rushed to the catheterisation laboratory. Instead, the focus should be on the instigation of guideline-recommended OMT, with PCI reserved for patients who remain symptomatic despite OMT. This article provides a review of the current evidence, including the findings of the ISCHEMIA trial, and assesses the potential implications for future clinical practice.

Introduction

The role of percutaneous coronary intervention (PCI) in the management of chronic coronary syndromes (CCS) has long been a subject of debate. Unlike acute coronary syndromes (ACS), where the benefits of invasive management have been clearly demonstrated, clinical trials have demonstrated limited benefit from revascularisation on hard clinical endpoints among patients with CCS. The latest of these studies, the International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA) trial [1], has reignited the debate on the role of PCI in management of CCS. This article provides a review of the current evidence, including the findings of the ISCHEMIA trial, and assesses the potential implications for future clinical practice.

Current trial evidence

The 2007 COURAGE trial was the first large-scale study to address the role of PCI in the management of CCS in the era of widespread intracoronary stenting. It randomised patients with CCS (defined as at least one proximal stenosis of ≥70% with objective evidence of myocardial ischaemia, or at least one stenosis of ≥80% with angina) to PCI with bare-metal stents plus optimal medical treatment (OMT) or OMT alone [2]. At a median follow-up of 4.6 years, the study found no reduction in the risk of death from any cause and nonfatal myocardial infarction (MI). A subsequent analysis of a subgroup of the original study population with extended follow-up (median 6.1 years) confirmed the absence of any reduction in mortality with PCI over OMT alone [3].

The subsequent BARI-2D trial that randomised patients with both type 2 diabetes and CCS to either revascularisation with OMT or OMT alone reported similar results. At 5 years, there was no significant reduction in all-cause mortality or major adverse cardiovascular events among patients undergoing PCI [4].

The results of COURAGE and BARI-2D raised significant questions over the value of PCI in the management of CCS. However, the use of primarily bare-metal stents in these studies led to concerns over their applicability to current clinical practice with the rapidly developing drug-eluting stent market. To this end, in 2014, Windecker et al. performed a meta-analysis of 100 trials comparing revascularisation, including newer drug-eluting stents, with OMT [5]. The results suggested that new generation drug-eluting stents were associated with reduced all-cause mortality (everolimus: hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.59–0.96; zotarolimus: HR 0.65, 95% CI 0.42–1.00) compared with OMT, a result not seen with balloon angioplasty (HR 0.85, 95% CI 0.68–1.04) or bare-metal stents (HR 0.92, 95% CI 0.79–1.05). However, this study was limited by its reliance on indirect comparisons between newer drug-eluting stents and OMT.

In the FAME (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) 2 trial, patients with CCS and at least one stenosis with an fractional flow reserve (FFR) ≤0.80 were randomised

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to either FFR-guided PCI (stenting of all lesions with FFR ≤0.80) plus OMT or OMT alone [6, 7]. At both two- and five-year follow-up, FFR-guided PCI was associated with a reduction in the composite endpoint of death, MI and urgent revascularisation (defined as unplanned hospitalisation that led to revascularisation). Like COURAGE, FAME 2 failed to demonstrate a benefit from targeted PCI on mortality, with the reduction in the primary endpoint explained by a lower rate of urgent revascularisation in the PCI group. Of note, there was a strong signal in favour of reduced MI in the PCI group (8.1% vs 12.0%; HR 0.66; 95% CI 0.43–1.00), with a landmark analysis excluding peri-procedural MI demonstrating a significantly reduced rate of spontaneous MI in the PCI group (6.5% vs 10.2%; HR 0.62 (95% CI 0.39–0.99).

Like COURAGE, FAME 2 failed to demonstrate a benefit from targeted PCI on mortality.

One limitation of FAME 2 is the trial was stopped early on the basis of a "soft" endpoint (urgent revascularisation). Although a subsequent meta-analysis of three contemporary trials (including FAME 2) addressed this concern by demonstrating a clear benefit from FFR-guided PCI over OMT alone with a composite endpoint of cardiac mortality and MI (HR 0.72, 95% CI 0.54–0.96; p = 0.02). This benefit was driven primarily by a reduced rate of MI in the PCI group [8]. Further limitations of FAME 2 include the absence of documented ischaemia via functional imaging prior to diagnostic coronary angiography (lesions with FFR ≤0.80 do not necessarily equate to reduced myocardial perfusion downstream in the case of adequate collateral blood flow). Furthermore, the absence of blinding meant that there may have been a lower threshold for revascularisation among patients in the control group.

The persistence of numerous unanswered questions and limitations related to the aforementioned trials led to the genesis of the ISCHEMIA trial.

ISCHEMIA

The ISCHEMIA trial randomised over 5000 patients with CCS and moderate-to-severe ischaemia on stress testing to either an invasive strategy with cardiac catheterisation followed by revascularisation (PCI or coronary artery bypass grafting [CABG]) or OMT alone (with revascularisation in the case of failed medical therapy) [1]. The majority of patients (73%) underwent coronary computed tomographic (CT) angiography to rule out left main coronary disease and nonobstructive coronary disease prior to inclusion (27% were exempt due to renal dysfunction or known coronary anatomy). Key exclusion criteria were an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 of body-surface area, a recent acute coronary syndrome (ACS), unprotected left main stenosis of at least 50% on CT, a left ventricular ejection fraction (LVEF) <35%, New York Heart Association (NYHA) class III or IV heart failure, and unacceptable angina despite the use of medical therapy at maximum acceptable doses. For patients in the invasive group, the presence of a ≥50% stenosis at an anatomical location compatible with documented ischaemia on stress imaging was sufficient to perform PCI directly. If a stenosis was <50% at an anatomically compatible location, PCI was only performed if FFR was ≤0.80. For any stenoses identified at coronary angiography that were not compatible with a location of documented ischaemia, those ≤80% required an FFR ≤0.80 to justify PCI.

In the invasive group, 74% of patients underwent PCI with the remainder undergoing CABG. The primary endpoint was a composite of cardiovascular mortality, MI, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest. After a median follow-up of 3.2 years, there was no significant difference between groups with regards to the primary endpoint (HR 0.93 95% CI 0.80–1.08; p = 0.34). This was equally true for the components of the primary endpoint. Of note, although there was no significant difference between groups with regards to the overall rate of MI, the invasive group was associated with a significantly higher rate of procedure-related MI but a significantly lower rate of spontaneous MI, explaining why the Kaplan-Meier curves for the primary endpoint crossed over at approximately 2 years. It is worth noting that a detailed sub-analysis of the trial has shown that procedure-related MI and spontaneous MI should not be considered the same entity, as the latter is associated with a worse prognosis [9]. Overall, the only apparent benefit of an initial invasive strategy was improved angina control and quality of life when compared with the conservative strategy [10].

In ISCHEMIA, the only apparent benefit of an initial invasive strategy was improved angina control and quality of life when compared with the conservative strategy.

An important limitation of the trial was the exclusion of numerous patient subgroups important in real-world clinical practice (e.g., left main stem disease, low LVEF, NYHA III or IV heart failure, very symptomatic). The strict inclusion criteria manifested as slow recruit-

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ment, ultimately leading to the expansion of the original primary endpoint (inclusion of resuscitated cardiac arrest, hospitalisation for unstable angina/heart failure), and a reduction in the target sample size [11]. Combined with the lower than expected event rates, this reduced the statistical power of the trial. Further limitations included the high crossover rate (23% crossover from OMT to revascularisation), and the high number of patients (35%) without angina in the four weeks preceding enrolment.

Despite these limitations, ISCHEMIA adds to the wealth of literature questioning the role of revascularisation in the management of CCS.

Practical implications – what now is the role of PCI in CCS?

The aim of treatment in patients with CCS should always focus on improving survival, reducing the risk of MI and improving quality of life. To this end, the results of ISCHEMIA seem definitive: PCI does not appear to improve survival or provide an overall reduction in MI in patients with CCS when compared with OMT after a period of 3–4 years.

However, it must not be forgotten that the trial population was a carefully selected subgroup of patients seen in real-world clinical practice. Consequently, one must always ask the question: is my patient similar to those enrolled in the trial? Clearly, conclusions cannot be drawn from ISCHEMIA regarding the management of the high-risk patient groups excluded from the trial, such as those with unprotected left main stem disease, a LVEF <35% or a recent history of ACS. However, for ISCHEMIA-like patients, clinical outcomes appear to be similar with either strategy and thus it is no longer necessary to rush to coronary angiography when a stress test demonstrates myocardial ischaemia. Instead, the focus should be on the instigation of OMT. Subsequently, for patients with persistent angina despite OMT, an invasive approach does appear to be valid option on the basis of ISCHEMIA. However, a blanket rule for all patients that fulfil the trial's inclusion criteria may not be appropriate. Instead, an approach tailored to specific clinical context would seem most reasonable. For example, for patients with particularly complex coronary lesions not easily amenable to revascularisation, or those with comorbidities that preclude the use of dual antiplatelet therapy, a focus on OMT would seem most appropriate. Conversely, patients with important levels of angina wishing to avoid polypharmacy, or those with uncomplicated disease with easily revascularisable lesions, a lower threshold for invasive management could be justified.

However, a blanket rule for all patients may not be appropriate. An approach tailored to specific clinical context would seem most reasonable.

However, a caveat for the use of PCI purely for the management of angina is this last statement is the ORBITA trial. This innovative double-blinded trial randomised 230 patients with angina and severe (≥70%) single-vessel stenosis to PCI with a current-generation drug eluting stent or a placebo procedure after six weeks of OMT. Patients underwent exercise testing and questionnaire-based symptom evaluation before randomisation and at six-week follow-up. The trial found that PCI did not significantly improve exercise time or symptoms, suggesting an important placebo effect from PCI and calling into question its role in the management of symptoms in patients with CCS. However, several limitations restrict the application of these results to real-world clinical practice, such as the trial being likely underpowered for its endpoints, the short six-week follow-up which may have been too short to see the benefits of the PCI, as well as the unusual situation of patients undergoing PCI continuing to receive anti-anginal therapy. Furthermore, it seems implausible that the improved angina control and quality of life seen in the invasive group of the ISCHEMIA trial could be explained solely by a placebo effect given the durability of these findings 3 years after PCI.

According to the ORBITA trial, there is a caveat for the use of PCI purely for the management of angina.

As for the impact of ISCHEMIA on the daily functioning of interventional cardiologists, we recently analysed 1000 consecutive PCIs performed in our university hospital. Interestingly, only 91 patients (9.1%) were deemed potentially ISCHEMIA-like, reflecting a high percentage of PCIs performed in the context of ACS or in CCS patients with at least one ISCHEMIA exclusion criteria. A sub-analysis considering only patients with stable coronary atery disease, found that only 28.4% would potentially fulfil the ISCHEMIA inclusion criteria [12]. These results are in line with a recent retrospective analysis of a national American PCI registry looking at interventions performed between 2017 and 2019. It found that only 13.5% of all PCIs performed during the study period met the ISCHEMIA inclusion criteria. Exclusively among patients with stable coronary atery disease, this corresponded to only 32.3% [13]. Practically, these results suggest that the impact of ISCHEMIA on the real-world practice of a tertiary hospital like

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Table 1: Definitions of high event risk for different test modalities in patients with established chronic coronary syndromes. Adapted from 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

Modality	Definitions of high event risk
Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score
SPECT or PET perfusion imaging	Area of ischaemia ≥10% of the left ventricle myocardium
Stress echocardiography	≥3 of 16 segments with stress-induced hypokinesia or akinesia
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease
Invasive functional testing	FFR ≤0.8, iwFR ≤0.89

CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; iwFR = instantaneous wave-free ration (instant flow reserve); LM = left main; PET = positron emission tomography; SPECT; single-photon emission computed tomography

ours will likely be limited. However, centres performing a higher proportion of PCIs for stable coronary artery disease would presumably be more affected.

What do the current guidelines say?

The European Society for Cardiology (ESC) guidelines from 2019 promote a stepwise approach to the evaluation of patients with suspected CCS [14]. Following the calculation of the pre-test probability of CCS, patients should undergo either functional or anatomical non-invasive testing to confirm or exclude the diagnosis of CCS. The role of revascularisation is limited to patients with severe symptoms refractory to OMT, left ventricular dysfunction linked to coronary artery disease, and those deemed at high risk of a clinical event, namely mortality and/or MI. However, the definition of the latter includes the presence of significant ischaemia as defined by functional testing (nuclear imaging, cardiac MRI, and stress echocardiography) (table 1). These criteria essentially define the moderate-to-severe ischaemia inclusion criteria of ISCHEMIA. As a result, the validity of these recommendations is now called into question and it is likely that the next iteration of the guidelines will need to reflect this, albeit while recognising the reduction in spontaneous MI seen with revascularisation in the trial.

The validity of the current ESC guideline recommendations is now called into question.

As for the instigation of OMT, the ESC guidelines provide an excellent stepwise approach to the introduction and escalation of anti-anginal therapy in patients with CCS according to their specific clinical features (fig. 1). Given the findings of ISCHEMIA, a good working knowledge of this algorithm seems critical for the optimal management of symptomatic CCS patients. [14].

Future directions: CTA and FFRCT

Given that the results of ISCHEMIA suggest that patients with CCS and significant ischaemia on stress testing no longer require systematic cardiac catheterisation, what does this mean for FFR, a test that is performed at the time of coronary angiography? Although FFR will always have a role in the evaluation of intermediate stenoses in CCS patients who are eventually referred for angiography, it seems likely that the results of ISCHEMIA will lead to a diminishing role for FFR procedures being performed in the evaluation of CCS. However, one promising non-invasive imaging modality that could replace the role of invasive coronary angiography in haemodynamic lesion-level analysis is CT angiography (CTA).

It seems likely that the role for FFR procedures being performed in the evaluation of CCS diminishes.

CTA has the benefit of identifying significant coronary stenoses including proximal lesions of clear prognostic significance (e.g., unprotected left main disease). In addition, CTA can also identify the significant proportion of patients without obstructive coronary artery disease despite positive functional imaging. Its systematic use for screening in the ISCHEMIA trial identified unprotected left main disease and no obstructive coronary disease in 9% and 17% of patients, respectively, providing evidence of its efficacity and feasibility in this context [1].

CTA has the added benefit of permitting a haemodynamic lesion-level analysis through the use of computational fluid dynamics to compute FFR (FFR computed tomography, FFRCT). This has been shown to demonstrate good diagnostic performance, as compared with FFR, in the identification of functionally significant

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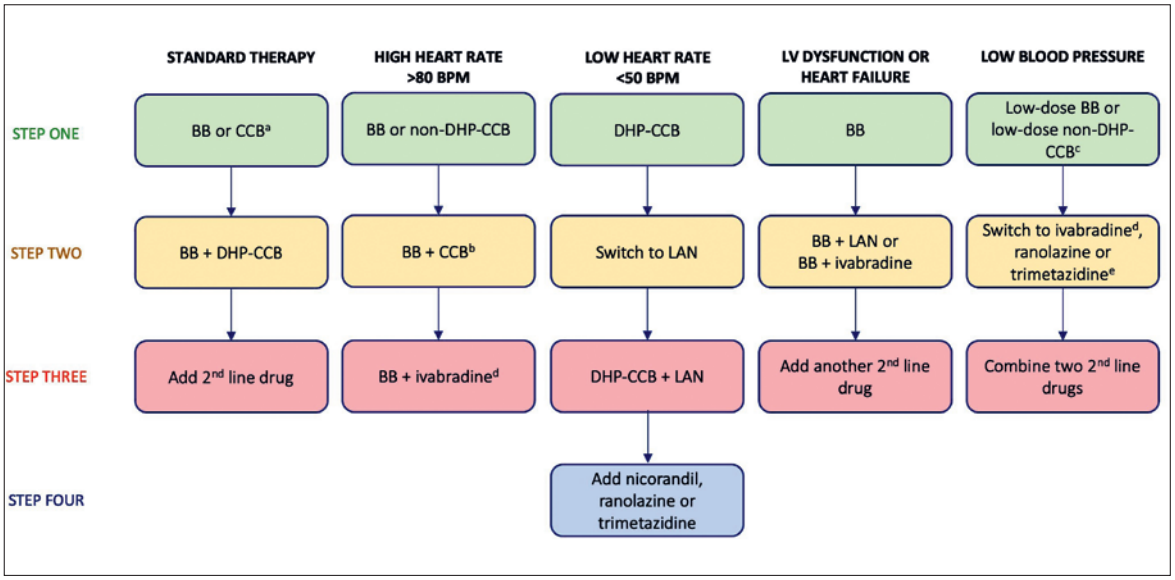

Figure 1: Stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB= non-dihydropyridine calcium channel blocker. [a] Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step. [b] The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure. [c] Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure. [d] Ivabradine should not be combined with non-DHP-CCB. [e] Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged. Adapted from 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

coronary artery stenoses [15]. Furthermore, FFRCT has been shown to be an effective tool in the triage of patients for invasive management, avoiding unnecessary cardiac catheterisation and reducing costs [16], although a recent study found cardiac magnetic resonance imaging to be potentially more cost effective with improved health benefits [17].

However, CTA has some important limitations that need to be considered. The accurate interpretation of CTA requires images of sufficient quality, which can be challenging given the lower spatial resolution it offers when compared with invasive coronary angiography (0.5 mm vs 0.16 mm) [18]. Furthermore, image quality can be affected by high heart rates, arrhythmias, obesity, coronary calcification and motion artefacts [18]. These factors result in an important reduction in the diagnostic accuracy of FFRCT around the cut-off of 0.8 when compared with invasively-measured FFR [19], which ultimately may require invasive testing to confirm or exclude the presence of a flow-limiting coronary lesion. CTA, like invasive coronary angiography, requires the use of significant doses of radiation and potentially nephrotoxic contrast agents. Finally, although the use of CTA in the investigation of suspected coronary artery disease has been shown to improve symptoms in cases where obstructive is either excluded or confirmed, this effect is attenuated among patients found to have moderate non-obstructive disease [20]. The likely explanation for the latter is that such patients do not receive the reassurance or a clear explanation for their symptoms.

To summarise, whilst recognising the limitations of CTA including the importance of obtaining images of sufficient quality in situations where optimal image quality can be obtained. Thus, the incorporation of CTA into the routine evaluation of patients with suspected CCS may well offer the highest yield in terms of the diagnosis (and exclusion) of CCS, and the identification of lesions of high prognostic significance (e.g., unprotected left main disease or stenoses with FFRCT ≤0.8) that would benefit from PCI. For patients with confirmed CCS and no lesions of high prognostic significance, the instigation of OMT would appear to be reasonable and safe first-line approach (fig. 1).

The controversy continues?

Since the publication of ISCHEMIA, the release of a large-scale meta-analysis by Navarese et al. has added further fuel to the debate [21]. The authors analysed 25

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randomised controlled trials (including ISCHEMIA, FAME-2, COURAGE) involving nearly 20,000 patients and comparing revascularisation plus OMT with OMT alone. The specific objective was to include the longest follow-up data available given the trend favouring revascularisation seen in studies such as FAME-2 and ISCHEMIA. After an average follow-up period of 5.7 years, revascularisation was associated with a significative reduction in cardiac death (relative risk [RR] 0.79, 95% CI 0.67–0.93) and spontaneous MI (RR 0.74, 95% CI 0.64–0.86). Of note, there was no significant difference between groups with regards to all-cause mortality or overall MI (spontaneous and procedure-related).

These results suggest that revascularisation may offer a significant mortality benefit after extended follow-up periods, a somewhat surprising result given previous meta-analyses finding no such benefit [22, 23]. However, these results should be interpreted with caution for several reasons. Firstly, the use of cardiac mortality as the primary outcome is debatable, given that all-cause mortality is considered the most unbiased method for reporting deaths and thus is recommended in the latest Academic Research Consortium-2 Consensus Document [24]. Importantly, when considering the latter, the authors found no significant difference between the two treatment strategies (HR 0.94, 95% 0.87–1.01). Secondly, the authors included studies from before the introduction of OMT, thus potentially exaggerating any benefit from revascularisation. Indeed, when studies from the OMT era alone are analysed, the reduction in cardiac mortality from revascularisation disappears [25]. For these reasons, these results do not change our interpretation of ISCHEMIA, although we recognise that longer-term follow-up from the trial could yield some interesting data.

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Learning points

- The goal of treating patients with CCS is to improve survival, reduce the risk of MI, and improve quality of life.
- The weight of evidence suggests that, for patients similar to those included in ISCHEMIA, PCI is more effective than OMT at controlling symptoms, but does not reduce mortality or the overall risk of MI.
- The focus for ISCHEMIA-like patients should be the instigation of guideline-recommended OMT, with PCI reserved for those who remain symptomatic despite OMT.
- Physicians must identify high-risk CCS patients not represented by the ISCHEMIA trial population (e.g., unprotected left main stenosis, LVEF <35%, severely symptomatic heart failure, severe angina despite maximal OMT), for whom early revascularisation may still represent the optimal treatment strategy.
- With adequate image quality, CTA combined with FFRCT can provide both an anatomical and functional evaluation of coronary artery disease (including exclusion of unprotected left main disease), and appears to be a cost-effective alternative to coronary angiography in the evaluation of CCS.

Conclusion

The ISCHEMIA trial, like several landmark trials before it, failed to show any significant reduction in mortality or MI with PCI when compared with OMT among patients with CCS. Thus, for ISCHEMIA-like patients encountered in clinical practice (i.e., those without trial exclusion criteria such as unprotected left main disease or LVEF <35%), a positive stress test no longer justifies immediate invasive coronary angiography. Instead, the focus should be on the instigation of guideline-recommended OMT, with PCI reserved for patients who remain symptomatic despite OMT. Given the likely diminishing role of coronary angiography in the evaluation and management of CCS, although CTA has numerous limitations, through its capacity to provide both anatomical and haemodynamic information, it appears to offer a comprehensive and cost-effective alternative that could soon be integrated into routine clinical practice.

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The full list of references is included in the online version of the article at https://cardiovascmed.ch/article/doi/CVM.2022.w10118.