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Letter to the Editor

Is protected PCI truly protective? Critical reflections following CHIP-BCIS3 and previous evidence

¿Es realmente protectora la PCI protegida? Reflexiones críticas a partir de CHIP-BCIS3 y la evidencia previa

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To the Editor:

We have read with great interest the CHIPBCIS3 trial, recently published in *The New England Journal of Medicine*, which evaluated elective left ventricular unloading (LVU) using a microaxial flow pump (Impella CP) in patients with severe ventricular dysfunction and extensive coronary artery disease undergoing complex high-risk percutaneous coronary intervention (PCI). [1] In a scenario where pathophysiological rationale has driven the expansion of so-called "protected PCI," this study provides direct randomized evidence against a strategy without planned mechanical support and compels a reappraisal of current practice assumptions.

Firstly, the ventricular unloading strategy did not reduce the primary hierarchical endpoint (all-cause death, disabling stroke, spontaneous myocardial infarction, cardiovascular hospitalization, or periprocedural myocardial injury), analyzed using the win ratio (0.85; 95% CI 0.63–1.15; P=0.30). [1] Moreover, an adverse signal was observed in hard outcomes: higher cardiovascular mortality (HR: 1.91; 95% CI: 1.11–3.30) and a trend toward higher all-cause mortality (HR: 1.54; 95% CI: 0.99–2.41) [1]. Given that the included population had marked ventricular dysfunction (median left ventricular ejection fraction [LVEF] 27%) and extensive coronary disease, and that event rates were high, these findings weaken the notion of clinical superiority of elective unloading as a routine strategy. [1]

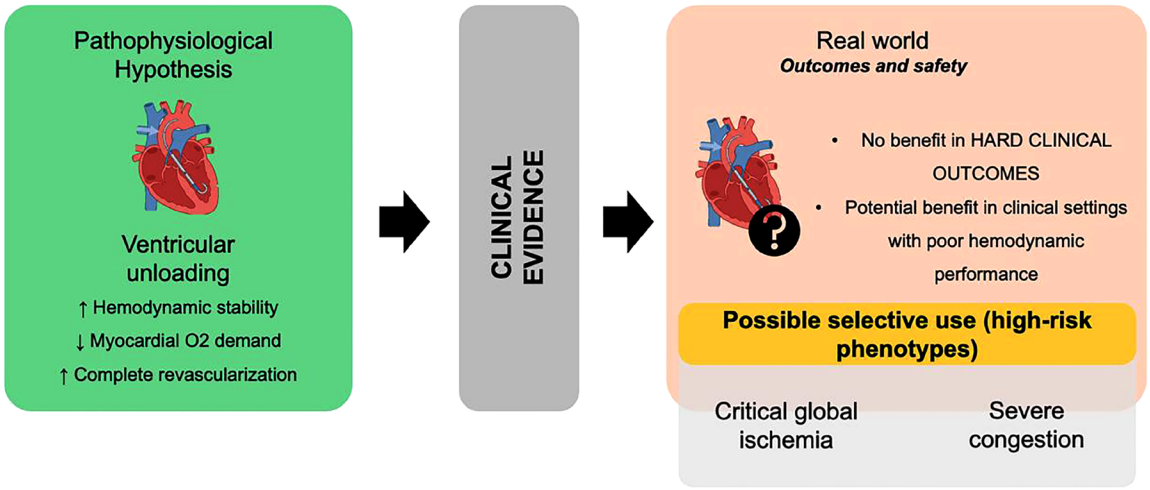
Secondly, CHIP-BCIS3 should be interpreted in continuity with prior randomized evidence on mechanical support during high-risk PCI. The PROTECT II trial, which compared Impella 2.5 with the intra-aortic balloon pump (IABP), was stopped early due to probable futility, limiting the ability to demonstrate net clinical benefit. [2] Likewise, in BCIS-1, elective IABP did not reduce major events compared with a strategy without planned support during high-risk PCI. [3] Furthermore, a meta-analysis of short-term outcomes in patients undergoing "protected high-risk PCI" did not show a consistent mortality benefit, reinforcing uncertainty regarding the impact on hard outcomes in this setting. [4] Altogether, this body of evidence suggests that intraprocedural hemodynamic improvement does not necessarily translate into improved survival and may, in some cases, create a false sense of procedural safety despite an apparently stable hemodynamic profile.

Thirdly, in CHIP-BCIS3, periprocedural injury was numerically more common with the pump (61.7% vs. 50.0%; RR 1.23; 95% CI 0.99–1.54). [1] That runs counter to the idea that ventricular unloading protects the heart. The authors rightly ask whether the higher frequency and greater extent of injury could explain the difference in cardiovascular mortality, and they point to a hemodynamic substudy that might shed light on mechanisms. [1] This matters clinically: we should not assume "protection" from hemodynamic stability alone—it must be shown by less net myocardial injury and fewer meaningful clinical events.

Fourthly, one of the arguments in favor of "protected PCI" is that support may allow for more complete revascularization. However, CHIPBCIS3 showed similar reductions in overall coronary disease burden: a median coronary revascularization index of 67% in both groups and similar residual SYNTAX scores. [1] Although timing differed (more revascularization during the index procedure with the pump and more staged revascularization in the standard group), the overall residual burden was comparable. [1] This weakens the hypothesis that elective unloading provides a consistent advantage in revascularization completeness capable of translating into improved outcomes. Conversely, reviews have emphasized the bleeding risk associated with Impella-supported high-risk PCI. [5-8]

Fifthly, from an economic and health policy perspective, the routine use of "protected PCI" with Impella raises serious questions regarding cost-effectiveness. The estimated cost of an Impella CP device ranges between USD 20,000 and USD 25,000 per case, not including costs related to complications, prolonged hospital stays, and the

Central Figure. Representation of the Ventricular Unloading Paradox
Impact on myocardial injury and cardiovascular mortality.



Elective ventricular unloading in CHIP PCIs does not translate into real myocardial protection. The higher periprocedural injury could explain the CV mortality signal.

need for intensive hemodynamic monitoring. [7,9] In the absence of demonstrated benefit in mortality or major cardiovascular events, and considering the adverse signal observed in cardiovascular mortality in CHIPBCIS3, widespread adoption of this strategy does not meet the criteria for rational resource use in healthcare systems with limited budgets. [4,7,8] An incremental cost-effectiveness analysis based on CHIPBCIS3 results would likely show an unfavorable ratio, reinforcing the need to identify specific subgroups in whom clinical benefits justify the incremental cost. [7,8]

In addition, the reviewed evidence suggests that support with a microaxial flow pump may be associated with ventricular functional recovery in certain high-risk patients. A recent review reported that, in a meta-analysis of nine studies including 2,370 patients undergoing CHIP PCI, microaxial pump support was associated with a significant improvement in LVEF at follow-up, with a mean increase of 6.7% (95% CI: 4.5–8.9%) at approximately five months. [9] This finding is clinically relevant, as it suggests that ventricular unloading may facilitate myocardial recovery after complex revascularization; however, this functional improvement has not yet translated into consistent evidence of reduced mortality or major cardiovascular events.

In parallel to these signals of recovery, anchoring the indication in invasive physiology—specifically left ventricular end diastolic pressure (LVEDP)—offers a pragmatic path toward selective use. A large cohort recently established LVEDP ≥26 mmHg as an independent predictor of high mortality in elective PCI. [10] This is physiologically linked to microcirculatory impairment, as elevated LVEDP correlates with higher IMR and worse myocardial perfusion. [11] Furthermore, recent prospective data in patients with LVEF <35% demonstrate that Impella-protected PCI significantly reduces LVEDP, proposing a threshold of 19 mmHg to identify patients most likely to derive hemodynamic benefit. [12] These findings support using baseline LVEDP as a simple, point-of-care metric to guide phenotypic selection for LV unloading.

This point becomes even more relevant when interpreted within the broader context of stable coronary artery disease. A review of the evidence highlights that multiple meta-analyses comparing PCI versus optimal medical therapy in stable coronary disease have not demonstrated a consistent reduction in mortality or myocardial infarction with a routine invasive strategy. [13-15] Although these studies were not specifically designed for CHIP populations or to evaluate mechanical ventricular unloading, they reinforce a central concept: in stable ischemic heart disease, physiological or anatomical improvements do not always translate into net prognostic benefit. Therefore, extrapolating the routine clinical benefit of "protected PCI" solely from its intraprocedural hemodynamic effects remains, at present, methodologically premature.

From a practical standpoint, the available evidence also compels careful consideration of complications and resource utilization. The use of Impella and other mechanical support strategies must be balanced against risks such as bleeding, vascular complications, hemolysis, and increased care complexity, in addition to the economic impact of their implementation. Current evidence indicates that the cost-effectiveness of routine use of these devices in complex high-risk PCI remains uncertain, particularly in the absence of a clear benefit in survival or MACE in stable populations. [1,7,8,16]

Accordingly, rather than supporting indiscriminate expansion of "protected PCI," current evidence points toward a model of selective indication based on a comprehensive assessment of

anatomical, functional, and hemodynamic risk. Given the contrast between neutral hard outcomes and functional gain, the net clinical benefit of ventricular unloading appears to be phenotype-dependent. We therefore propose two clinical phenotypes in which hemodynamic reserve is essentially absent:

I. **Critical global ischemia:** Patients with unprotected left main coronary artery disease or equivalent (large myocardial territory at risk), in whom any transient coronary occlusion during PCI (balloon inflation or stent deployment) may trigger immediate hemodynamic collapse that the left ventricle is unable to compensate for.

II. **Severe intraventricular congestion:** Patients with markedly elevated filling pressures (LVEDP >20 mmHg) in whom ventricular unloading acts as a therapeutic intervention by reducing wall stress, improving diastolic compliance, and enhancing microvascular perfusion prior to epicardial revascularization.

Author´s contribution

FQC: conceptualization, research, formal analysis, drafting of the original manuscript, review, and editing. **TC:** validation, critical review of the intellectual content, drafting, review, and editing.

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