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In Reply Ms Zhang and colleagues make excellent points in response to our recent clinical review.[1] It is true that dydrogesterone is not available in the US, and we were not previously familiar with its use. We appreciate the information provided about this agent, as well as the other hormone preparations mentioned in their Letter. This global perspective helps inform adolescent clinical care around the world.

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Review of Cardiogenic Shock After Acute Myocardial Infarction

To the Editor The recent Review[1] on cardiogenic shock after acute myocardial infarction described the lack of evidence supporting use of percutaneous mechanical circulatory support devices in these patients.

Although temporary percutaneous mechanical circulatory support is not a cure for cardiogenic shock, it is a strategy used solely to temporarily suspend imminent death to facilitate another clinical development or intervention that can improve prognosis. With reversible myocardial injury, successful coronary revascularization or sufficient recovery of stunned myocardium may allow weaning of percutaneous mechanical circulatory support. If myocardial injury is irreversible, suitability for and successful implementation of a long-term left ventricular assist device (LVAD) or cardiac transplant will determine prognosis. Any form of percutaneous mechanical circulatory support can be deemed to have "failed" only if these exit strategies are clearly possible but not reached.

All major cardiogenic shock trials to date have used all-cause mortality at 30 days as a primary end point.[2] Given that percutaneous mechanical circulatory support for 30 days is relatively rare, inclusion of patients at study onset without an exit strategy (those with irrecoverable myocardial injury who are not candidates for LVAD or cardiac transplant) could lead to erroneous conclusions. Death due to unavoidable planned withdrawal of percutaneous mechanical circulatory support because of the lack of an exit strategy meets primary end point criteria in such trials but does not support the conclusion that the percutaneous mechanical circulatory support was ineffectual. In these cases, it is the lethal combination of irrecoverable myocardial injury with no exit strategy that dictates prognosis.

International guidelines have essentially placed a moratorium on intra-aortic balloon pump (IABP) use based on results from the IABP-SHOCK II trial.[3] In this study, the median length of time patients received IABP support was 3 days and the median age of randomized patients was 70 years, which is older than optimal for transplant, especially in the setting of salvaged cardiogenic shock. The current reality that IABPs remain frequently used[4] suggests that clinicians continue to see benefits with IABP support on an individual patient basis despite the IABP-SHOCK II trial conclusions.

A 2019 study[5] of the percutaneous LVAD Impella, which also used all-cause mortality at 30 days as a primary end point, similarly revealed negative results. Moreover, an ongoing trial of venoarterial extracorporeal membrane oxygenation for patients with cardiogenic shock is also using the same primary end point of all-cause mortality at 30 days (NCT03813134).

With ongoing use of all-cause mortality at 30 days as a primary end point, are we in danger of generating a plethora of spurious "antievidence" for all current and emerging percutaneous mechanical circulatory support devices for cardiogenic shock?

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In Reply In his Letter to the Editor about our recent Review,[1] Dr Dalzell makes a case for continued use of temporary percutaneous mechanical circulatory support devices and questions the utility of using 30-day mortality as an end point in trials of these devices. We agree that percutaneous mechanical circulatory support devices are neither a definitive treatment nor a cure for cardiogenic shock. These devices are deployed to temporarily augment systemic perfusion while the etiology of clinical decompensation (in the case of acute myocardial infarction, an occluded epicardial coronary artery) is identified and treated so that the shock state can be reversed. As noted, percutaneous mechanical circulatory support devices can be removed when the acute shock state has resolved and after demonstrating that the heart can maintain adequate systemic perfusion. Alternatively, removal of a percutaneous mechanical circulatory support device should be considered if a patient experiences a device-related complication and the risk of continued use outweighs potential benefit.

It appears that the crux of the proposal put forth by Dalzell is 2-fold: (1) the use of mortality alone as an end point in randomized trials may obscure the benefit of temporary percutaneous mechanical circulatory support if the trial does not also include some "exit strategy," such as LVAD placement or cardiac transplant and (2) the inclusion of patients who may not be candidates for advanced therapies such as LVAD or cardiac transplant in randomized trials diminishes the potential benefit of percutaneous mechanical circulatory support because it does not allow for the assessment of these devices as a "bridge" to these advanced therapies.

We agree in part with the argument put forth by Dalzell but offer these important caveats. Mortality from cardiogenic shock is still high, and any device therapy that carries risk must prove that it reduces mortality before it is widely implemented. If a device shows that it improves survival or, at the very least, does not reduce survival, then other outcomes such as hospital/intensive care unit length of stay or surrogate outcomes can be studied. Moreover, the use of a 30-day mortality end point would include patients who survive to receive advanced therapies. Dalzell's comment about the inclusion of patients who are not candidates for advanced therapies is well taken; however, older patients may be at higher risk of developing cardiogenic shock, and there is a dearth of evidence for effective therapies in older patients. Systematic exclusion of a specific patient subgroup with a potentially worse outcome would limit external validity and study generalizability. We propose that any trial of percutaneous mechanical circulatory support should strive to oversample patient groups in whom the evidence base is particularly sparse.

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Discussion of Diagnostic Excellence

To the Editor In discussing the concept of diagnosis, a recent Viewpoint[1] assumed that a "correct" diagnosis is always possible. However, many patients have diagnoses that are and remain uncertain.[2] These patients with uncertain diagnoses are not acknowledged in medical records, do not participate in clinical studies, and lose access to testing, treatment, and reimbursement services.

A recent workshop[3] examined the causes, characteristics, and opportunities provided by diagnostic uncertainty. Uncertainty occurs when stakeholders with different sociologic or biologic purposes define diagnosis names differently. Sociologically purposed names are binary and time insensitive, exclusive of atypical patients, and rigid in definitions of disease onset (eg, first time a diagnosis name appears in a medical record or first time a patient fulfills classification criteria). Insurers, clinical trialists, and public health officials accept standard *International Classification of Diseases*–identified (but not new) diagnosis names.

Biologically purposed names are analogue, time sensitive, and inclusive. They accept that knowledge, biomarkers, disease mechanisms, and biologies change and that use of a name varies with choice of time of onset (eg, genetic predisposition, trigger event, symptom, physician visit, or fulfillment of consensus criteria). Biologically purposed names, standard or new, help physicians communicate, intervene, and prognosticate.

The bases for assigning a diagnosis name—etiology, symptom pattern, laboratory test, and treatment response—have quantifiable objectivity, subjectivity, concatenation, and heterogeneity and, hence, quantifiable uncertainty. A bone fracture's cause, onset, diagnostic tests, and treatment responses are objective, so the diagnosis is binary and certain. In contrast, undifferentiated connective tissue disease's onset is slow and variable, with subjective and heterogeneous symptoms and ambiguous diagnostic tests, so the diagnosis is analogue and uncertain.

I believe that a consensus vocabulary that quantitates uncertainty, distinguishes between sociologic and biologic definitions, understands the difference between clinical syndrome and illness mechanisms, and accepts change over time will improve patient care, medical science, and administration.

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