Hajjar et al.1 designed, conducted, and now report in this issue an elegant randomized double-blind controlled trial of vasopressin (0.01 to 0.06 U/min) versus norepinephrine (10 to 60 μg/min) post cardiac surgery with vasodilatory shock (Vaso-pressin versus Norepinephrine in Patients with Vasoplegic Shock After Cardiac Surgery [VaNCS] trial). Open-label norepinephrine was added if there was an inadequate response to blinded study drug. Vasodilatory shock was defined by hypotension requiring vasopressors and a cardiac index greater than 2.2 l·min·m⁻². The primary endpoint was a composite: “mortality or severe complications.” Patients with vasodilatory shock within 48 h post cardiopulmonary bypass weaning were eligible. Three hundred patients were included, and there was a highly significant decrease in the primary endpoint in the vasopressin compared to the norepinephrine group (absolute risk reduction 17%, number needed to treat 6). There was also a significantly lower rate of atrial fibrillation in the vasopressin versus norepinephrine group (perhaps expected because of lack of β1-adrenergic stimulation with vasopressin). The vasopressin group also had sparing of norepinephrine (shorter duration), shorter duration of study drug infusion, shorter intensive care unit stay, shorter duration of dobutamine, less acute kidney injury, less need for renal replacement therapy, and lower sepsis-related organ failure assessment scores than the norepinephrine group. The authors conclude that vasopressin is superior to norepinephrine in vasodilatory shock after cardiac surgery. There was no difference in 28-day mortality in the composite—the vasopressin signal was driven by severe complications and not by mortality in the mortality or severe complications composite.

Strengths of VANCS include the blinded randomized treatment, careful follow-up, calculation of the composite outcome, achieving adequate and planned sample size, and evaluation of vasopressin pharmacokinetics. Nearly 20 yr ago, Landry et al.2-6 discovered relative vasopressin deficiency and benefits of prophylactic (i.e., pre cardiopulmonary bypass) and postoperative low-dose vasopressin infusion in patients with vasodilatory shock after cardiac surgery. Previous trials of vasopressin versus norepinephrine in cardiac surgery were small and underpowered for mortality assessment.2-6

Vasopressin stimulates arginine vasopressin receptor 1a, arginine vasopressin receptor 1b, V2, oxytocin, and purinergic receptors causing vasoconstriction (V1a), corticosteroid axis stimulation (V1b), and antidiuresis (V2), as well as release of procoagulant von Willebrand multimers (V2). Mechanisms of vasopressin benefit in VANCS include sparing of norepinephrine7 or other nonhemodynamic effects (because hemodynamics such as mean arterial pressure, cardiac index, lactate, and fluid balance were similar in vasopressin and norepinephrine groups). Trials of vasopressin versus norepinephrine in septic shock show no difference between vasopressin and norepinephrine in efficacy or adverse effects,8-11 contrasting with the possible efficacy and the atrial fibrillation avoidance benefit of vasopressin in the randomized controlled trial by Hajjar et al.1 Dunser et al.12 found fewer tachyarrhythmias with vasopressin compared with norepinephrine in vasodilatory shock. Why was vasopressin possibly beneficial in vasodilatory syndrome after cardiac surgery in VANCS1 but not in septic shock in the Vasopressin and Septic Shock trial (VASSST; registered with http://www.controlled-trials.com, ISRCTN94845869; supported by grant no. MCT 44152

Image: S. Shernan, Brigham and Women’s Hospital.
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from the Canadian Institutes of Health Research, Ottawa, Canada) or Vasopressin versus Noradrenaline as Initial therapy in Septic shock trial (VANISH)\textsuperscript{8,11} The most obvious difference is the primary outcome—mortality and severe complications in VANCS, 28-day mortality in VASST,\textsuperscript{8} and kidney failurefree days in VANISH.\textsuperscript{11,13} Although vasopressin doses in VANISH, VANISH,\textsuperscript{11} and VANCS\textsuperscript{1} were similar, peak vasopressin levels on vasopressin treatment were much lower in the VANCS (20 to 25 pmol/l) than in the VASST (80 to 100 pmol/l) or the VANISH pilot trial\textsuperscript{10,11} (300 pmol/l). Perhaps lower vasopressin levels in VANCS are the optimal vasopressin level in vasodilatory shock due to septic shock or post cardiac surgery. This aligns with the observation that the vasopressin beneficial signal in VANCS was restricted to lower rates of adverse effects of vasopressin.

Aspects of variability of patient response to vasopressin infusion and other purported mechanisms of action of vasopressin (and V1a agonist) deserve emphasis. Interindividual responses to vasopressin may be due to polymorphisms of leucyl/cystinyl aminopeptidase, the enzyme that catalyzes vasopressin\textsuperscript{15} or the V1a receptor. Recently, V1a agonism\textsuperscript{14–16} was found to decrease vascular leak in models and possibly in patients with septic shock,\textsuperscript{17} perhaps by limiting increases in angioptoitin-2,\textsuperscript{16,18} and may be another reason for vasopressin efficacy in the trial by Hajjar et al.\textsuperscript{1}

Hajjar et al.\textsuperscript{1} note that vasodilatory shock after cardiac surgery is common in patients previously treated with \( \beta \)-blockers or angiotensin-converting enzyme inhibitors. In their trial, 65% of patients were on \( \beta \)-blockers and 46% of the norepinephrine group and 35% of the vasopressin group were on angiotensin-converting enzyme inhibitors. The vasopressin benefit occurred in patients with or without \( \beta \)-blockers, but only in the patients on angiotensin-converting enzyme inhibitors. These are hypothesis-generating \textit{post hoc} subgroup analyses to be interpreted with caution. Perhaps Hajjar et al.\textsuperscript{1} discovered a novel interaction of vasopressin with angiotensin-converting enzyme pathways, a possible scenario from a biological standpoint.

The mortality rates were high—16 and 15% at 28 days and 17 and 16% at 90 days (norepinephrine \textit{vs.} vasopressin)—in VANCS\textsuperscript{1}; remarkably, mortality rates were not reported in previous smaller trials of vasopressin \textit{versus} norepinephrine for vasodilatory shock\textsuperscript{12} after cardiac surgery.\textsuperscript{2,5,6,19}

There are limitations of the current trial, including that it is a single-center trial. The major limitation is that the primary endpoint was changed after the trial had enrolled some patients, an important protocol amendment. How many patients had been included by then? Was a change in protocol registered? How did this alter the sample size and power calculations? The sample size and power calculation of the initial endpoint (days alive and free of organ dysfunction [Brussels score]) should be stated. The authors explain well the rationale and process for changing the primary endpoint in the electronic supplement. Interestingly, the vasopressin group had significantly more days alive and free of cardiovascular and renal dysfunction compared to the norepinephrine group.

There is concern about generalizability of these results in other countries and healthcare settings. The lengths of intensive care unit stay (6 days) and hospital stay (10 to 13 days) appear prolonged because patients with vasodilatory shock have more profound derangements after cardiac surgery that extend intensive care unit and hospital stays. The literature is sparse regarding expected lengths of stay after vasodilatory shock complicating cardiac surgery, which is the reason that Hajjar et al.\textsuperscript{1} changed the primary outcome. It would also be useful to understand how the lengths of stay of vasodilatory shock patients compared to those of patients in the hospital of Hajjar et al.\textsuperscript{1} in Brazil who did not have vasodilatory shock post cardiac surgery.

In summary, this remarkable trial shows that in settings such as the study hospital, vasopressin infusion for treatment of vasodilatory shock after cardiac surgery may improve some clinically important outcomes. Pocock and Stone\textsuperscript{20} emphasize limitations of “positive” trials, including having the primary \( P \) value merely less than 0.05 as being inadequate to change practice (they suggest \( P < 0.001; P = 0.0014 \) in VANCS), magnitude of the treatment benefit (absolute risk reduction was 16%—impressive—in VANCS), having an important primary outcome (mortality and severe complications are clinically important), careful inspection of composite outcomes (vasopressin decreased severe complications), having supportive secondary outcomes (atrial fibrillation was lower with vasopressin), consistency across subgroups (some consistency; \textit{e.g.}, \( \beta \)-blockers yes/no subgroups), stopping early (not the case in VANCS), flaws in trial design or conduct (the change in primary endpoint in VANCS as discussed), and applicability to a reader’s patients, an issue I addressed. Accordingly, this trial deserves replication in other multicenter healthcare settings to create confidence about generalizability. A selective V1a agonist may be more effective than vasopressin by limiting von Willebrand factor release and vascular leak, rationales for future randomized controlled trials of V1a agonism in vasodilatory shock after cardiac surgery.

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**Competing Interests**

Dr. Russell reports patents owned by the University of British Columbia (UBC), Vancouver, Canada, that are related to PCSK9 inhibitor(s) and sepsis and the use of vasopressin in septic shock. He is an inventor on these patents. He is a founder, director, and shareholder in Cyon Therapeutics Inc., Vancouver, Canada (developing a sepsis therapy). He has share options in Leading Biosciences Inc., San Diego, California. He is a shareholder in Molecular You Corp., Vancouver, Canada. He reports receiving consulting fees from Merck, Kenilworth, New Jersey (developing antibiotics), Leading Biosciences (developing a sepsis therapeutic), Fer-
Correspondence
Address correspondence to Dr. Russell: jim.russell@hli.ubc.ca

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