Vasopressin *versus* Norepinephrine after Cardiopulmonary Bypass

To the Editors:

We read with great interest the paper by Hajjar *et al.*, "Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial," and the accompanying editorial.[1,2] There are a number of limitations inadequately addressed by the authors and in the editorial that limit the generalizability of VANCS findings to clinical practice.

First and most importantly, the VANCS treatment protocol used doses of vasopressin and norepinephrine that are not equivalent. Vasopressin was dosed at 0.01 to 0.06 U/min, which is similar to dosing in common clinical practice and to the regimens used in large randomized controlled trials of vasopressin *versus* norepinephrine in sepsis (Vasopressin and Septic Shock Trial [VASST] and the Vasopressin *vs.* Norepinephrine as Initial Therapy in Septic Shock [VANISH]).[3,4] On the other hand, norepinephrine was dosed at 10 to 60 μg/min (~0.14 to 0.86 $\mu g \cdot kg^{-1} \cdot min^{-1}$), which is approximately five times higher than the dose typically used following cardiopulmonary bypass at our center and many others. This dose also far exceeds that used in VASST (5 to 15 μg/min) and VANISH (maximum of 12μg/min). Using lower doses, neither VASST nor VANISH found significant differences in acute kidney injury or other outcomes between vasopressors.

Second, other than management of vasopressin and norepinephrine, clinical treatment was not protocolized. Balanced use of fluids, pressors, inotropes, and vasodilators is needed to assure adequate blood pressure and organ perfusion after cardiopulmonary bypass. VANCS patients randomized to the norepinephrine group subsequently required longer duration of treatment with the intervention vasopressor, greater use of dobutamine (P = 0.007), and greater use of open-label norepinephrine (19% *vs.* 11%; P = 0.06). Although intraoperative epinephrine was used in more than 25% of patients in both treatment groups, its postoperative use was not described. Similarly, the authors note that there were no differences in fluid administration between groups, but data on urine output were not provided. We suspect that greater use of dobutamine was required to offset intense vasoconstriction from the high dosage of norepinephrine.

Third, the unequal dosing regimens for vasopressin and norepinephrine had potential to unmask the clinical care teams to treatment allocation. In our experience, initiating norepinephrine at 10 μg/min causes a more dramatic rise in blood pressure than vasopressin at 0.01 U/min. Differences between treatment groups in duration and alternative pressor/inotrope usage would also have been noticeable to clinicians. Successful prediction of treatment allocation by clinicians could have introduced bias in the observed outcomes.

Fourth, the overall complication rates reported in this study are much higher than expected. With a baseline EuroSCORE of 5, one might expect a mortality of 3 to 5% instead of the 15% rate observed.[5] Similarly, the 60 to 80% incidence of atrial fibrillation is much higher than the 26 to 32% rate reported in other studies.[6,7] These outcome differences suggest a systematic difference in care that limits generalizability of findings.

VANCS investigators conclude that vasopressin causes lesser kidney injury and atrial fibrillation and should be considered for first-line treatment of vasoplegia after cardiopulmonary bypass. We caution against generalizing these results across centers, and bias against specific drug classes. Vasopressin and norepinephrine have distinct pharmacologic properties associated with benefits and risks. Given the fact that hypotension after cardiopulmonary bypass can be caused by a number of different pathologic processes, including ventricular dysfunction, hypovolemia, and vasodilation, it remains unclear which pressor(s) and dose provide optimal outcome for treatment of shock after cardiopulmonary bypass, or if a single regimen can be applied with equal effectiveness to all patients.

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Competing Interests

The authors declare no competing interests.

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In Reply:

Drs. Fan and Faraday write with concerns about the Vasopressin and Cardiac Surgery Trial[1] and my editorial[2]; I agree with some, but not all, of their points. My first point of agreement is the criticism that clinical treatment was not protocolized; however, in most randomized controlled trials, nonrandomized care is most often not protocolized for simple logistical reasons. The point is that nonprotocolized care was used in both masked arms of the Vasopressin and Cardiac Surgery Trial. Greater use of dobutamine in the norepinephrine group in the Vasopressin and Cardiac Surgery Trial could have been because vasopressin had less negative inotropic effects than norepinephrine, as vasopressin has some vasodilation action due to release of nitric oxide.[3,4]

Another point of agreement is Drs. Fan and Faraday's "caution against generalizing these results across centers and to bias against specific drugs classes." Indeed, I stated: "in settings such as the *study hospital* [my italics for emphasis herein], vasopressin infusion for treatment of vasodilatory shock after cardiac surgery may improve some clinically important outcomes."[2] I also stand by my recommendation that "this trial deserves replication in *other multicenter healthcare settings* [my italics for emphasis herein] to create confidence about generalizability."

Drs. Fan and Faraday state that in the Vasopressin and Cardiac Surgery Trial masked infusion doses of vasopressin and norepinephrine were not equivalent, and that norepinephrine doses (10 to 60 μg/min) were about five times higher than those used in their center (a citation or a table of their actual data would be helpful here). They state that in the Vasopressin and Septic Shock Trial[5] norepinephrine doses were 5 to 15 μg/min, but that is not correct. Supplemental Digital Content (http://links.lww.com/ALN/B337) shows mean doses of 15 to 17 and upper SD of 27 μg/min in the Vasopressin and Septic Shock Trial. The literature regarding norepinephrine doses in vasodilatory shock after cardiovascular surgery helps somewhat here[6–9]: norepinephrine doses were up to (upper SD) 40 μg/min,[6] 10 μg/min,[8] and 30 μg/min,[9] suggesting that norepinephrine doses may have been lower in previous studies of vasopressin *versus* norepinephrine in cardiovascular surgery than in the Vasopressin and Cardiac Surgery Trial.

My points of disagreement include unequal dosing regimens for vasopressin and norepinephrine having the potential to unmask the clinical care and that "differences between treatment groups in duration and alternative pressor/inotrope usage would also be noticeable to clinicians." I am not sure how one can ever prove that masked treatment arms were effectively unmasked in blinded, randomized controlled trials. Drs. Fan and Faraday assume that the vasoconstriction and increased blood pressure effects would have been greater in the norepinephrine arm; however, they do not mention that in both arms, patients are also randomly improving or deteriorating, so mean arterial pressure is changing independent of vasopressin or norepinephrine effects, therefore making efforts to unmask a risky business at best.

Another point of partial disagreement is in the assertion that "overall complication rates reported in this study are much higher than expected." I am not entirely sure this is true because one has to review such rates in the remarkably few reported cohorts and randomized controlled trials of patients with vasodilatory shock after cardiovascular surgery. The 60 to 80% incidence of atrial fibrillation in the Vasopressin and Cardiac Surgery Trial does seem high and may indicate that patients in the Vasopressin and Cardiac Surgery Trial were sicker than those in other vasodilatory cohorts and randomized controlled trials. I also previously stated that "mortality rates were high—16 and 15% at 28 days and 17 and 16% at 90 days (norepinephrine *vs.* vasopressin)—in the Vasopressin and Cardiac Surgery Trial; remarkably, mortality rates were not reported in previous smaller trials of vasopressin *versus* norepinephrine for vasodilatory shock after cardiac surgery."[6,8–10]

To conclude, I recommend that Drs. Fan, Faraday, and others: (1) create multicenter registries of vasodilatory shock after cardiovascular surgery to understand risks and outcomes of same; (2) do proof-of-principle randomized controlled trials of novel compounds, such as the selective V1a agonist selepressin[11,12] and angiotensin 2[13]; and (3) do large, pivotal, randomized controlled trials of vasopressin *versus* norepinephrine in North America to see whether the Vasopressin and Cardiac Surgery Trial results are applicable in this setting.

Competing Interests

Dr. Russell reports patents owned by the University of British Columbia (Vancouver, British Columbia, Canada) that are related to PCSK9 inhibitor(s) and sepsis, and related to the use of vasopressin in septic shock. He is an inventor on these patents. Dr. Russell is a founder, director, and shareholder in Cyon Therapeutics, Inc. (Vancouver, British Columbia, Canada; developing a sepsis therapy). He has share options in Leading Biosciences, Inc. (Carlsbad, California), and he is a shareholder in Molecular You Corp. (Vancouver, British Columbia, Canada). Dr. Russell also reports receiving consulting fees from: Cubist Pharmaceuticals (now owned by Merck, New York, New York; formerly was Trius Pharmaceuticals; developing antibiotics); Leading Biosciences (developing a sepsis therapeutic); Ferring Pharmaceuticals (Copenhagen, Denmark; manufactures vasopressin and is developing selepressin); Grifols (Barcelona, Spain; sells albumin); La Jolla Pharmaceuticals (San Diego, California; developing angiotensin II; Dr. Russell chairs the DSMB of a trial of angiotensin II); CytoVale, Inc. (San Francisco, California; developing a