Reviewer
Samuel P. Carmichael II, MD MS

Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: A randomized clinical trial
Lamontagne F, Richards-Belle A, Thomas K, Harrison D, et al. JAMA 2020 Feb 12;323(10);938-949.

Link to article
https://jamanetwork.com/journals/jama/article-abstract/2761427

Context
The 2012 Surviving Sepsis Guidelines advocated consideration of mean arterial pressure (MAP) goals >65mmHg for older, comorbid patients (i.e. atherosclerosis, uncontrolled hypertension). However, meta-analysis from previous trial data suggests that the duration of vasopressor therapy may be associated with mortality in adults ≥65.[1] Thus, the present investigation hypothesizes that decreased exposure to vasopressors in vasodilatory hypotension via permissive hypotension (MAP target 60-65) would result in decreased 90-day mortality.

Methods
- Multicenter, pragmatic, randomized clinical trial conducted in 65 National Health Service intensive care units in the United Kingdom from July 2017 to March 2019
- Inclusion criteria: patients ≥65 years of age or older with vasodilatory hypotension, as determined by the attending physician
    - Patients were randomized 1:1 by clinical research teams via central randomization system within 6 hours of starting vasopressor infusion, targeting either MAP 60-65mmHG or usual care, as determined by the attending physician
        - Fluid resuscitation may have been completed or ongoing
        - Vasopressor was expected to continue for >6 hours
        - Vasopressor choice was determined by attending physician (i.e. norepinephrine (NE), vasopressin, terlipressin, phenylephrine, epinephrine, dopamine and metaraminol)
- Exclusion criteria (copied from eMethods section within Supplementary Online Content)
    - Contraindications to permissive hypotension
        - Vasopressors being used solely as therapy for bleeding, acute ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
        - Ongoing treatment for brain injury or spinal cord injury
        - Death perceived as imminent
        - Previous enrolment to the current “65 trial”
- Endpoint criteria
    - Dose reduction or discontinuation of vasopressor when MAP >65
    - Deviation considered failure to reduce or discontinue vasopressor if MAP >65 for 3 hours
- Statistical evaluation
    - Power calculation: 90% power with estimation of 35% mortality at 90 days in usual care group versus predicted 29% in permissive hypotension group based on prior data[1] (6% absolute risk reduction) = approximately 2600 patients (1300 per group)
    - $P<0.05$ for significance
    - Doses of each vasopressor were converted to NE equivalents

    - Fisher's exact test for binary (categorical) data (i.e. between groups differences and primary outcome)
    - Absolute risk reduction reported with 95% confidence interval
    - T-test or Wilcoxon rank sum tests for non-binary (continuous) data (i.e. duration data)
    - Post hoc linear regression analysis for calculation of odds ratio for primary outcome in subgroups
- Primary outcome was all-cause mortality at 90 days
- Secondary outcomes
    - Mortality at discharge from ICU
    - Mortality at discharge from hospital
    - Duration of survival to longest available follow-up
    - Duration of advanced respiratory and renal support during ICU stay
    - Days alive and free of advanced respiratory support and renal support within first 28 days
    - Duration of ICU and treating acute care hospital stay
    - Cognitive decline assessed using the Informant Questionnaire on Cognitive Decline in the Elderly in survivors at 90 days and 1 year
    - Health related quality of life, assessed using the EuroQoL questionnaire in survivors at 90 days and 1 year

Findings

- N=2600 patients met inclusion criteria from July 2017 to March 2019 in 65 NHS ICU facilities
- Mean age 75
- No differences in measured demographics between groups, excepting greater proportion of patients requiring assistance with daily living in permissive hypotension group
- At time of randomization, no differences in mean or median MAP, NE equivalents or time to randomization (approximately 3h) between groups
- Patients in the permissive hypotension group had a lower exposure to vasopressors compared with those in the usual care group (median duration 33 hours compared with 38 hours (difference, –5.0; 95% CI, –7.8 to –2.2), mean duration, 46.0 hours compared with 55.9 hours (mean difference, –9.9 hours; 95% CI, –14.3 to –5.5), and median total dose (norepinephrine equivalent), 17.7 mg compared with 26.4 mg (difference, –8.7 mg; 95% CI, –12.8 to –4.6 mg)
- At 90 days, there was no significant difference in all-cause mortality (41% [500/1221] permissive hypotension versus 43.8% [544/1242] usual care, absolute risk difference -2.85%, 95% CI, -6.75 to 1.05; P=0.15)
- No other differences were noted in outcome metrics

Commentary

The present investigation is a multicenter, pragmatic, randomized clinical trial among adults ≥65 years of age receiving vasopressors for vasodilatory hypotension in intensive care units throughout the United Kingdom. The strengths of the trial are several-fold: 1) the large sample size represents a diverse group of patients with vasodilatory hypotension and contributes to the applicability of the results 2) the hypothesis is a question commonly encountered by critical care physicians in every-day practice 3) there is potential benefit to both positive and negative results related to the hypothesis. The study was adequately powered to detect the appropriately predicted 6% absolute reduction in mortality at 90 days via decreased vasopressor exposure.

There were also important limitations of the study, as mentioned by the authors. Given the intervention (i.e. MAP targets), blinding of the attending physician was not possible, thus introducing the possibility of bias to "usual care" (i.e. augmenting blood pressures beyond what would have been maintained otherwise). That said, causes of death also were not assessed, such that complications related to MAP augmentation or vasopressor dose may not directly be hypothesized. Interestingly, the permissive hypotension group was not maintained at MAPs between 60-65 mmHg, ranging in Table 2 from 64.5 to 69.8 while receiving vasopressors. This observation illustrates the difficulty with attempts at maintaining physiologic parameters, particularly in large data sets, involving multiple ICUs and employing various pharmacologic agents. As a result, the comparison between the two groups with the primary outcome in mind is somewhat limited. Though this paper ultimately produced negative data (i.e. there was no mortality benefit at 90 days in the permissive hypotension group), perhaps an alternative conclusion might be rendered here, based on subgroup analysis: it may be safe to tolerate a lower (i.e. normal) MAP in the chronically hypertensive or atherosclerotic patient during critical care.

Implications for practice

The present trial includes a large group of patients with multiple types of shock, managed with multiple pharmacologic agents across 65 ICUs, making a take-home message and application to clinical practice difficult to discern. Furthermore, as the test group never truly achieved permissive hypotension (MAP 60-65), it is additionally challenging to make a statement of either safely or benefit about this range. Nonetheless, it does appear that a subgroup analysis in patients ≥65 years of age with cardiovascular comorbidity suggests no additional benefit to artificial pressure augmentation beyond MAP 65mmHg.

References

1. Lamontagne F, Day AG, Meade MO, et al. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med*. 2018;44(1):12-21. doi:10.1007/s00134-017-5016-5