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# Adverse events after prehospital nitroglycerin administration in a nationwide registry analysis

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ABSTRACT

*Objective:* Nitroglycerin (NTG) is a vasodilator used in the prehospital setting with chest pain patients. Potential adverse effects include hypotension, bradycardia or tachycardia, and mental status change. However, it is unclear which factors, if any, are associated with patients having an adverse event after receiving NTG. The objective of this study was to determine demographic and clinical factors associated with adverse events after prehospital NTG administration.

*Methods:* The ESO Data Collaborative (Austin, TX), containing records from 1322 EMS agencies, was queried for 911 encounters where NTG was administered to patients ≥18 years old by EMS. Adverse event outcomes were defined as a new systolic blood pressure (SBP) < 90, heart rate (HR) < 50 or > 120, mean arterial pressure (MAP) < 65, or change in mental status following NTG administration. Descriptive statistics and logistic regression models adjusting for age, sex, race, ethnicity, intravenous (IV) access, and initial vital signs were used to assess for adverse event-related factors.

*Results:* Among 80,760 encounters, the mean age was 61 (IQR 50–72), with 52% males, 71% white race, and 7% Hispanic ethnicity. Adverse events occurred in 7% of encounters. Adverse events were found to be less common among Black patients (OR = 0.74, 95% CI:0.69–0.80). IV access obtained prior to NTG administration was associated with fewer adverse events (OR = 0.92, 95%CI:0.85–0.99). Increasing age (OR = 1.02, 95%CI:1.01–1.02) and HR (OR = 1.03, 95%CI:1.02–1.03) were associated with increased odds of adverse events while SBP (OR = 0.99, 95%CI:0.98–0.99) was inversely associated.

*Conclusions:* Adverse events following prehospital NTG administration were rare, especially in patients with an SBP > 110 and a HR < 100, and less frequent in those with existing IV access. Demographics were not found to be clinically significant.



## 1. Introduction

Nitroglycerin (NTG) is a core medication in the treatment of prehospital patients with chest pain that works by dilating coronary vessels and reducing preload to improve ischemic chest pain [1,2]. Adverse events associated with the administration of sublingual NTG occur in up to 1.3% of patients and include nausea, headache, vomiting, lightheadedness, flushing, palpitations, reflex tachycardia, syncope, hypotension, bradyarrhythmia, and asystole [2-7]. NTG has been historically withheld in hypotensive, bradycardic, and tachycardic patients due to increased concern for adverse events. Although there is no survival benefit to giving NTG, guidelines continue to recommend NTG administration for symptomatic improvement in cardiogenic chest pain and pulmonary edema [ 8-13].

Given these limitations, some have questioned the safety and effectiveness of administering prehospital NTG [2,3,14-16]. Prehospital providers have expressed concern over these potential adverse events may choose to forgo NTG administration, but this may deprive the patient of a potentially therapeutic intervention. Previous studies have examined the risks of NTG administration in tachycardic and hypotensive patients [14], but no study has attempted to identify risk factors based on patient demographics or prior intravenous (IV) access. By defining at-risk populations, prehospital providers may be more comfortable to administer NTG in low-risk populations and to withhold NTG or be better prepared for adverse events in high-risk populations.

The primary objective of this retrospective cross-sectional study was to investigate the patient level characteristics of those who receive NTG in the prehospital setting in an attempt to identify risk factors and populations associated with NTG-induced hypotension, bradycardia, tachycardia, and altered mental status. By identifying these risk factors and populations, prehospital care providers may be able to more

*Abbreviations:* NTG, nitroglycerin; IV, intravenous; EMS, emergency medical service; BLS, basic life support; ALS, advanced life support; EHR, electronic health record; SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; IQR, interquartile range; OR, odds ratio.

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comfortably administer NTG to treat ischemic chest pain and improve patient comfort.

## 2. Methods

### 2.1. Study design and setting

A national retrospective cross-sectional study of patients with chest pain across the United States was performed over a 1-year period (1/2019–1/2020) by querying records from 1322 emergency medical service (EMS) agencies that had agreed to share their de-identified data in the ESO Data Collaborative (ESO Inc., Austin, TX). All agencies, basic life support (BLS) and advanced life support (ALS), that participate in the ESO data collaborative were included. Prehospital providers manually entered data into the ESO electronic health record (EHR) to document the care they provided for each patient. The ESO EHR software facilitates the collection of comprehensive clinical information, including event dispatch data, patient demographic characteristics, clinical presentation and course, intervention and treatment, and outcome at transfer of care. Data elements collected within the ESO database were compliant with the National EMS Information System (NEMSIS) [17]. The institutional review board at Wake Forest University Health Sciences approved this investigation and waived the requirement for informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines helped direct the research and article development processes [18].

### 2.2. Participants

All adult (age ≥18 years) 9–1-1 encounters with a chief complaint or impression of "chest pain" that were given oral or sublingual NTG by EMS personnel were included in the analysis. Encounters without demographic information were excluded. If no vital signs were obtained within 10 min of NTG administration, the encounter was excluded. Encounters requiring advanced airway interventions via positive pressure ventilation prior to NTG administration were excluded. Patients with 1) a systolic blood pressure (SBP) less than 90 mmHg, 2) a mean arterial pressure (MAP) less than 65 mmHg, 3) a heart rate (HR) <50 or >120 beats per minute (bpm), or 4) altered mental status prior to NTG administration were excluded. Interfacility transport patients were excluded. Fig. 1 represents the case-selection flow diagram.

### 2.3. Variables

Adverse events were defined as 1) a SBP less than 90 mmHg, 2) a MAP less than 65 mmHg, 3) a HR <50 or >120 bpm, or 4) a change in mental status from alert using the AVPU scale. These events were required to have occurred within 10 min of NTG administration by an EMS provider.

### 2.4. Statistical methods

Descriptive statistics were used to characterize the sample. Counts and percentages were determined for categorical variables and median and interquartile range (IQR) were determined for continuous variables. Sex, race, ethnicity, and IV access were treated as categorical variables. Race was categorized as White, Black, or Other—self-identified when able, by driver's license, or by the provider. Age, HR, and SBP were treated as continuous variables. The adverse event outcome was treated as categorical. Multivariable logistic regression modeled the effects of age, sex, race, ethnicity, initial vital signs, and IV access on adverse event occurrence. Results are reported as adjusted odds ratios (OR) and are reported with exact 95% confidence intervals (95%CI). An a priori alpha level of 0.05 was determined. Formal power calculations were not performed as the sample size was fixed by the duration of the study period. Given the number of observations and the number of covariates in the model, the risk of the model being overfit was minimal.

## 3. Results

There were 80,760 encounters included in analysis (Tables 1-2). The median age was 61 years (IQR 50–72). The median initial SBP and HR were 86 mmHg (IQR 138–179) and 86 bpm (IQR 74–98). Males accounted for 52% ($n = 41{,}942$) of the sample, white patients accounted for 71% ($n = 55{,}387$), and Hispanic patients accounted for 7% ($n = 5130$). IV access was obtained prior to NTG administration in 84% ($n = 67{,}667$) of the encounters. Adverse events occurred in 7% ($n = 5948$) of encounters (Table 3). Hypotension occurred in 2% ($n = 1533$ and 1725) of encounters, bradycardia or tachycardia in 5% ($n = 3967$), and altered mental status found in 0.2% ($n = 132$). Logistic regression demonstrated that adverse events following NTG administration were less common among Black (OR = 0.74, 95%CI:0.69–0.80) patients and in those with established IV access (OR = 0.92, 95% CI:0.85–0.99) (Table 4). Increasing age (OR = 1.02, 95%CI:1.01–1.02) and HR (OR = 1.03, 95%CI:1.02–1.03) were directly associated with adverse events while higher SBP (OR = 0.99, 95%CI:0.98–0.99) was inversely associated.

Subgroup analysis of the adverse event population (Fig. 2) demonstrated that an initial SBP less than 120 mmHg produced 34% of adverse events due to hypotension, with those less than 130 mmHg producing 54%. An initial HR greater than 110 bpm produced 25% of adverse events due to tachycardia, with those greater than 100 bpm producing 48% (Fig. 3). Adverse event likelihood due to hypotension was shown to increase as initial SBP decreased (Fig. 4), with notable increases found within the 100–120 mmHg domain. Adverse event likelihood due to tachycardia was shown to increase as initial HR increased, although this process was gradual and does not demonstrate a notable domain of effect (Fig. 5).

## 4. Discussion

This nationwide retrospective prehospital study demonstrates that adverse events associated with receiving NTG are rare but that they occur more frequently than previously thought, occurring in nearly 7% of encounters. Despite the known adverse effects of NTG, the infrequency of these adverse events should provide reassurance to prehospital providers and EMS medical directors that NTG is safe in the prehospital environment in patients with an SBP >110 and a HR <100.

Our study demonstrated that Black patients have fewer adverse events when compared to other races. The cause of this outcome is unclear and warrants further investigation. Adverse events were shown to increase linearly with age, suggesting that NTG should be cautiously considered in the geriatric population but not contraindicated. Sex and ethnicity were not found to influence rates of adverse events. Prehospital providers should not emphasize demographic data when making clinical decisions regarding NTG administration. While the population size allowed for the discovery of statistical significance with race and age, the magnitude of their influence was not found to be sizeable enough to affect clinical outcomes. NTG should be administered when appropriate, regardless of demographic data.

Initial vital signs demonstrated a significant effect on adverse event occurrence. Higher initial SBP was associated with fewer adverse events, while lower initial SBP was associated with more adverse events. Several studies have demonstrated the hypotensive effects of NTG [2-5,7,14,15]. These hypotensive effects on an already diminished SBP place the patient at an increased risk for hypotensive crisis. A SBP less than 90 mmHg or a MAP less than 65 mmHg have been shown to increase mortality due to end-organ ischemia [19,20]. This study suggests that NTG should be administered with care as the

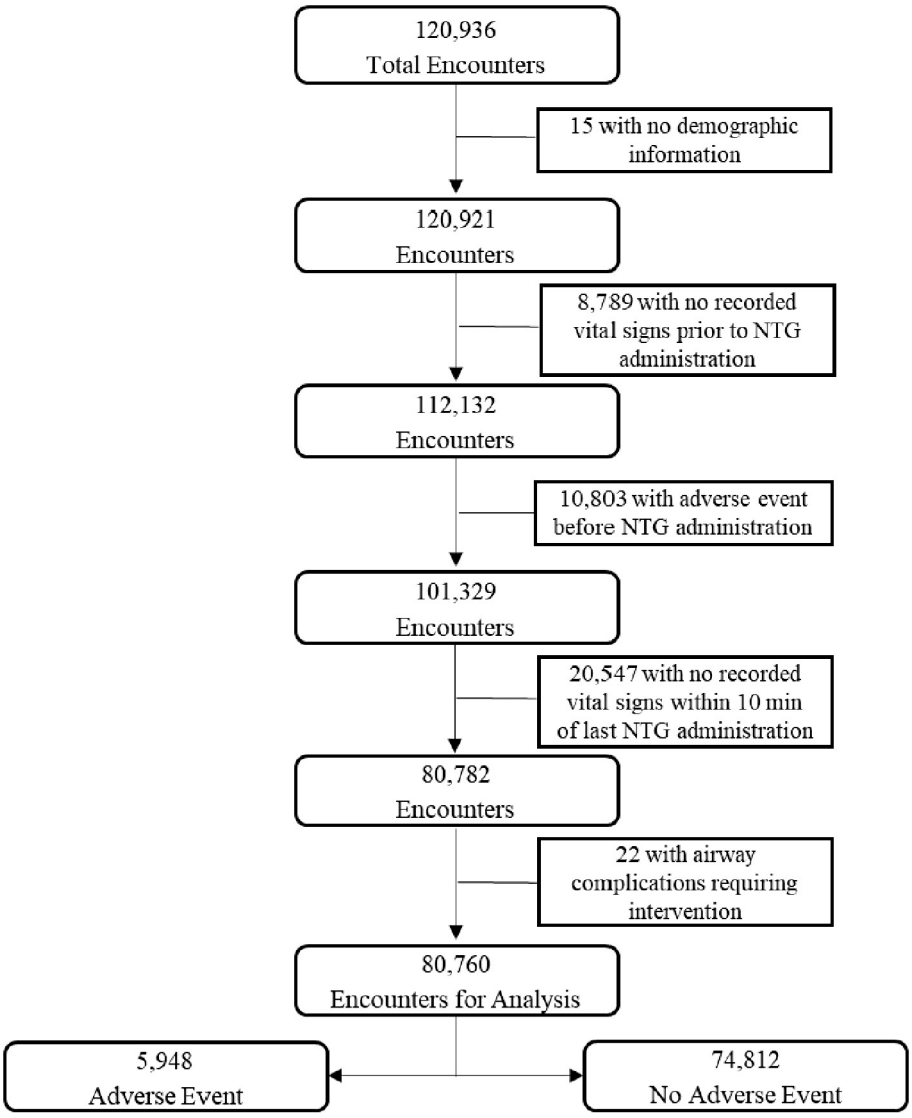


**Fig. 1.** Case-selection flow diagram.

initial SBP approaches 110 mmHg. Further studies should examine the cardiovascular risk-benefit of NTG use in this population. Tachycardia prior to NTG administration was also shown to increase the risk of adverse events, but SBP proved to be more discriminating [14].

**Table 1**
Categorical demographics of encounters with adverse event and no adverse event subgroups

| Characteristic | Adverse n (%) | No adverse n (%) | Total n (%) |
|---|---|---|---|
| Sex | | | 80,336 (99) |
| Male | 3132 (53) | 38,810 (52) | 41,942 (52) |
| Female | 2782 (47) | 35,612 (48) | 38,394 (48) |
| Race | | | 78,356 (97) |
| White | 4448 (77) | 50,939 (70) | 55,387 (71) |
| Black | 965 (17) | 16,696 (23) | 17,661 (22) |
| Other | 369 (6) | 4939 (7) | 5308 (7) |
| Ethnicity | | | 69,493 (86) |
| Hispanic | 348 (7) | 4782 (7) | 5130 (7) |
| Not Hispanic | 4807 (93) | 59,556 (93) | 64,363 (93) |
| Intravenous access | | | 80,760 (100) |
| Yes | 4957 (83) | 62,710 (84) | 67,667 (84) |
| No | 991 (17) | 12,102 (16) | 13,093 (16) |

Adverse events were less common in patients who had IV access prior to NTG administration. While the presence of IV access was unlikely to prevent the event from occurring, the ability to provide IV fluids likely reduced the number of adverse events reported by EMS personnel. This could suggest that NTG administration leads to rates of adverse events higher than suggested by this study. IV access is either required or highly recommended prior to NTG administration in most prehospital ALS systems. This allows for emergent fluid challenge following hypotension that is most often therapeutic [21-23], but not always possible. Many EMS protocols also allow BLS providers to

**Table 2**
Continuous demographics of encounters with adverse event and no adverse event subgroups

| Characteristic | Adverse median (IQR) | No adverse median (IQR) | Total median (IQR) |
|---|---|---|---|
| Age (y) | 63 (52–75) | 61 (50–72) | 61 (50–72) |
| Initial sbp (mmHg) | 146 (127–168) | 156 (138–179) | 156 (138–179) |
| Initial heart rate (bpm) | 93 (77–107) | 85 (74–97) | 86 (74–98) |

Abbreviations: interquartile range (IQR), systolic blood pressure (sbp), millimeters of mercury (mmHg), beats per minute (bpm).

**Table 3**
Number of adverse events by causal criteria type

| Criteria | n (% [1]) |
|---|---|
| Systolic blood pressure (<90 mmHg) | 1533 (2) |
| Heart rate (<50 bpm or >120 bpm) | 3967 (5) |
| MAP (<65 mmHg) | 1725 (2) |
| Mental status (altered[2]) | 132 (0.2) |
| Total[3] | 5984 (7) |

1. Percent of encounters with specific adverse criteria.
2. Includes responsive to voice, pain, and unresponsive.
3. Excludes encounters meeting multiple criteria.

Abbreviations: millimeters of mercury (mmHg), bpm (beats per minute), mean arterial pressure (MAP).

**Table 4**
Logistic regression for the impact of demographics on adverse events with nitroglycerin administration

| Variable | OR | 95% CI |
|---|---|---|
| Sex (female vs male) | 0.98 | 0.92–1.03 |
| Race (black vs white) | 0.74 | 0.69–0.80 |
| Race (other vs white) | 0.98 | 0.83–1.15 |
| Ethnicity (Hispanic vs not Hispanic) | 0.95 | 0.82–1.10 |
| IV (access vs no access) | 0.92 | 0.85–0.99 |
| Systolic blood pressure | 0.99 | 0.98–0.99 |
| Heart rate | 1.03 | 1.02–1.03 |
| Age in years | 1.02 | 1.01–1.02 |

Abbreviations: odds ratio (OR), confidence interval (CI).

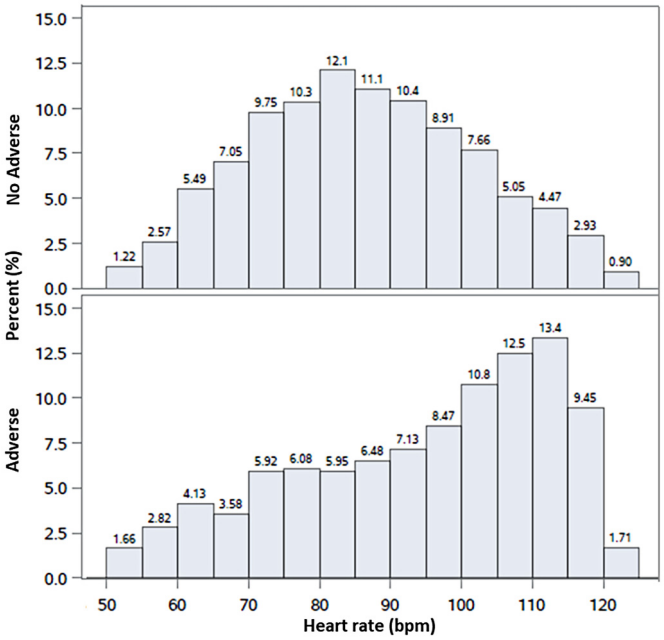


**Fig. 3.** Histogram of the initial heart rate of adverse and no adverse event encounters due to bradycardia or tachycardia.

administer NTG [24]. If an adverse event occurred in this setting, the prehospital provider would be unable to address the deterioration of the patient within their scope of practice. IV access should be encouraged when available to allow for treatment should an adverse event occur.

The risk of adverse events following NTG deserve consideration prior to medication administration, but these risks must be weighed against potential benefit. While the survival benefit of NTG is controversial, prehospital studies have suggested a symptomatic benefit of NTG in patients with chest pain [8-13]. This study demonstrated that adverse events following NTG administration were rare. NTG administration should be recommended when allowed by protocol to reduce chest pain [25], and patient demographics should not deter from its use.

## 5. Limitations

This cross-sectional study retrospectively analyzed a single EHR provider database of patients from EMS systems that have agreed to share their de-identified data for the purposes of research and benchmarking. The data in this convenience sample were heavily focused in the southern US and may not be generalizable to all patients with chest pain that are treated by EMS. Manual data input by prehospital providers could lead

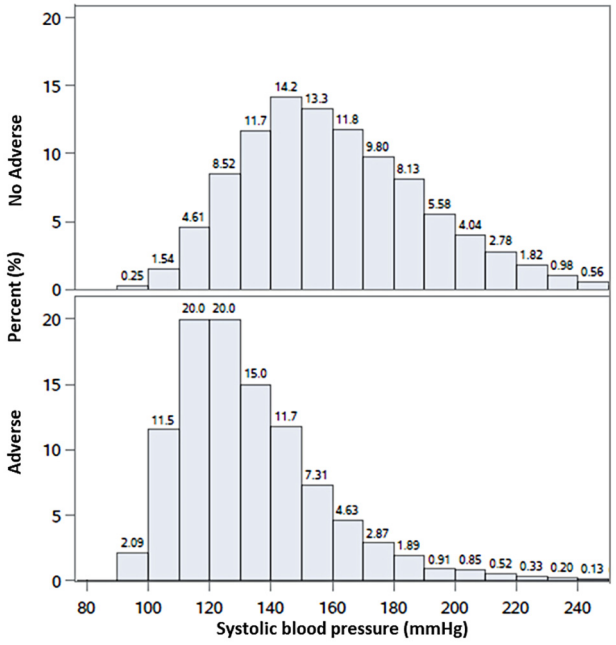


**Fig. 2.** Histogram of the initial systolic blood pressure of adverse and no adverse event encounters due to hypotension.

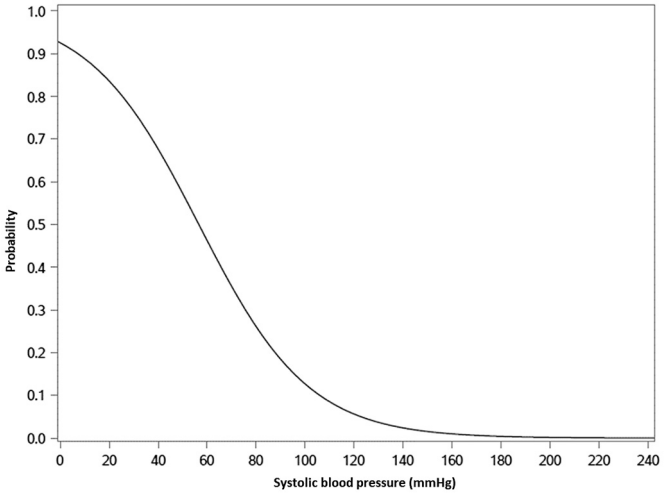


**Fig. 4.** Effects of initial systolic blood pressure on probability of adverse event due to hypotension.

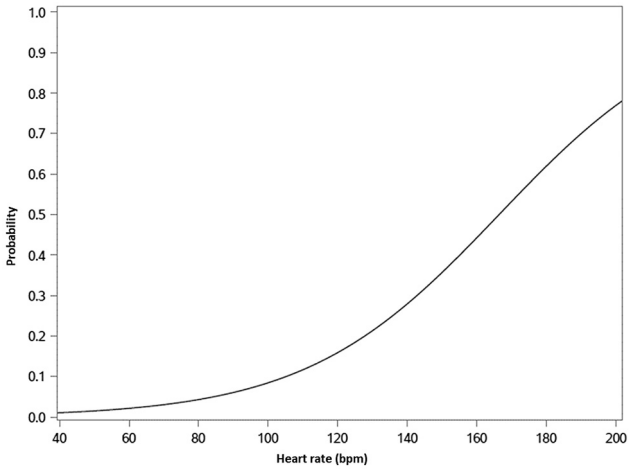


**Fig. 5.** Effects of initial heart rate on probability of adverse event due to tachycardia.

to unintended data collection errors. Potential bias of prehospital providers submitting data could also lead to errors in adverse event rates. Characteristic of prehospital research, the EMS dataset is limited and unable to be linked with outcomes data, which prevents analysis of long-term mortality following adverse events associated with NTG use. Adverse event occurrence required definition by prehospital presentation only. Patient allergies to NTG and home medications like phosphodiesterase inhibitors were not examined. Patients who self-administered NTG prior to EMS arrival were included, assuming NTG was also administered by EMS personnel during the encounter. Due to the unknown time of self-administration, residual effects of the previous NTG could interact with the assessed dose by EMS. This error would be limited by the exclusion of patients already experiencing an adverse event prior to NTG administration by EMS. Medication interactions were not addressed in this study. Due to the inevitability of hypotensive, bradycardic, or tachycardic patients requiring additional medications, this study was not designed to assess these interactions. The number of NTG doses administered in each encounter was tracked but not ultimately included in the analysis of this study. Providers withheld further NTG administrations to patients with adverse events and continued to administer to those that did not, inappropriately suggesting that increased NTG administrations led to lower rates of adverse events. Future studies should analyze the dose-dependent relationship between NTG and adverse events.

## 6. Conclusion

This large national prehospital study demonstrated that adverse events following NTG administration were more common than previously thought but rare in patients with an SBP > 110 and a HR < 100. Demographics were not found to be clinically significant and should not deter EMS personnel from administering NTG. IV access should be established prior to NTG administration when available to treat adverse events should they occur.

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## Meetings

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## Disclosures

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## Author contributions

Study concept and design: LMP, LML.
Acquisition of the data: JPS, NPA.
Analysis of the data: LMP, JPS.
Drafting of the manuscript: LMP.
Critical revision of the manuscript: NPA, LML, JPS.
Approval of final manuscript: LMP, NPA, LML, JPS.

## Credit author statement

**Lucas Popp**: Conceptualization, Methodology, Visualization, Writing – Original Draft; **Luke Lowell**: Conceptualization, Writing – Review & Editing; **Nicklaus Ashburn**: Supervision, Writing – Review & Editing; **Jason Stopyra**: Supervision, Writing – Review & Editing.

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