Adverse events from nitrate administration during right ventricular myocardial infarction: a systematic review and meta-analysis

Matt Wilkinson-Stokes 1,2, Jason Betson, 2 Simon Sawyer 3

ABSTRACT

Background The current guidelines of the American Heart Association (AHA) and European Society of Cardiology (ESC) recommend that when right ventricular myocardial infarction (RVMI) is present patients are not administered nitrates, due to the risk that decreasing preload in the setting of already compromised right ventricular ejection fraction may reduce cardiac output and precipitate hypotension. The cohort study (n=40) underlying this recommendation was recently challenged by new studies suitable for meta-analysis (cumulatively, n=1050), suggesting that this topic merits systematic review.

Methods The protocol was registered on PROSPERO and published in Evidence Synthesis. Six databases were systematically searched in May 2022: PubMed, Embase, MEDLINE Complete, Cochrane CENTRAL Register, CINAHL and Google Scholar. Two investigators independently assessed for quality and bias and extracted data using Joanna Briggs Institute tools and methods. Risk ratios and 95% CIs were calculated, and meta-analysis performed using the random effects inverse variance method.

Results Five studies (n=1113) were suitable. Outcomes included haemodynamics, GCS, syncope, arrest and death. Arrest and death did not occur in the RVMI group. Meta-analysis was possible for sublingual nitroglycerin 400 μg (2 studies, n=1050) and found no statistically significant difference in relative risk to combined inferior and RVMI at 1.31 (95% CI 0.81 to 2.12, p=0.27), with an absolute effect of 3 additional adverse events per 100 treatments. Results remained robust under sensitivity analysis.

Conclusions This review suggests that the AHA and ESC contraindications are not supported by evidence. Key limitations include all studies having concomitant inferior and RVMI, not evaluating beneficial effects and very low certainty of evidence. As adverse events are transient and easily managed, nitrates are a reasonable treatment modality to consider during RVMI on current evidence.

PROSPERO registration number CRD42020172839.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Two leading guidelines on myocardial infarction (American Heart Association and European Society of Cardiology) recommend avoiding nitrates when right ventricular myocardial infarction (RVMI) is present, due to the belief that reducing preload may precipitate hypotension.

⇒ This is based on a single 1989 study of 40 patients, recently challenged by more rigorous cohort studies of 1050 patients that found no statistically significant difference.

WHAT THIS STUDY ADDS

⇒ Meta-analysis did find a non-statistically significant difference in adverse event rates from nitrates based on the cardiac region infarcting.

⇒ Adverse events were noted to be minor and transient, suggesting nitrates are a reasonable treatment modality to consider in this cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ Contraindicating nitrates during concomitant inferior and RVMI is no longer supported by evidence.

INTRODUCTION

Withholding nitrates in the setting of right ventricular myocardial infarction (RVMI) is currently recommended by the American Heart Association (AHA’s 2015 guidelines (with this recommendation last revised in 2010) and the 2017 European Society of Cardiology (ESC) guidelines. 1 2 This is due to the belief that decreased right preload will reduce left end diastolic volume and lead to clinically impactful hypotension, a belief that primarily stemmed from a 1989 study of 40 patients by Ferguson et al. 3 If the references of the current AHA guidelines are interrogated, they all rely either directly on Ferguson et al, 3 on papers that recommend giving nitrates, 4–6 on papers that do not discuss nitrates and RVMI 7–10 or on evidence limited by inadequate reporting 11; the ESC guidelines provide no references (for more detail, see online supplemental appendix X). 12 13

For all other infarctions, it is commonly accepted that adverse events from nitrates—the primary of which is hypotension—are transitory and respond favourably to fluid challenge, and therefore nitrates remain widely recommended as a first-line analgesic for angina. 1 2 Over the past 5 years, larger cohort studies, cumulatively including 1050 patients, concluded that nitrate administration to combined inferior and RVMI was not associated with a different rate of adverse events, suggesting that this topic merits systematic review. 12 13
Systematic review

Review question
Is nitrate administration to patients with RVMI associated with increased adverse events compared with nitrate administration to patients with myocardial infarctions only in other regions?

Inclusion criteria
Population
The population included patients diagnosed with an acute myocardial infarction and where a subset of the sample had RVMI. One modification to the population criteria listed in the protocol has been made to exclude coronary vasospasm: as nitrates are a primary treatment in arresting coronary vasospasm, inclusion would inappropriately skew the results towards a finding of increased nitrate safety. These excluded articles have been identified in online supplemental appendices II–IV.

Exposure of interest
The exposure was the administration of nitrates, via any route and dose.

Outcomes
The outcomes included all forms of adverse events reported in literature.

Types of studies
This review includes experimental and analytical observational study designs. This review only includes studies published in English, with no other limiters.

METHODS
This review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology. A preliminary search of PROSPERO, Medline, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted and no current systematic reviews on the topic were identified. Public input was encouraged by publishing the title and protocol with PROSPERO (CRD42020172839) and in Evidence Synthesis. Patients were not involved in the production of this research.

The methods are as outlined in the protocol, with three modifications. First, the exclusion of coronary vasospasm from the population, with reasoning discussed under ‘Inclusion criteria’ section. Second, compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, resulting in minor variations from the protocol (which referenced PRISMA 2009). Finally, the inclusion of meta-analysis, which became feasible after requesting additional information from authors.

Search strategy
As per the JBI recommended method, a three-step search strategy was used, detailed in online supplemental appendix I. First, a preliminary search of PubMed and Embase was undertaken to develop a comprehensive list of search terms. Second, this full string was searched on 5 May 2022 on six databases: PubMed (PubMed, 1946–present), Embase (Ovid, 1883–present), Medline Complete (Ovid, 1946–present), Cochrane CENTRAL Register (Cochrane Library), CINAHL (EBSCO, 1961–present) and Google Scholar (Google). No date limiters were applied, non-human studies were considered for inclusion and grey literature was considered for inclusion.

A reference list was generated using Mendeley V.1.19.8 (Mendeley, Elsevier, The Netherlands) and duplicates removed. Two reviewers independently screened the articles retrieved against the inclusion criteria, initially by title and abstract, and then by full text. Disagreement was resolved by a third reviewer, and in one case confirmed via external consultation. Third, all articles that progressed to critical appraisal had their reference lists screened for any additionally potentially relevant studies. In addition, the reference lists of articles excluded due to observational descriptive methodology were screened, as it was considered likely that case reports and case series, although unable to provide a rate of adverse events, may contain useful literature. The results of the search are reported in online supplemental appendices I–IV.

Assessment of methodological quality
Remaining studies underwent quality assessment using the standard JBI appraisal tools. As outlined in the protocol, a simple indicator of quality was used. Studies that met 100% of criteria were considered of high quality; studies that met 75%–99% of criteria were considered of moderate quality; studies that met <75% of criteria were rated as being of low quality and excluded from primary meta-analysis to ensure the synthesised result is of high quality. All studies, regardless of quality, were intended for inclusion in secondary meta-analysis. The results of quality assessment are presented in online supplemental appendices V and VI. The risk of selection bias, information bias and publication bias were directly addressed for each included study, with the results presented in online supplemental appendix VIII.

Data extraction
Data extraction was performed using the JBI data extraction tools by two independent reviewers. Data extracted included, as a minimum, information on the article, population, exposure of interest and outcomes. Studies reporting beneficial outcomes have been categorised as showing ‘no difference’ in the rates of adverse events. Data extraction results are summarised in online supplemental appendix VIII.

Data synthesis
Extracted quantitative data of homogenous interventions were pooled for meta-analysis in JBI SUMARI. This was only possible for the dichotomous adverse event data regarding nitroglycerin 400 μg sublingual, due to a single study each of other interventions being returned. Heterogeneity was assessed using the standard $\chi^2$ and I$^2$ tests; as these tests are unavoidably limited by the low number of included studies, they were interpreted cautiously. The standard $\chi^2$ test was assessed using a p value of 10%, and the I$^2$ test was interpreted using the 0%–40%, 30%–60%, 50%–90%, 75%–100% method. Due to differences in geography, demographics and methods across studies, meta-analysis was performed using the random effects model, and therefore the DerSimonian and Laird inverse variance method used. Relative risk, absolute risk and their 95% CIs were calculated, and additionally presented as a forest plot.

As the current standard practice of using a significance level of 5% is essentially arbitrary and risks a loss of information by reducing results to a dichotomous significant or not significant conclusion, the results are presented as CIs. To limit the possibility of a type 1 error occurring, subgroup analyses was
not performed. Sensitivity analysis was conducted using JBI SUMARI. Due to the low number of studies, neither the Beggs nor Egger tests were used to assess for publication bias. Pooling of data was not possible for three included studies, each of which had a unique intervention; the findings of these three studies are presented in narrative form. MW-S had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Assessing certainty in the findings
The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system for evaluating the certainty of evidence was followed. A summary of findings table was created using GRADEPro Guideline Development Tool (accessed May 2022) (McMaster University, Ontario, Canada) at the outcome level.

RESULTS
Study inclusion
The results of the search are presented in a PRISMA flow diagram and reported in full in online supplemental appendices I–IV. Three articles were unable to be retrieved by professional library technicians. Reasons for exclusion for articles undergoing full-text review are provided in online supplemental appendices III and IV.

Methodological quality
Overall, methodological quality was moderate, with four studies achieving a moderate score, one achieving a high score and two achieving a low score (and subsequently being excluded from synthesis as per the protocol). Results and reasoning are provided in online supplemental appendix V and VI.

Characteristics of included studies
There were five studies that met both inclusion criteria and that were subsequently assessed to be of suitable quality under JBI tools. A summary of the characteristics of included studies is provided in table 1.

Review findings
The findings of included studies are summarised in table 2.

Meta-analysis was appropriate for the two studies using nitroglycerin 400 μg as their intervention. It is reasonable to expect that pooling of studies with other routes of administration, drug formulations or dosages would have different adverse events, and consequently confound the synthesis; therefore, these were not included. A secondary meta-analysis of low-quality studies was not performed as the two studies excluded for low quality both contain insufficient information for pooling. Heterogeneity testing of McConnell et al and Robichaud et al found a $\chi^2$ of 39% and $I^2$ of 0%, supported by a forest plot with good visual overlap (figure 1). The synthesised results had a statistically insignificant effect, with all CIs crossing the null effect line. Arrest or death did not occur.

Sensitivity analysis performed by testing the results of Ferguson et al was included; despite no information on the route or dosage, as this study is the basis of current AHA and ESC international guidelines, we considered it important to determine how much it impacts results. Sensitivity analysis was also conducted using the fixed effects model.

In all cases, the 95% CI crossed the null effect line, and no statistically significant difference in outcomes was found. A summary of sensitivity analysis is provided in table 3, with forest plots provided in online supplemental appendix IX.

Nitroglycerin was administered by unknown dose via sublingual, oral, transdermal and intravenous routes in one small paper (n=40). The risk ratio of adverse events from administration of nitrates during combined inferior and RVMI in this study is 4.06 (95% CI 1.83 to 8.98), and this paper is the basis for current guidelines. However, practical application of this study is limited by no information on dosage and multiple routes of administration. Additionally, when included in meta-analysis, the results were statistically insignificant.

A pilot study of inhaled nitric oxide 80 ppm at 30 L/m (n=13) recorded no adverse events. A second pilot study of nitroprusside infusion found a dosage of 0.4–2.1 μg/kg/min (mean of 1.2 μg/kg/min) was required to decrease in mean arterial pressure

<table>
<thead>
<tr>
<th>Year</th>
<th>First author</th>
<th>Country</th>
<th>Setting</th>
<th>Design</th>
<th>RVMl (AE/total)</th>
<th>All other MIs (AE/total)</th>
<th>Demographics</th>
<th>Intervention</th>
<th>Outcomes measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>McConnell</td>
<td>UK</td>
<td>Prehospital</td>
<td>Cohort</td>
<td>11/19</td>
<td>10/27</td>
<td>Mean age 67 (SD 14)</td>
<td>GTN, SL 400 μg, provided every 5min if indicated to a maximum of 6 doses</td>
<td>SBP &lt;100 mm Hg or drop &gt;1/3, HR &lt;60 bpm, GCS drop of 2+, syncope, arrest, death</td>
</tr>
<tr>
<td>2016</td>
<td>Robichaud</td>
<td>Canada</td>
<td>Prehospital and ED</td>
<td>Cohort</td>
<td>7/86</td>
<td>73/918</td>
<td>Mean age 64 (SD 15)</td>
<td>GTN, SL 400 μg, provided while indicated with no maximum dose</td>
<td>SBP &lt;90 or drop of &gt;30 mm Hg</td>
</tr>
<tr>
<td>2004</td>
<td>Inglessis</td>
<td>USA</td>
<td>In-hospital</td>
<td>Before-after</td>
<td>0/13</td>
<td>-/-</td>
<td>Mean age 65 (SD 3)</td>
<td>NO, Inhaled 80 ppm</td>
<td>MAP, PVR, PAP, RAP, PCWP, HR, CI, SVI, SVR</td>
</tr>
<tr>
<td>1989</td>
<td>Ferguson</td>
<td>USA</td>
<td>In-hospital</td>
<td>Cohort</td>
<td>15/17</td>
<td>5/23</td>
<td>Mean age 60 (SD 11)</td>
<td>GTN, POS/LTDIV, dosage unknown</td>
<td>SBP drop &gt;30 mm Hg</td>
</tr>
<tr>
<td>1985</td>
<td>Dell’Italia</td>
<td>USA</td>
<td>In-hospital</td>
<td>Before-after</td>
<td>0/10</td>
<td>-/-</td>
<td>Mean age 55 (SD unknown)</td>
<td>Nitroprusside, infusion 1.2 μg/kg/min mean, titrated for a 10% reduction in MAP</td>
<td>HR, RAP, PCWP, CI, SVR, SV, RVPP, LVEF</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, cardiac index; GTN, nitroglycerin; IV, intravenous; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NO, nitric oxide; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PO, per oral; RAP, right atrial pressure; RVFP, right ventricular filling pressure; RVMI, right ventricular myocardial infarction; SBP, systolic BP; SL, sublingual; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; TD, transdermal.


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by 10%. Several haemodynamic benefits were noted, with the sole complication being a negligible increase in heart rate (72±12 to 75±12 bpm).5–20

## DISCUSSION

This systematic review provides low certainty evidence that there is no statistically significant difference in the rate of adverse events when nitrates are administered to RVMI compared with other cardiac regions. Hypotension is the primary adverse event reported. As nitrates have a serum half-life of 1–4 min,21 hypotension is likely to be transient in nature—this was explicitly stated to be the case in five articles.11 21–24 The studies adopting stricter definitions of hypotension (eg, study by McConnel et al (<90 mm Hg) results and Ferguson —the study finding the highest relative risk of adverse events, although still not reaching statistical significance—had a larger contribution of weighting.13 McConnel et al also conducted a study on inferior+other MI and inferior only MI, finding no statistically significant difference.12 13 It would be reasonable to expect a higher rate of adverse events as the penumbra increases; this comparison may make RVMI appear unsafe, whereas the increased risk may be instead due to increased area of infarction (regardless of RVMI being the additional region involved). This theory is supported by the results of Robichaud et al, where isolated inferior infarction was the safest at 6.10% and the rate of adverse events in concomitant inferior and RVMI was actually lower than the rate in concomitant inferior and other myocardial infarctions at 8.14% compared with 8.40%, respectively.12

Second, McConnell et al—the study finding the highest relative risk of adverse events, although still not reaching statistical significance—had a larger contribution of weighting.3 23 McConnell et al also conducted a study on inferior+other MI and inferior only MI, finding no statistically significant difference.12 13 It would be reasonable to expect a higher rate of adverse events as the penumbra increases; this comparison may make RVMI appear unsafe, whereas the increased risk may be instead due to increased area of infarction (regardless of RVMI being the additional region involved). This theory is supported by the results of Robichaud et al, where isolated inferior infarction was the safest at 6.10% and the rate of adverse events in concomitant inferior and RVMI was actually lower than the rate in concomitant inferior and other myocardial infarctions at 8.14% compared with 8.40%, respectively.12

There is a sharp difference in findings that cannot be easily reconciled between the meta-analysed 400 µg sublingual nitroglycerin results and Ferguson et al (nitroglycerin by unknown dosage and multiple routes). There are several potential

<table>
<thead>
<tr>
<th>Year</th>
<th>Region of MI</th>
<th>McConnell 2017</th>
<th>Robichaud 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Inferior</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>2016</td>
<td>Inferior</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 2 Results of included studies intervention groups

<table>
<thead>
<tr>
<th>First author</th>
<th>Sample</th>
<th>Region of MI</th>
<th>AEs</th>
<th>No AEs</th>
<th>Rate of AEs (%)</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>McConnell</td>
<td>RVMI+inferior</td>
<td>11</td>
<td>8</td>
<td>57.89</td>
<td>400 µg SL GTN is more likely to result in AEs when given to inferior MI with RVMI than without, however this difference did not reach statistical significance (RR 1.56, 95% CI 0.84 to 2.92, p value 0.16)</td>
<td></td>
</tr>
<tr>
<td>McConnell</td>
<td>Inferior</td>
<td>10</td>
<td>17</td>
<td>37.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robichaud</td>
<td>Inferior+other</td>
<td>45</td>
<td>491</td>
<td>8.40</td>
<td>400 µg SL GTN is equally likely to result in AEs when given to inferior+other MI or other MI than to inferior+RVMI, and less likely during inferior only MI (RR 1.02, 95% CI 0.49 to 2.15, p value 0.95)</td>
<td></td>
</tr>
<tr>
<td>Robichaud</td>
<td>Other</td>
<td>18</td>
<td>200</td>
<td>8.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robichaud</td>
<td>RVMI+inferior</td>
<td>7</td>
<td>79</td>
<td>8.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robichaud</td>
<td>Inferior</td>
<td>10</td>
<td>154</td>
<td>6.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inglessis</td>
<td>RVMI+inferior</td>
<td>0</td>
<td>13</td>
<td>0.00</td>
<td>80 ppm inhaled NO does not lead to AEs during RVMI+inferior MI</td>
<td></td>
</tr>
<tr>
<td>Ferguson</td>
<td>RVMI+inferior</td>
<td>15</td>
<td>2</td>
<td>88.24</td>
<td>An unknown dose and route of GTN is four times as likely to result in AEs when given to inferior+RVMI than inferior only MI (RR 4.06, 95% CI 1.43 to 11.53, p value 0.00)</td>
<td></td>
</tr>
<tr>
<td>Ferguson</td>
<td>Inferior</td>
<td>5</td>
<td>18</td>
<td>21.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dell'Italia</td>
<td>RVMI+inferior</td>
<td>0</td>
<td>10</td>
<td>0.00</td>
<td>1.2 µg/kg/min infused nitroprusside does not lead to AEs during RVMI+inferior MI</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse events; GTN, glyceryl trinitrate; MI, myocardial infarction; NO, nitric oxide; Other, all myocardial regions and arteries other than the right ventricle or right coronary artery; RVMI, right ventricular myocardial infarction; SL, sublingual.

Two factors mean the synthesised result for nitroglycerin 400 µg sublingual may be overstating the actual risk. First, McConnell et al compared joint inferior and RVMI with isolated inferior infarction. It would be reasonable to expect a higher rate of adverse events as the penumbra increases; this comparison may make RVMI appear unsafe, whereas the increased risk may be instead due to increased area of infarction (regardless of RVMI being the additional region involved). This theory is supported by the results of Robichaud et al, where isolated inferior infarction was the safest at 6.10% and the rate of adverse events in concomitant inferior and RVMI was actually lower than the rate in concomitant inferior and other myocardial infarctions at 8.14% compared with 8.40%, respectively. Second, McConnell et al—the study finding the highest relative risk of adverse events, although still not reaching statistical significance—had a larger contribution of weighting. McConnell et al is the study with the smallest sample size (the RVMI group being the additional region involved). This theory is supported by the results of Robichaud et al, where isolated inferior infarction was the safest at 6.10% and the rate of adverse events in concomitant inferior and RVMI was actually lower than the rate in concomitant inferior and other myocardial infarctions at 8.14% compared with 8.40%, respectively. There is a sharp difference in findings that cannot be easily reconciled between the meta-analysed 400 µg sublingual nitroglycerin results and Ferguson et al (nitroglycerin by unknown dosage and multiple routes). There are several potential

<table>
<thead>
<tr>
<th>Study</th>
<th>RVMI Events</th>
<th>Total</th>
<th>Other infarction Events</th>
<th>Total</th>
<th>Relative Risk</th>
<th>Weight, IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robichaud 2016</td>
<td>7</td>
<td>86</td>
<td>73</td>
<td>918</td>
<td>41.31%</td>
<td>1.02 [0.49, 2.15]</td>
</tr>
<tr>
<td>McConnell 2017</td>
<td>11</td>
<td>19</td>
<td>10</td>
<td>27</td>
<td>58.69%</td>
<td>1.56 [0.84, 2.92]</td>
</tr>
</tbody>
</table>

Figure 1 Primary meta-analysis. RVMI, right ventricular myocardial infarction.
of evidence currently favours the meta-

... possible that one study was affected by sampling error, and that this may be responsible for the different findings. F

nitrates during inferior myocardial infarction, for fear that this... suggests this would be misguided; isolated inferior myocardial infarction in that study had a lower rate of adverse events compared with all other myocardial regions, at 6.10%.

... by current evidence.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sensitivity analysis results for nitroglycerin 400 µg sublingual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change to synthesis</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>Unclear dosage (inclusion of Ferguson et al)</td>
<td>1.84</td>
</tr>
<tr>
<td>Fixed effects model (Mantel-Haenszel)</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Possible explanations for this disagreement. The first is that there is a genuine difference in the rate of adverse events for routes and dosages outside of 400 µg sublingual. The second is that the definition of hypotension accounts for the difference; while the synthesised studies used hypotension defined as a systolic BP <100 mm Hg, <90 mm Hg and a relative drop of greater than one-third, the single study reporting increased adverse events instead defined hypotension as a systolic BP drop of >30 mm Hg. Third, as the single study with a higher rate of adverse events provides no information on the dosage administered, this may be responsible for the different findings. Finally, it is possible that one study was affected by sampling error, and that the sample does not represent the true effect. Given the limited data provided in the single study suggesting and increased rate of adverse events (such as no data on dosages, which is potentially a significant factor in instigating hypotension), the weight of evidence currently favours the meta-analysed results for the safety of nitroglycerin.

It is commonplace in clinical guidelines—especially in teams who do not routinely take right-sided leads—to contraindicate nitrates during inferior myocardial infarction, for fear that this may also include an RVMI whose identification may be missed. However, the results of Robichaud et al suggest this would be misguided; isolated inferior myocardial infarction in that study had a lower rate of adverse events compared with all other myocardial regions, at 6.10%.

Therefore, by contraindicating all inferior infarctions in an attempt to avoid the 40% that have concomitant RVMI, nitrates are actually being withheld from the population for whom they are safest.

**Limitations**

First, all studies’ samples were of combined inferior and RVMI; the safety of nitrates during isolated RVMI cannot be determined. Second, as dichotomous outcomes are used, the severity or clinical significance of hypotension cannot be determined. Third, McConnell et al was only published as an abstract; additional information to complete this review was generously provided by the authors but has not been peer reviewed. Fourth, Robichaud et al uses a more lenient definition of hypotension (systolic BP <90 mm Hg), likely resulting in lower numbers of inclusions and an increased likelihood of concluding nitrates are safe. This is addressed directly by the authors, who justify this by stating that transient decreases in BP are unlikely to be clinically meaningful. Considering that McConnell et al used a definition of <100 mm Hg and found comparable results, we consider that this did not impact findings.

Fifth, this review has not compared beneficial outcomes. Sixth, three studies were unable to be retrieved by our library technicians. Seventh, each study carries the usual limitations of their methodology (three retrospective cohort and two uncontrolled before-after studies). Finally, the certainty of evidence under the GRADE criteria is very low, as outlined in table 4.

**CONCLUSIONS**

This review suggests that the AHA and ESC contraindications on nitrate administration when RVMI is present are not supported by current evidence.

### Table 4  Summary of findings

**Patient or population:** concomitant inferior and RVMI.

**Setting:** out of hospital, ED and admitted patients.

**Intervention:** administration of 400 µg sublingual nitrates during concomitant inferior and RVMI.

**Comparison:** administration of 400 µg sublingual nitrates during other infarctions.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of participants (studies) Follow-up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Risk during other infarctions</th>
<th>Risk difference during RVMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, bradycardia, altered consciousness, syncope* (nitroglycerin, 400 µg, sublingual) Assessed with: patient record review</td>
<td>1050 (2 observational studies)</td>
<td>@○○○ Very low†</td>
<td>RR 1.31 (0.81 to 2.12)</td>
<td>9 per 100</td>
<td>3 more per 100 (2 fewer to 10 more)</td>
</tr>
</tbody>
</table>

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Recommendations for practice
From a clinical perspective, the benefit of analgesia and the potential reduced sympathetic stimulation it provides must be balanced against the risk of transient hypotension. Given that the rate of hypotension appears consistent with concomitant inferior and RVMI to other myocardial regions, and that hypotension is both transient and readily managed with Trendelenburg positioning and a fluid challenge, nitrates are a reasonable treatment modality.

From a practical perspective, a modification to current practice—which as downgrading of a contraindication to a precaution—is highly feasible. Nitrates are already widely available and have a retail cost of several cents per dose; current savings on medication withholding can reasonably be assumed to be minimal.

Recommendations for research
The key gaps in current literature on the safety of nitrates during RVMI that need addressing are: (1) larger studies on outcomes from inhaled nitric oxide and (2) studies with large sample sizes that solidify a reliable rate of clinically meaningful adverse events. Further individual case studies are unlikely to add clarity to the current evidence. It is strongly recommended that any studies use prospective, multipatient methodologies and measure meaningful clinical outcomes—as noted by Bosson et al., transient hypotension is not necessarily of clinical significance. Severe or sustained hypotension and associated complications such as syncope or change in infarct size are reasonable end points, as are long-term outcomes such as mortality, length of stay and ongoing cardiac function.

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