**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

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<th>Date Submitted for review:</th>
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**Clinical question.**

In patients with suspected ACS/STEMI in the ED and prehospital settings (P), does the use of nitroglycerin (I), compared with no nitroglycerin (C), improve outcome (O).

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet:

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

Key words:
- nitroglycerin
- Acute coronary syndrome
- Myocardial infarction
- Acute myocardial infarction
- Emergency Department
- Pre-hospital

Databases Searched

- Cochrane Database: keywords myocardial infarction and nitroglycerin
- AHA Endnote Master library

References were reviewed and each article was reviewed for new citations. Primary studies were presented instead of subgroup analyses when available.

**State inclusion and exclusion criteria**

Inclusion: All patients treated with nitroglycerin at the time of presentation in the emergency department or prehospital setting

Exclusion criteria: Initiation of treatment>24 hours after symptom onset, initiation of therapy post invasive procedure, initiation of therapy after 24 hours from presentation

**Number of articles/sources meeting criteria for further review:** 135 articles met criteria based on the primary search. 55 articles were reviewed, 27 included in the analysis. Reason for exclusion: Initiation of nitroglycerin >24 hours after symptom onset (18), post procedure (7), 24 hrs after admission (3)
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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A = Return of spontaneous circulation endpoint  
B = Survival of event studies  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other

*Italics = Animal*
### Evidence Neutral to Clinical question

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<thead>
<tr>
<th>Level of Evidence</th>
<th>Evidence</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Good</td>
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<td>GISSI-3 1994, 1115 (B)</td>
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<tr>
<td>Fair</td>
<td>Gobel 1995, 1633 (E)</td>
<td>Leesar 2001, 2935 (E)</td>
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<tr>
<td>Poor</td>
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<td>Fukuyama 1980, 317 (E)</td>
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<td>Curfman 1983, 276 (E)</td>
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<td>Flaherty 1983, 576 (E)</td>
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### Evidence Opposing Clinical Question

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<td>Good</td>
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<td>Come 1976, 624 (E)</td>
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<tr>
<td>Fair</td>
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<td>Romeo 1995, 692 (E)</td>
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<td>Poor</td>
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<td>Nicolini 1994, 662 (E)</td>
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<td>Ohlin 1998, 1463 (E)</td>
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### Level of Evidence

A = Return of spontaneous circulation endpoint
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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Discussion: It has been well established that nitroglycerin reduces infarction size and mortality in patients presenting to the hospital with an acute myocardial infarction. This action is mediated through vasodilation and preservation of left ventricular function.

The benefit of nitroglycerin in myocardial infarction has been established by numerous large clinical trials. Two separate meta-analysis revealed a benefit in mortality in patients treated with nitroglycerin in the acute myocardial infarction. In a meta-analysis of 7 randomized controlled trials of patients presenting with 24 hours of symptom onset and diagnosed with a myocardial infarction an absolute reduction of 7.5% in mortality was noted in those patients receiving intravenous nitroglycerin. (Held 1992, 25S) Yusuf et al reported a reduction in mortality of 4% in patients treated with nitroglycerin. (Yusuf 1988, 1088). In the studies included in these analyses nitroglycerin was titrated to a reduction in systolic blood pressure of 10-15%. Multiple small trials have reported a reduction in infarction size and improved left ventricular function. (Bussmann 1981, 615, Jugdutt 1988, 906) In addition the use of nitroglycerin has been shown to decrease ischemic events in patients with unstable angina. In a study by Kalrberg et al. The use of sublingual nitroglycerin resulted in an absolute 8% reduction in recurrent anginal events. (Karlberg 1988, 25.) It is important to note that all studies evaluating the use of nitroglycerin exclude patients with hypotension (SBP<100mmHg or <90mmHg).

Despite the benefits noted by using nitroglycerin, multiple studies suggest that concomitant use with thrombolysis may result in decreased reperfusion. Ohlin et al. performed a prospective study in patients treated with nitroglycerin immediately following thrombolytic therapy or 3 hours after treatment. They noted in those patients treated immediately there was a reduction in lipid peroxidation a marker of reperfusion and therefore concluded that intravenous nitroglycerin in conjunction with thrombolytics may negative impact reperfusion. (Ohlin 1998, 1462). It has also been reported that concurrent nitroglycerin with TPA decreases t-PA antigen concentrations and therefore impair thrombolytic therapy. (Nicolini 1994, 662). This interaction has not been studied in patients receiving reteplase or tenecteplase.

The use of nitroglycerin in the prehospital or emergency department has not been extensively evaluated. In the emergency department a Gobel et al. noted a reduction diltiazem resulted in a 17% greater reduction is recurrent ischemia than using nitroglycerin but there was no control arm in this study. (Gobel, 1995, 1653). However other studies that enrolled patients in the intensive care unit setting, conclude that early administration of nitroglycerin results in greater reduction in infarct size. Jugdutt et al. studied 310 patients with an acute myocardial infarction admitted to an intensive care unit within 12 hours of symptom onset. When the analysis was stratified by duration of pain, those patients who had nitroglycerin administered within 4 hours of symptom onset had a 21% greater reduction in infarction size than those in whom nitroglycerin treatment was initiated >4 hours from symptom onset. (Jugdutt 1988, 906). Roas et al. evaluated the impact of intravenous nitroglycerin on infarction size in 95 patients admitted to an
intensive care unit. They reported that early administration resulted in a reduction in infarction size. (Roas 1995, 5)

Acknowledgements:
Level 5, good, neutral
Eligible patients were had ST depression or elevation and were admitted to the coronary care unit within 24 hours of symptom onset. In patients treated with transdermal nitroglycerin there was no reduction in mortality. However there was a 2.4% reduction the combined outcome of death and heart failure in patients >70 when compared to the control group. (OR 0.88, 95%CI 0.78-1.0).


Level 5, fair, support
A total of 60 patients with an myocardial infarction were treated with nitroglycerin (31) in doses of 0.75, 1.5, or 3 mg/hr or no specific therapy (29). The group treated with nitroglycerin was divided into an early group treated within 8 hrs of symptoms and those treated later. All patients had a Swan Ganz cather. CK curves were measured during the first 48 hours. There was a significant reduction in infarct size in both the late and early presentation group.


Level 5, poor, support.
In patients admitted to an intensive care unit, the effect of 2 different doses of nitroglycerin were assessed. Using precordial mapping the dose if 3mg/hour was associated with a 3mv decline in ST elevation and therefore the authors report that this dose results in a decline in ischemia.


Level 5, fair, support
Patients were enrolled at admission and there was no documentation where treatment was administered. Nitroglycerin was infused with the aim of reducing blood pressure by 20mmHG. There was no difference in mortality. In the nonQ wave MI there was a reduction in CK by almost 50%.

**Level 5, poor, against**

*This is a retrospective analysis of 54 patients receiving IV nitroglycerin or sublingual nitroglycerin. All patients had a Swan Ganz catheter placed. Hypotension and bradycardia was noted in 11% of all the patients.*


**Level 5, poor, neutral**

*Patients admitted to the coronary care unit with the diagnosis of unstable angina with 2 ischemic episodes within 48 hours. Patients were randomized to nitroglycerin or isosorbide. Nitroglycerin was titrated to a 20% reduction in systolic blood pressure or a dose of 200 ug/min. The primary outcome measure was the number of ischemic episodes per day. There were no significant difference in ischemic outcomes per group, however this study was underpowered to detect a difference.*


**Level 5, poor, neutral**

*This study enrolled 104 patients admitted to the CCU with suspicion of MI within 12 hours of symptoms. Patients were randomized to receive NTG or placebo. The nitroglycerin was titrated to a decline in MAP of 10% and continued for 48 hours. The clinical composite endpoint of new heart failure, myocardial infarction of death. The groups were further subgrouped into treatment initiated within or more than 10 hours. There was absolute reduction of 35% in the composite endpoint between early and late NTG and 33% between early NTG and early placebo. This study however is underpowered and has wide confidence intervals around the effect size.*


**Level 5, poor, support**

*Patients admitted to the hospital with an acute anterior myocardial infarction received nitroglycerin IV. Using myocardial mapping improved ST segment changes*
resulting with the greatest improvement in those with a reduction in left ventricular function.


Level 2, neutral, fair
This is an animal study of dogs. Coronary occlusion was replicated in 50 mongrels which were randomized to receive nitroglycerin or nothing. There was no difference in infarction size between the 2 groups.


Level 5, poor, support
This is a prospective trial of patients with a diagnosed anterior AMI admitted 24 to 48 hours prior to study enrollment. A total of 24 patients were randomized to nitroglycerin or placebo and crossed over after a washout period. Nitroglycerin infusion was started at 6mL/h and increased to a maximum of 160 ug/min. Pulse doppler echocardiography was performed at baseline and every 4 minutes. An adverse event of hypotension occurred in 4 patients. Patients were seperated into a group with and E/A ≥ 1.4 or not. Echocardiographic parameters were improved only in the group with a restrictive pattern. This study used only a short infusion of nitroglycerin and it is unclear what the long term effects of infusion on these parameters would be.


Level 2, fair neutral.
Patients were identified in the emergency department as having unstable angina or electrocardiographic changes of ST depression, transient ST elevation, or T wave inversions. A total of 129 patients were randomized to intravenous diltiazem of 25 mg and then 5 mg/h infusion that could be increased twice or a glyceryl trinitrate infusion starting with 1mh/hrand increased to 5 mg/h. The final outcome measure was refractory angina, myocardial infarction, or death at 48 hrs. The benefit in the composite outcome was driven by a reduction by a decrease in refractory ischemia. The was an absolute reduction of 17% in those treated with diltizaem compared with glyverin trinitrate.


Level 5, good, support
This is a systematic review of 7 trials of utilizing intravenous nitroglycerin. The investigators note an absolute reduction in death of 7.5%. In all trials treatment was initiated within 24 hours of symptom onset. No study specifically treated patients within the ED or prehospital setting. Similar benefit in mortality reduction was not noted in those patients treated with oral nitrates.


Level 5, fair, support
Patients admitted to a the coronary care unit were randomized to receive IV glyceryl nitrate or placebo. Nitroglycerin was titrated to a 10% decrease in systolic blood pressure or a maximum level. Of the patients enrolled only 85 had elevated creatinine kinase levels. There was a 23% reduction in infarction size in the overall study. This difference was only statistically significant in those patients with an inferior myocardial infarction (33% reduction).


Level 5, poor, support
In this study 22 patients in the CCU were randomized within 5.9 hours of the MI to receive NTG or placebo. The NTG was titrated to a 10% decline the MAP. The decline in left ventricular asynergy persisted to 10 days. There were no complications in the NTG group where the control group compared to 6 of the control patients with complications.


Level 5, fair, support
This is a study of 22 patients admitted to a cardiac care unit who were within 12 hours of symptom onset and had an anterior myocardial infarction. All subjects had a Swan Ganz catheter placed. Subjects were treated with intravenous nitroglycerin which was titrated to a 10% of the MAP control value but not less than 80mmHg. The maximum reduction in MAP was seen at 30 minutes. There was a an 10 % decline in asynergy in the group treated with NG thus suggesting that low dose NTG may decrease infarction size.


Level 5, support, fair
Study enrolled 310 consecutive patients admitted to the coronary care unit with AMI within 12 hours of pain onset. Patients were randomized to placebo or nitroglycerin NTG IV was titrated to a 10% reduction in MBP on normotensive patients and 30% reduction in hypertensive patients. Infarct expansion was defined as a second acute event after 48 hrs of the initial infarct and evidence of LV dysfunction. CK-infarct size was 27% less in the NTG group irrespective of infarct location. When patients were stratified by time of initiation of therapy within 4 hrs of pain or > than 4 hrs, the reduction infarct size was less in those treated early. In the NG group there was an 11% reduction in 7 day mortality. This mortality benefit of NTG extend out to 6 month.


Level 5, support, fair
This study enrolled 162 patients referred to the CCU with suspected ACS. All patients had chest pain within 24 hours and a history of CAD or positive stress test or ECG changes. Any patient with elevated CK was excluded. Patients were randomized to IV NTG or placebo and the dose or NTG was titrated to a 20% decrease in SBP, 10% decrease in HR, or headache. Primary outcome was recurrent ischemia defined as 2 anginal attacks responding to SL NTG <20 min or 1 attack >20 min. There was a 8% absolute reduction in the 2 anginal events.


Level 5, support, poor
Patients were enrolled if the had ST depression and chest pain was within 4 hours of symptoms. Patients were randomized to receive morphine or SL NTG. SL NTG was given 0.4mg to 1.6 mg every 5 minutes for the first 30 minutes and then at varying intervals until pain was relived. A total 30 subjects were enrolled and the outcome measure was pain relief and Q wave morphology. Complete pain relief occurred in 127 minutes in the NTG group and 134 minutes in the morphine group.


Level 5, support, poor
This study enrolled 96 patients with acute MI, unstable angina or other thromboembolic disease and randomized them to 3 arms (IV heparin, IV heparin and IV NTG, and IV isosorbide dinitrate and IV heparin. No information was given regarding time from hospital admission to randomization or treatment. The outcome measure
was antithrombin III activity. There was no difference in this level between groups.


Level 5, Support, fair
This is a prospective study of 77 patients age <70 within 8 hours of symptom onset with an acute myocardial infarction randomized to standard therapy or control. Nitroglycerin was given IV for 48 hours and titrated to maximal dose or a decrease in mean arterial pressure of 15% lower than when angina resolved. All patients had a Swan Ganz catheter. A significant reduction in pulmonary artery pressure was noted in the first 60 minutes without a further significant change of approximately 30% in patients irrespective if heart failure was present or not. Infarction size was 3% smaller in the nitroglycerin goroup that the controls. Infarct size was reduced by 37% in those with LV dysfunction and mean infarct mass was decreased by 40% in those with preserved function but peak value of CK-MB were similar.


Level 5, poor, support
This is a prospective study of 75 patients admitted to the hospital via a mobile care unit. The enrollment criteria is unclear. All patients has daily echocardiograms. During on echocardiogram the apteint was given 500ug of sublingual nitroglycerin and echocardiogram was performed. Of the 75 patients only 20 received nitroglycerin and all of these pateints had an acute myocardial infarction. OF the 20 11 had an anterior MI and the administration of SLG NTG resulted in an increase in septal excursion, diastolic septal excursion, diastolic septal velocity, and systolic septal velocity. The magnitude of effect was not stated and calculated amongst all patients. The study was underpowered to detect significant differences and the investigators attribute the changes to a change in afterload.


Level 5, fair, support
This is a double blind study of 100 patients admitted for coronary intervention with stable or unstable angina. Patients were randomized to receive 100 ug of IV nitroglycerin for 12 hours after revascularization. Primary outcome measure was pain score and myocardial necrosis. Only 20 patients had chest pain during the 12 hours observation period. There was a significant difference in the mean troponin level 12
hours after the procedure in the nitroglycerin and control group respectively (0.047 umol/L and 0.129 umol/L, p=0.26). Patients receiving nitroglycerin had a higher percentage of hypotension <90 mmHg (28% vs 16%).


Level 5, fair, neutral
This is a prospective study of patients admitted to the hospital for percutaneous coronary angiography with either stable or unstable angina. Patients were randomized to 4 hours of intravenous nitroglycerin beginning 24 hours prior to the coronary intervention. During the coronary intervention balloon inflation occurred 3 times 5 minutes apart to mimic ischemia. The chest pain score and ST segment shift was lower in the nitroglycerin pretreatment group. No difference was noted in the coronary collateral function. The study is small and may not have adequate power. The patients were stable and not administered treatment in the emergency department setting. Nitroglycerin was titrated to maintain a blood pressure >100mmHg.


Level 5, fair, neutral
Patients with clinical and electrocardiographic signs of myocardial infarction admitted to an intensive care unit within 24 hours of admission were eligible for inclusion. Patients were randomized to nitroglycerin or placebo. Nitroglycerin was titrated to a reduction in systolic blood pressure. Primary outcome measure was functional ability at 3 months. There was no difference in outcome in those patients randomized to nitroglycerin when compared to placebo. No power calculation was provided therefore it is possible that this study was underpowered to detect a significant difference.


Level 5, poor, support.
In a CCU, 14 patients with symptoms of MI were given IV metoprolol. After a period of defined time patients were then randomized to a second dose of IV metoprolol or metoprolol with NTG. NTG was titrated to a decline <10% of MAP or a decline in HR<10%. The investigators report a decline in PVR at time 24 hrs of 21.4±4 to 19.7±5.


Level 3, poor, support
This is a prospective observational study of 16 patients with chest pain thought to be ischemic in nature. Patients were treated with NTG boluses. There was an
average decline in SBP of 12 mmHg. This study was underpowered to determine any relevant differences.


Level 5, poor, against
This is a study of 47 patients who the treating physician decided if they would receive TPA (11 pts) or TPA with NTG (36 pts). Patients were enrolled in the CCU and were excluded if they received SL NTG. Of those patients receiving NTG there was a 15% reduction in blood pressure 105 ± 4 mmHg compared with 88 ± 3 mmHg. The primary outcome was measure of t-PA antigen. It was significantly higher in those patients treated with TPA alone suggesting that NTG interacted with TPA.


Level 5, poor, support
This is a prospective study of patients receiving NTG immediately after thrombolytic therapy or 3 hours later. The authors note a decline in the BP of patients treated immediately of 37± 33mmHG compared to 14±15 mmHg in patients treated with NTG. There was also a decline in plasma MDA which is a marker of lipid peroxidation in those treated with early nitroglycerin. The exact location of NTG administration is not documented.


Level 5, poor, support
This is a prospective study of 95 patients with an AMI admitted to the CCU within 6 hours of the onset of pain. It is unclear how the groups were determined and appears to be a convenience sample. NTG dose was titrated to a decline of 10% of the MAP. The groups were further subdivided into those presenting within 3 hours or more and those presenting within 3 hours. The investigators conclude that early administration of NTG decreases infarct size.


Level 5, fair, against
160 patients with AMI were eligible. Patients given NTG in the ED were excluded from analysis. A total of 33 patients were given TPA and 27 were given NTG and TPA. Patients were given 100ug/min of NTG for 8 hours. Patients treated with NTG had a 20% reduction in reperfusion at 2 hours and a 27% increase in persistent occlusion of the culprit artery.


RUSSIAN ONLY


Level 5, fair, support
Using male mongrel dogs the investigators aimed to determine if NTG prevents rethrombosis. The mean time to reocclusion in the NTG group compared to the controls was 210 minutes to 61 minutes. In addition only 1 vessel of 6 occluded after direct vessel injury which was statistically different that the controls.


Level 5, good, support
This is a systematic review of patients treated with nitroglycerin for acute myocardial infarction. In the included trials nitroglycerin was titrated to a reduction in systolic blood pressure of 10-15%. There was an absolute reduction of 4.1% in early deaths in those treated with nitroglycerin compared to controls. Therefore 25 people needed to be treated with nitroglycerin to prevent 1 death.