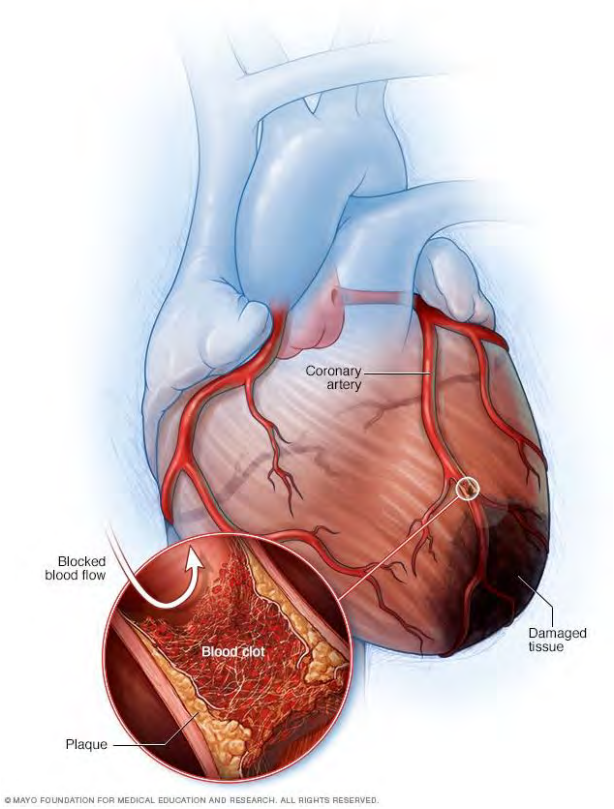
“Pain-Killer” or “Killer”? The Controversial Use of Morphine for Acute Coronary Syndromes



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Learning Objectives:

For Pharmacists:

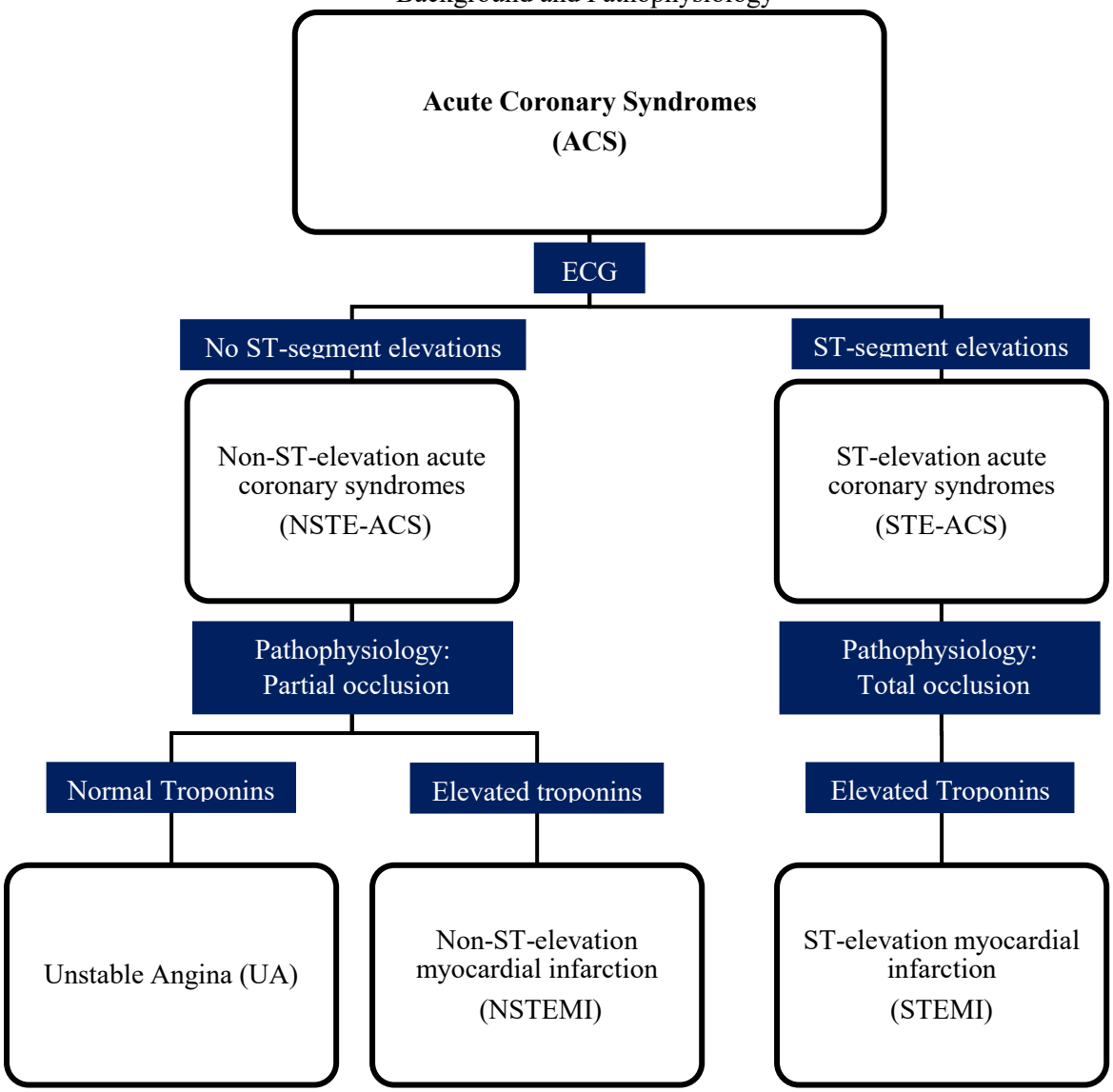
1. Explain the rationale for the use of morphine in acute coronary syndromes.
2. Describe the mechanism by which morphine may impair the efficacy of $P2Y_{12}$ inhibitors.
3. Summarize the evidence assessing morphine use in acute coronary syndromes.

For Pharmacy Technicians:

1. State the purpose of using morphine in acute coronary syndromes.
2. Recognize the drug interaction between morphine and $P2Y_{12}$ inhibitors.
3. Recall why morphine use in acute coronary syndromes is controversial.

Acute Coronary Syndromes

Background and Pathophysiology[1-2]



Unstable Angina (UA)

- Symptoms of myocardial ischemia
- Absence of ST-segment-elevation
- Absence of biomarkers indicating myocardial necrosis

NSTEMI

- Symptoms of myocardial ischemia
- Absence of ST-segment-elevation
- Positive biomarkers indicating myocardial necrosis

STEMI

- Symptoms of myocardial ischemia
- Persistent electrocardiographic ST elevations
- Positive biomarkers indicating myocardial necrosis

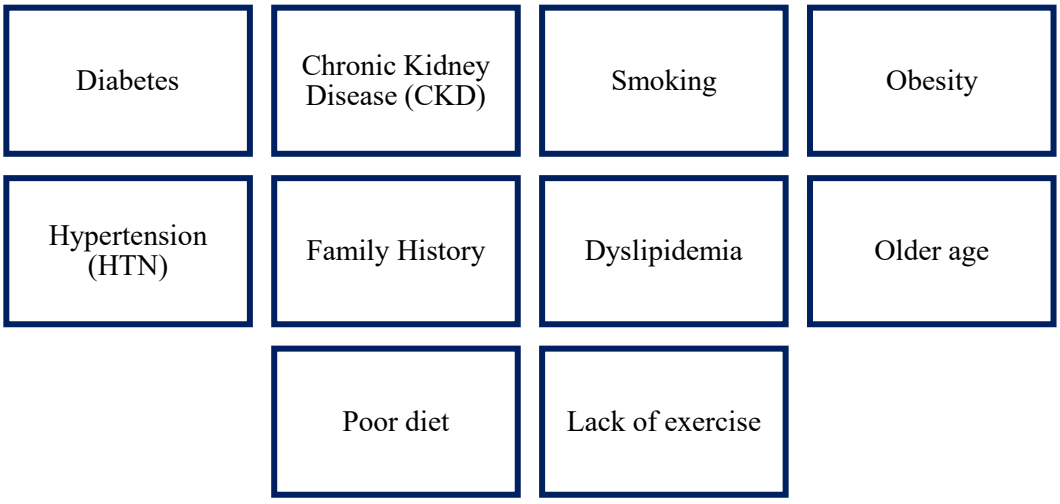
Epidemiology [3-7]

- Heart disease is the leading cause of death in adults > 35 years old in the US
  - Deaths in 2017: 647,457 → 1 in every 4 deaths
  - Percentage of total deaths (23%)
  - Coronary heart disease is the most common type (370,000 deaths annually)
  - Each year 735,000 Americans have a heart attack
- ~75% non-ST-elevation ACS (NSTE-ACS)
  - Typically have more risk factors than patient with STEMI
- ~25 to 40% STEMI
  - In-hospital mortality from STEMI ~7-10% vs 5% for NSTE-ACS
- NSTE-ACS incidence increasing while STEMI incidence is decreasing
- Lifetime risk of coronary heart disease in the US in patients with ≥ 2 major risk factors:
  - 37.5% for men
  - 18.3% for women

Pathophysiology[1-2,8]

- Mismatch between myocardial oxygen supply and demand
  - Plaque rupture → formation of blood clot (most common cause)
  - Vasoconstriction
  - Plaque erosion with intact fibrous cap
- NSTE-ACS: incomplete occlusion
- STEMI: complete occlusion → myocardial tissue death

Risk Factors for ACS[9-11]



Risk Calculators for Mortality Post-ACS[12-14]

- Global Registry of Acute Coronary Events (GRACE) Score
  - Predicts in-hospital and post-discharge mortality or MI to 6 months

GRACE Risk Factors	
Killip Class for CHF	Creatinine
SBP at presentation	Cardiac Arrest at admission
HR at presentation	ST-segment deviation on the index ECG
Age	Elevated cardiac enzymes

- TIMI Risk Score for NSTE-ACS
  - Predicts 30 day and 1-year mortality in NSTE-ACS
  - Calculator gives risk at 14 days for all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization

TIMI Risk Factors	Score
Age ≥ 65 y	1
≥3 risk factors for CAD*	1
Known CAD (stenosis ≥ 50%)	1
ASA use in past 7 d	1
Recent (≤24 hours) severe angina	1
Increased cardiac markers	1
ST-deviation ≥ 0.5 mm	1
Risk at 14 days according to score	
Score 0 to 1: 5% Score 2: 8% Score 3: 13%	Score 4: 20% Score 5: 26% Score ≥ 6: 41%

*family history of CAD, HTN, hypercholesterolemia, diabetes, smoking

- TIMI Risk Score for STEMI
  - Predicts all-cause mortality at 30 days

TIMI Risk Factors	Score
Age < 65 y	0
Age 65 to 74 y	+2
Age ≥ 75 y	+3
DM or HTN or Angina	+1
SBP < 100 mmHg	+3
HR > 100 bpm	+2
Killip Class II to IV	+2
Wt < 67 kg (147.7lbs)	+1
Anterior ST Elevation or LBBB	+1
Time to Treatment > 4 hours	+1
Risk at 14 days according to score	
Score 0: 0.8% Score 1: 1.6% Score 2: 2.2% Score 3: 4.4% Score 4: 7.3%	Score 5: 12.4% Score 6: 16.1% Score 7: 23.4% Score 8: 26.8% Score ≥ 9: 35.9%

Complications of ACS[1-2, 15-16]

- Heart failure
- Cardiogenic shock
- Cardiac arrhythmias (VF/VT/AF/sinus bradycardia)
- Recurrent myocardial infarction
- Stent thrombosis (ST)

Risk Factors for Stent Thrombosis		
Stent type-related	**Patient Specific Traits**	**Procedure-related**
Early-generation DES	Diabetes Impaired LVEF Malignancy Genetics High platelet reactivity	Primary PCI Complex lesion morphology Stent undersizing Residual stenosis ↓ TIMI flow

Guideline Directed Medication Management for ACS[1-2]

- Goal: reduce oxygen demand and supply mismatch

Therapy	Recommendation	Mortality
Morphine	For pain relief	?
Oxygen	For patients with O_2 sat <90%	No effect
Nitrate	For angina, HTN, pulmonary edema, or recurrent ischemia	No effect
Aspirin	For all patients in acute phase	↓
B-blocker	Within 24 hours of cardiac event	↓
GPIIb/IIIa inhibitor	For patients with high-risk features and residual clot burden	No effect
$P2Y_{12}$ inhibitor	For all patients without contraindications	↓ (ticagrelor)
Anticoagulant	For 48 hours or until PCI	No effect

- $P2Y_{12}$ Inhibitor
  - Prevent platelet activation and aggregation
  - Reduces major cardiac adverse events
  - Clopidogrel (CURE)[17]
    - Clopidogrel 300 mg loading dose then 75 mg daily versus placebo in patients with NSTE-ACS
    - Reduced composite of death from cardiovascular (CV) causes, nonfatal MI, or stroke (9.3% vs 11.4%; p<0.001)
  - Prasugrel (TRITON TIMI)[18]
    - Prasugrel 60 mg loading dose then 10 mg daily versus clopidogrel 300 mg loading dose then 75 mg daily in patients with ACS
    - Reduced composite of CV mortality, nonfatal MI, or nonfatal stroke (9.9% vs 12.1%; p<0.001)
  - Ticagrelor (PLATO)[19]
    - Ticagrelor 180 mg loading dose then 90 mg BID versus clopidogrel 300 mg loading dose then 75 mg daily in patients with ACS
    - Reduced composite of vascular mortality, MI, or CVA (9.8% vs 11.7%; p<0.001)
    - Reduced all-cause mortality (4.5% vs 5.9%; p<0.001)
  - Cangrelor (CHAMPION PHOENIX)[20]
    - IV cangrelor 30 mcg/kg then 4 mcg/kg/min for 2 hours or duration of procedure (whichever is longer) versus placebo infusion then clopidogrel loading dose of 300 mg or 600 mg in patients undergoing percutaneous intervention
    - Reduced composite of all-cause mortality, MI, ischemia-driven revascularization, or stent thrombosis (4.7% vs 5.9%; p=0.005)

Drug	clopidogrel[21]	prasugrel[22]	ticagrelor[23]	cangrelor[24]
Loading Dose	300 to 600 mg	60 mg	180 mg	30 mcg/kg, then 4 mcg/kg/min
Onset of Action	2 hours	< 30 min	< 30 min	< 2 min
Time to Max IPA	4 hours	~4 hours	~2 hours	< 2 min
Duration of Action	5 days	5 to 9 days	3 days	<1 hour
Reversibility	No	No	Yes	Yes

IPA: inhibition of platelet aggregation

Why is morphine use in ACS controversial?

Mechanism of Action and Rationale in ACS

Role of Morphine in ACS[1-2]

- No mortality benefit
- Recommended for pain relief

NSTE-ACS Guideline Recommendation[2, 25]

- Morphine may be considered in NSTE-ACS
  - Usefulness/efficacy less well established
  - Greater conflicting evidence from single randomized or nonrandomized studies
  - Benefit ≥ Risk
- Previously graded Class IIa (2007 AHA/ACC NSTE-ACS Guidelines)
  - Benefit >> Risk

Guideline	Evidence Grading
2007 AHA/ACA Guideline for the Management of Patients with Non-ST-elevation Acute Coronary Syndromes	IIa
2014 AHA/ACA Guideline for the Management of Patients with Non-ST-elevation Acute Coronary Syndromes	IIb

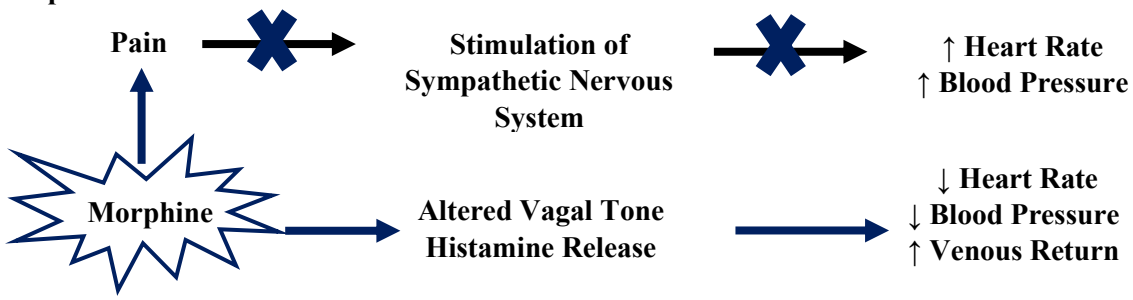
STEMI Guidelines Recommendation[1]

- Morphine is the drug of choice for pain relief in STEMI
- ↓ work of breathing, ↓anxiety, and favorably affects ventricular loading

Guideline	Evidence Grading
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction	Not Graded

- Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors contraindicated due to:[1-2]
  - ↑ Death
  - ↑ Re-infarction
  - ↑ Cardiac rupture
  - ↑ Hypertension
  - ↑ Renal insufficiency
  - ↑ Heart failure

Morphine's Mechanism of Action in ACS:[26-28]



Overall Effect of Morphine in ACS	
↓ Myocardial Oxygen Demand	↑ Myocardial Oxygen Supply

History of the Management of ACS[27]

1912-1961:	•Bedrest, Morphine, Oxygen, & Nitrates
1960-1986:	•Coronary Units
1986-2000:	•Fibrinolytics, Aspirin, Anticoagulants, β-blockers, & RAAS inhibitors
2000s:	•$P2Y_{12}$ Inhibitors, Statins, Angioplasty ± stents
2005:	•CRUSADE trial
2014:	•ATLANTIC trial •ACC/AHA downgrade morphine recommendation •PK/PD data of morphine with clopidogrel published
2015-2016:	•PK/PD data of morphine with prasugrel & ticagrelor published
2017-2019:	• Meta-Analysis & Systematic Reviews

What sparked the controversy of using morphine in ACS?[26-28]

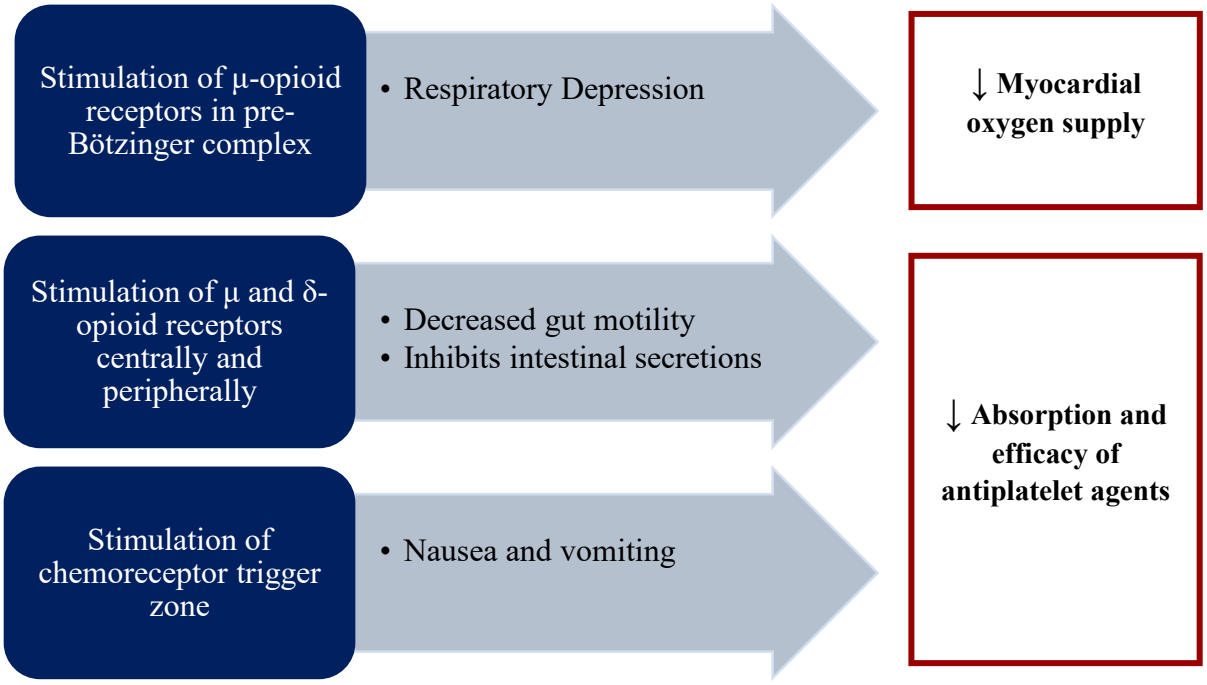
- CRUSADE Trial (2005): ↑ mortality in NSTE-ACS
  - Patients treated with morphine did not receive optimal medical treatment
  - Morphine use may indicate a more critically ill patient
  - Analgesia removes signs of severe angina
  - Morphine is associated with delayed activity of $P2Y_{12}$ inhibitors
- Pharmacokinetic and Pharmacodynamic (PK/PD) Data:[29-33]

Trial	$P2Y_{12}$ Inhibitors	Pharmacokinetic Effect	Pharmacodynamic Effect
Parodi (2015)	Prasugrel 60 mg Ticagrelor 180 mg Ticagrelor 360 mg	----------	• ↑ Platelet reactivity at 2 hours • ND between $P2Y_{12}$ inhibitors
Hobl (2016)	Prasugrel 60 mg	AUC: ND C_{max} ↓	• Onset of action: ND
Hobl (2016)	Ticagrelor 180 mg	AUC ↓ C_{max} ↓ T_{max} ↑	• Whole blood aggregation: ND • Platelet plug formation under high shear: ND

Hobl (2014)	Clopidogrel 600 mg	AUC ↓ C_{max} ↓ T_{max} ↑	• Delayed max platelet aggregation inhibition • ↑ Residual platelet aggregation • Delayed inhibition of platelet plug formation under high shear
Kubica (2016)	Ticagrelor180 mg	AUC ↓ C_{max} ↓ T_{max} ↑	----------

AUC: area under the curve (total drug exposure), C_{max}: maximum serum concentration, T_{max}: time taken to reach the maximum concentration in serum, ND: no difference

- Unwanted adverse effects of morphine:[28]



Clinical Question:

- Should morphine be used in patients with ACS to help relieve pain?

Literature Review

Table 1. Meine TJ et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005; 149: 1043-9.[34]

Objective	Evaluate the safety and efficacy of morphine in non-ST-segment elevation acute coronary syndromes
Methods	
Study design	Multicenter, observational, retrospective chart review from 2001 to 2003
Population	**Inclusion Criteria** • Ischemic symptoms at rest within 24h of presentation • High-risk features* **Exclusion Criteria** • Patients transferred to another institution
Intervention	Inclusion into groups based on IV morphine use then comparison between: • IV morphine vs no IV morphine • IV morphine vs IV nitroglycerin (NTG) • IV nitroglycerin vs IV morphine + IV nitroglycerin
Outcomes	• In-hospital death • Recurrent myocardial infarction • Congestive heart failure • Cardiogenic shock
Statistical Analysis	• Kruskal-Wallis and Wilcoxon rank-sum tests were used for continuous variables • X^2 tests were used for categorical variables • Multivariate risk-adjusted analyses performed for each comparison and overall comparison • Subgroup analysis conducted for in-hospital mortality • Propensity matched analyses to account for nonrandom treatment assignment
Results	

Baseline characteristics

Characteristic	No morphine (n=40,036)	Morphine (n=17,003)	P value
Age (y)	70	65	<0.0001
Male sex	58.4	61.8	<0.0001
History of CAD	34.6	38	<0.0001
Hypertension	69.7	67.2	<0.0001
Diabetes mellitus	33	31.5	0.0004
Smoking	24.8	32.9	<0.0001
Hyperlipidemia	46	47.3	0.009
Prior MI	30.5	32.6	<0.0001
Prior PCI	20.6	23.9	<0.0001
Prior CABG	20.3	20.7	0.4
Prior CHF	19.3	17.7	<0.0001
Renal Insufficiency	14.3	12.7	<0.0001
Admission signs/symptoms			
ST depression	39.1	42.1	<0.0001
Transient ST elevation	9	12.9	<0.0001
Positive cardiac markers	87.2	89.4	<0.0001
Signs of CHF	22.7	22.1	0.1
Heart rate	83	81	<0.0001
Systolic BP	144	144	0.4
Active Medications			
Aspirin	90.9	91.9	0.0002
All heparin	79.7	87.8	<0.0001
β-blocker	77.2	80.1	<0.0001
Clopidogrel	38.1	44.5	<0.0001
GP IIb/IIIa inhibitor	30.6	45.7	<0.0001
In hospital procedures			
Diagnostic catheterization	62.9	73.7	<0.0001
PCI	33.6	43.2	<0.0001
CABG	11.2	12.2	0.001

Outcomes

IV morphine vs no IV morphine

Outcome	No morphine	Morphine	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Death	4.7%	5.5%	1.22 (1.10-1.34)	1.48 (1.33-1.64)
Death or MI	7.1%	8.5%	1.26 (1.17-1.35)	1.44 (1.34-1.56)
Post-Admission MI	3.0%	3.8%	1.28 (1.17-1.41)	1.34 (1.22-1.48)
Cardiogenic Shock	2.3%	3.8%	1.63 (1.45-1.82)	1.71 (1.53-1.91)
CHF	9.1%	10.3%	1.16 (1.09-1.24)	1.27 (1.19-1.36)

IV morphine vs IV NTG

Outcome	IV NTG only	IV Morphine only	Adjusted OR (95% CI)
Death	3.8%	6.8%	1.49 (1.25-1.77)
Death or MI	7.1%	8.5%	1.40 (1.22-1.62)
Post-Admission MI	3.2%	3.5%	1.18 (0.99-1.41)
Cardiogenic Shock	2.4%	4.0%	1.44 (1.19-1.74)
CHF	8.8%	10.5%	1.06 (0.93-1.20)

IV morphine + IV NTG vs IV NTG

Outcome	Adjusted OR (95% CI)
Death	1.41 (1.21-1.64)
Death or MI	1.34 (1.19-1.50)
Post-Admission MI	1.31 (1.14-151)
Cardiogenic Shock	1.49 (1.27-1.74)
CHF	1.28 (1.17-1.41)

Author's Conclusions

Use of IV morphine alone or in combination with IV NTG for patients with NSTE-ACS associated with higher mortality, recurrent MI, cardiogenic shock, and congestive heart failure

Critique

Strengths

- Large population size
- Endpoints adjusted for differences in baseline characteristics using multivariate analysis
- Endpoints assessed using propensity matching
- Propensity matching improves internal validity
- Duration of study appropriate
- Multi-centered design improves external validity

Weaknesses

- Retrospective observational design
- Additional medications that may inhibit clopidogrel effectiveness not reported (ie, PPIs)
- Ethnicity not reported, which may affect efficacy of clopidogrel (ie, CYP2C19 polymorphisms)
- Limited to patients with NSTE-ACS
- Morphine doses not reported
- Adjustments may not account for all differences in baseline characteristics
- Used CK-MB for diagnosis of ACS instead of cardiac troponins reduces external validity
- Propensity matching did not address guideline directed medical treatment differences
- In-hospital outcomes reported by site and not adjudicated by independent clinical events committee

Take Away Summary

IV morphine alone or in combination with IV NTG associated with a higher risk of mortality, recurrent MI, CHF, and cardiogenic shock in patients presenting with NSTE-ACS

* ST-segment depression ≥ 0.5 mm, transient ST-segment elevation 0.5 to 1.0 mm (lasting for 10 min), and/or creatinine-kinase (CK)-MB > upper limit of normal (ULN) for the local laboratory assay)

Table 2. Lapostolle F, et al. Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine. Am J Cardiovascular Drugs. 2019. 19;173-183.[35]

<table>
<tr><td>Objective</td><td colspan="2">Evaluate whether interaction between morphine and ticagrelor was associated with differences in outcomes in STEMI patients pre-PCI</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study design</td><td colspan="2">Post-hoc analysis of ATLANTIC study (multicenter, randomized, double-blinded trial)</td></tr>
<tr><td>Population</td><td><u>Inclusion Criteria</u>
• STEMI <6h from onset
• Scheduled for primary PCI
• Expected time to balloon < 120 min</td><td><u>Exclusion Criteria</u>
• Patient treated with clopidogrel
• Contraindication to ticagrelor
• Oral anticoagulation that cannot be stopped
• Planned fibrinolytic treatment</td></tr>
<tr><td>Intervention</td><td colspan="2">• Received pre- vs. in-hospital ticagrelor 180 mg loading dose
• Post-hoc analysis compared patients who received morphine vs. those who did not</td></tr>
<tr><td>Outcomes</td><td>• Prior cardiovascular history (CABG, STEMI, PCI, TIA, stroke)
• Initial clinical features (TIMI risk score, Killip class > 1)
• Culprit artery</td><td>• Management (anticoagulant use, GP IIb/IIIa inhibitor use, sheath insertion site, thromboaspiration, timing from chest pain to ECG to PCI)
• Clinical efficacy (death, MI, stroke, urgent revascularization, stent thrombosis, bleeding)</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Student’s t tests were used for continuous variables
• X^2 tests were used for categorical variables
• Logistic regression models used for association of morphine with co-primary endpoints</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>Morphine (n=921)</th><th>No Morphine (n=941)</th><th>P value</th></tr>
<tr><td>Age (y)</td><td>60.3</td><td>65</td><td>0.08</td></tr>
<tr><td>Male sex (%)</td><td>80.6</td><td>61.8</td><td>0.68</td></tr>
<tr><td>STEMI (%)</td><td>8.8</td><td>38</td><td>0.70</td></tr>
<tr><td>PCI (%)</td><td>7.3</td><td>7.8</td><td>0.69</td></tr>
<tr><td>CABG (%)</td><td>0.5</td><td>0.7</td><td>0.59</td></tr>
<tr><td>Hypertension (%)</td><td>44.2</td><td>41.2</td><td>0.20</td></tr>
<tr><td>Diabetes mellitus (%)</td><td>13.2</td><td>13.9</td><td>0.67</td></tr>
<tr><td>Dyslipidemia (%)</td><td>36.5</td><td>33.7</td><td>0.21</td></tr>
<tr><td>TIMI risk score (mean)</td><td>2.1</td><td>2.2</td><td>0.13</td></tr>
<tr><td>Killip Class > 1 (%)</td><td>9.4</td><td>10</td><td>0.69</td></tr>
<tr><td>Chest pain to ECG (median; minutes)</td><td>68</td><td>78</td><td><0.01</td></tr>
<tr><td>Chest pain to LD (median; minutes)</td><td>85</td><td>97</td><td>0.01</td></tr>
<tr><td>Chest pain to PCI (median; minutes)</td><td>155</td><td>163</td><td>0.20</td></tr>
<tr><td>Culprit Artery LAD (%)</td><td>43</td><td>34.9</td><td>----</td></tr>
<tr><td>IV anticoagulation (%)</td><td>89.3</td><td>87.1</td><td>0.16</td></tr>
<tr><td>GP IIb/IIIa Inhibitors (%)</td><td>41.9</td><td>34.8</td><td><0.01</td></tr>
<tr><td>Thromboaspiration (%)</td><td>54.7</td><td>46.4</td><td><0.001</td></tr>
<tr><td>PCI (%)</td><td>91.6</td><td>83.5</td><td><0.0001</td></tr>
<tr><td>Any stent (s)</td><td>86</td><td>79.1</td><td><0.0001</td></tr>
<tr><td>DES (%)</td><td>53.7</td><td>47.9</td><td>0.01</td></tr>
<tr><td>No PCI or CABG (%)</td><td>6.9</td><td>15.2</td><td><0.0001</td></tr>
</table>
</td></tr>
<tr><td>Outcomes</td><td colspan="2"><u>Co-Primary outcomes: morphine vs no morphine</u>
<table>
<tr><th>Outcome</th><th>Morphine</th><th>No Morphine</th><th>OR (95% CI)</th><th>P value</th></tr>
<tr><td>Absence of pre-PCI TIMI 3 flow in culprit artery</td><td>85.8</td><td>79.7</td><td>1.54 (1.19-1.99)</td><td>0.001</td></tr>
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Absence of pre-PCI≥ 70% ST-segment elevation resolution	88.8	85.7	1.32 (0.98-1.77)	0.07
Absence of pre-PCI TIMI 3 flow in culprit artery and/or pre-PCI ≥ 70% ST-segment elevation resolution	77.1	68.9	1.52 (1.21-1.91)	<0.001
Absence of pre-PCI TIMI 3 flow in culprit artery and pre-PCI ≥ 70% ST-segment elevation resolution	95.5	93.1	1.57 (1.00-2.46)	0.05

Clinical outcomes: morphine vs no morphine

Outcome	Morphine	No Morphine	OR (95% CI)	P value
Death/MI/stroke/urgent revascularization	1.7	1.1	1.64 (1.74-3.63)	0.22
Death /MI/stroke/urgent revascularization/definite acute stent thrombosis	1.8	1.6	1.16 (0.57-2.33)	0.685
Death/MI/urgent revascularization/definite acute stent thrombosis	2.0	1.7	1.15 (0.58-2.26)	0.69
Death/MI/ urgent revascularization/definite acute stent thrombosis/bail-out use of GP IIb/IIIa inhibitors	12.7	9.4	1.40 (1.05-1.88)	0.02
MI/definite acute stent thrombosis	0.5	0.9	0.63 (0.21-1.95)	0.43
All-cause mortality	1.1	0.6	1.70 (0.62-4.71)	0.30
MI	0.4	0.2	2.04 (0.37-11.18)	0.41
Urgent revascularization	0.4	0.2	2.04 (0.37-11.18)	0.41
Definite acute stent thrombosis	0.2	0.6	0.34 (0.07-1.68)	0.18
Bail-out use of GP IIb/IIIa inhibitors	11.3	7.9	1.48 (1.09-2.03)	0.01
Stroke, any	0.1	0.1	1.02 (0.06-16.29)	0.99

Bleeding was more likely in morphine-treated patients

- Major bleeding per TIMI: 1.1% vs 0.1%; p=0.02
- Major life-threatening/fatal bleeding per PLATO: 1.3% vs 0.3%; p=0.02

Author's Conclusions

Morphine associated with less TIMI 3 flow in culprit artery, higher use of GP IIb/IIIa inhibitors, and more bleeding compared to not using morphine.
No difference was seen in relation to mortality, MI, stroke, or stent thrombosis.

Critique

Strengths

- Prospective, randomized control trial
- Criteria for perfusion and bleeding based on TIMI, PLATO, GUSTO, and STEEPLE definitions

Weaknesses

- Post-hoc analysis not powered for clinical endpoints
- Pain intensity not collected or reported
- Doses of morphine not reported and may vary between patients
- Differences in baseline characteristics may affect results
- Data limited to morphine use with ticagrelor
- Data limited to STEMI patients only
- Possible funding bias by AstraZeneca
- Composite outcome driven by bail-out use of GP IIb/IIa inhibitors

Take Away Summary

Use of morphine in patients with STEMI and planned PCI that have received a ticagrelor loading dose is associated with less TIMI 3 flow, more frequent use of GP IIb/IIIa inhibitors, and more bleeding.

Table 3. McCarthy et al. In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine. J Interven Cardiol. 2018; 31: 150-158.[36]

Objective	Evaluate the safety and efficacy of morphine in patients with STEMI and NSTE-ACS
Methods	
Study design	Single-center, observational, retrospective study from 2009 to 2016
Population	**Inclusion Criteria** • STEMI and NSTE-ACS undergoing coronary angiogram +/- PCI **Exclusion Criteria** • None
Intervention	• Comparison of patients that received morphine vs those that did not with STEMI and NSTE-ACS
Outcomes	• Inpatient mortality • Post procedure cardiogenic shock • Infarct size as measured by troponin • Post procedure acute renal failure • Length of hospital stay
Statistical Analysis	• Student's t-tests for continuous variables • X^2 tests were used for categorical variables • Multivariate analyses performed with and without propensity matching* • Logistic regression performed for binary outcomes • Linear regression performed for continuous outcomes
Results	
Baseline characteristics	

Baseline characteristics of STEMI patients			
Characteristic (%)	**No morphine (n=928)**	**Morphine (n=359)**	**P value**
Age (yr)	62	60	0.03
Female sex	27	22	0.09
Smoking	29	33	0.12
Medical History (%)			
CVD	7	8	0.42
PVD	8	8	0.72
Chronic Lung Disease	7	9	0.27
CHF	5	5	0.75
Family History of CAD	21	26	0.06
HLD	91	95	0.02
HTN	60	57	0.24
Previous CABG	4	5	0.40
Previous PCI	15	22	0.007
Previous MI	15	21	0.004
Creatinine	1.13	1.07	0.04
Pre-Procedural Characteristics (%)			
Supplemental Oxygen	81	87	0.01
Shock at start of PCI	12	7	0.004
Cardiac arrest (prior 24h)	12	7	0.03
Door to balloon time (min)	56	68	0.0005
Pre-Procedural Medications (%)			
β-blockers	30	29	0.74
Clopidogrel	70	74	0.15
Ticagrelor	23	21	0.31
Aspirin	93	90	0.11

Baseline characteristics of NSTE-ACS patients			
Characteristic (%)	**No morphine (n=1316)**	**Morphine (n=424)**	**P value**
Age (yr)	67	64	0.0005
Female sex	26	29	0.29
Smoking	18	27	<0.0001

Medical History (%)				
CVD	16	22	0.005
PVD	16	25	<0.0001
Chronic Lung Disease	13	13	0.80
CHF	17	18	0.52
Family History of CAD	22	23	0.72
HLD	96	96	0.87
HTN	76	78	0.54
Previous CABG	17	20	0.33
Previous PCI	29	34	0.05
Previous MI	33	40	0.01
Creatinine	1.32	1.25	0.26
Prior valvular surgery	3	1	0.03
Pre-Procedure characteristics (%)			
Supplemental Oxygen	83	82	0.01
Shock at start of PCI	4	3	0.48
Cardiac arrest (prior 24h)	2	1	0.16
Door to balloon time (min)	119	124	0.88
Pre-Procedural Medications (%)			
β-blockers	75	75	0.19
Ranolazine	1	3	0.003
Clopidogrel	80	85	0.01
Ticagrelor	15	11	0.05
Aspirin	91	90	0.63
Procedural Characteristics (%)			
Coronary thrombus	8	13	0.002

Outcomes

Clinical Outcomes: STEMI patients

Outcome	No morphine	Morphine	Unadjusted OR (95% CI), P value	Adjusted OR (95% CI), P value
Mortality	7.54%	4.18%	0.53 (0.30-0.95), P=0.03	0.36 (0.08-1.68), P=0.19
Post-procedural cardiogenic shock	3.13%	1.95%	0.62 (0.27-1.42), P=0.26	0.56 (-.17-1.78), P=0.32
Post-procedural renal failure	3.77%	1.95%	0.51 (0.22-1.15), P=0.11	0.55 (0.12-2.59), P=0.45
Length of hospital stay (days)	5.91	5.40	P=0.29	P=0.61
Infarct size as measured by troponin (ng/mL)	1.29	0.75	P=0.02	P=0.32

Clinical Outcomes: NSTE-ACS patients

Outcome	No morphine	Morphine	Unadjusted OR (95% CI), P value	Adjusted OR (95% CI), P value
Mortality	2.51%	3.77%	1.53 (0.83-2.80), P=0.17	1.58 (0.51-4.92), P=0.43
Post-procedural cardiogenic shock	0.84%	0.71%	0.85 (0.24-3.05), P=0.80	0.60 (0.06-5.94), P=0.67
Post-procedural renal failure	2.13%	4.25%	2.04 (1.12-3.73), P=0.02	2.11 (0.80-5.55), P=0.13
Length of hospital stay (days)	4.78	6.58	P<0.0001	P<0.0001

Infarct size as measured by troponin (ng/mL)	0.90	1.16	P=0.05	P=0.02

In-hospital outcomes in propensity matched patients

Outcome	No morphine	Morphine	Adjusted OR (95% CI), P value
STEMI Patients			
Mortality	11%	8%	0.58 (0.19-1.78), P=0.34
Length of hospital stay (days)	7.71	6.98	P=0.81
Infarct size	1.84	1.11	P=0.67
NSTE-ACS Patients			
Mortality	2%	5%	2.55 (0.95-6.86), P=0.06
Length of hospital stay (days)	4.89	6.50	P=0.004
Infarct size	0.83	1.14	P=0.01

Adjusted for age, sex, BMI, family history of CAD, shock at the start of PCI, hypotension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior CABG, CHF, cerebrovascular disease, and renal insufficiency

Author's Conclusions	Morphine associated with a larger infarct size, longer hospital stay, and a trend towards increased mortality in NSTE-ACS patients, but had no adverse effect on outcomes in STEMI patients	
Critique	**Strengths** • Assessed both STEMI and NSTE-ACS • Endpoints adjusted for differences in baseline characteristics in multivariate analysis • Matched propensity analysis improves internal validity	**Weaknesses** • Retrospective, observational design • Single center • Medications that may inhibit clopidogrel effectiveness not reported (PPIs) • Patient ethnicity not reported, which may affect efficacy of clopidogrel (CYP2C19 polymorphisms) • Morphine dose not reported • Adjustments may not account for all differences in baseline characteristics • Difference in $P2Y_{12}$ inhibitor use not adjusted for in propensity analysis • Stent re-thrombosis and recurrent MI not assessed • Matched propensity analysis did not account for potential differences in medications that may affect mortality • Underpowered for clinical endpoints
Take-Away Summary	Morphine had no effect on in-hospital outcomes for STEMI; however, it was associated with increased mortality, length of stay, and infarct size in NSTE-ACS.	

* Matched for: age, gender, history of CVD, history of PVD , history of chronic lung disease, history of DM s, prior CABG, prior PCI, prior MI, administration of β-blocker, administration of a calcium channel blocker, administration of anti-anginal agent

Table 4. Duarte GS, et al. Morphine in acute coronary syndrome: systematic review and meta-analysis. BMJ Open 2019; 9:e025232.doi:10.1136/bmjopen-2018-025232[37]

Objective	Synthesize current literature on safety of morphine use in acute coronary syndrome
Methods	
Study design	Systematic review and meta-analysis
Population	**Inclusion Criteria** • Longitudinal studies evaluating the impact of morphine in cardiovascular outcomes or platelet reactivity measures • Studies comparing morphine to placebo, control, or other analgesic non-opioid • Patients with ACS (STEMI or NSTE-ACS) • Studies from inception of CENTRAL, MEDLINE, EMBASE, and clinicaltrials.gov through November 2018 **Exclusion Criteria** • None
Intervention	• Comparison of patients that received morphine vs those that did not with STEMI and NSTE-ACS Risk of bias evaluated using Cochrane risk of bias tool for RCTs and ROBINS-I tool for observational studies
Outcomes	• In-hospital mortality • Major adverse cardiovascular events (MACE) • Safety outcomes (as defined by included studies) • Platelet reactivity using VerifyNow
Statistical Analysis	• Random-effects model to pool data • Heterogeneity assess using I^2 • Subgroup analyses based on study design and ACS type • Risk of bias for each study determined as high or low using Cochrane risk of bias tool • Sensitivity analysis excluding RCTs with high risk of bias and observational studies at critical risk of bias • Adjusted the within-study-variance-covariance matrix with a precision correction of 0.1 for observational studies with a critical risk of bias to provide a conservative pooled estimate
Results	
Characteristics of Included Studies	17 studies included for qualitative and quantitative synthesis: 5 RCTS and 12 observational • N=69,993 • 2 RCTs at high risk of bias • 2 observational studies at critical risk of bias

Characteristics of randomized controlled trials

Study	Study Design	Follow up	Patients	Outcomes
Bressan N=40	Prospective	24h	Admit for MI, chest pain, and sx <6h	Assessment of analgesic effect of indoprofen
Everts N=265	Retrospective	6mo	Admit to coronary care unit for sx of MI	Assessment of analgesic effect of metoprolol
Kubica N=70	Retrospective	Hospital Stay	STEMI or NSTEMI	Assess morphine effect on PK/PD of ticagrelor
Lapostolle N=1,862	Prospective	30d	STEMI	TIMI flow 3 in culprit vessel and ST segment elevation resolution pre-PCI ≥ 70%
Thomas N=12	Posthoc of RCT	24h	STEMI	VerifyNow platelet reactivity

Characteristics of Non-randomized studies				
Study	**Study Design**	**Follow up**	**Patients**	**Outcomes**
Bellandi N=182	Prospective	2yr	STEMI	Myocardial reperfusion by early ST-segment resolution
Bonin N=969	Retrospective	1yr	STEMI	MACE
Danchin N=3,548	Retrospective	1yr	STEMI	All-cause mortality
Farag N=300	Prospective	30d	STEMI	MACE and major bleeding
Franchi N=46	Posthoc of RCT	1yr	STEMI	Pharmacokinetic and pharmacodynamics
Grendahl N=20	Prospective	---	Uncomplicated AMI <48h of sx	Circulatory effects of morphine
Johnson N=106	Posthoc	1.5yr	STEMI	Platelet reactivity
McCarthy N=3027	Retrospective	Hospital stay	STEMI and NSTE-ACS	Mortality
Meine N=57,039	Retrospective	2.5yr	NSTEMI	In-hospital death, recurrent MI, CHF, cardiogenic shock
Puymirat N=2,438	Retrospective	2 months	STEMI with sx <48h	MI management practices and medium to long term outcomes
Siller-Matula N=32	Prospective	2yr	STEMI treated w/ prasugrel LD	If abciximab is a bridging therapy to achieve platelet inhibition
Silvain N=37	Posthoc of RCT	14h	STEMI	Coronary reperfusion prior to PCI with ticagrelor LD

Outcomes

Increased in-hospital mortality with morphine (N=65,349)

- Adjusted pooled analysis: RR 1.45; 95% CI 1.10 to 1.91; I^2=0%
- No differences between subgroup based on study design (P=0.67) and ACS type (P=0.25)
- Sensitivity analysis showed no difference between morphine and control (RR 1.41; 95% CI 0.87 to 2.27; I^2=0%; n=5872)

Increased MACE with morphine (N=61,429)

- Adjusted pooled analysis: RR 1.21; 95% CI 1.02 to 1.45; I^2=0%
- No differences between subgroup based on study design (P=0.44) and ACS type (P=0.98)
- Sensitivity analysis showed no difference between morphine and control (RR 1.40, 95% CI 0.85 to 2.30; I^2=0%; n=1952)

No difference in major or minor bleeding (N=552 and N=58,022 respectively)

- Major bleeding (RR 0.62; 95% CI 0.18 to 2.12; I^2=0%)
- Minor bleeding (RR 0.62; 95% CI 0.18 to 2.12; I^2=40%)
- No differences between subgroup based on study design and ACS type for both major (p=0.85) and minor bleeding (p=0.20)

Platelet Reactivity increased with morphine (N=310)

- 1 hour after administration: 59.37 platelet reactivity units (PRU) (95% CI 36.04 to 82.71; I^2=23%)
- 2 hour after administration: 68.28 PRU (95% CI 37.01 to 99.55; I^2=28%)
- Subgroup analysis showed no difference based on study design (P=0.25) and ACS type (p=0.24)

	No differences in cardiogenic shock, heart failure, hypotension, nausea/emesis, respiratory insufficiency	
Author's Conclusions	Morphine associated with increased risk of in-hospital mortality and MACE; however, risk of bias leads to low confidence in these results. Morphine decreases the effect of $P2Y_{12}$ inhibitors in the first 2 hours after morphine administration, the risk of bias with this outcome is low.	
Critique	**Strengths** • Large patient population • Assessed both STEMI and NSTE-ACS • Low heterogeneity for outcomes of mortality and MACE • Subgroup analysis performed for study design and ACS type improve internal validity • Categorized studies risk of bias using well defined tools • Sensitivity analysis performed to test robustness of results • Subgroups determined a priori rather than post-hoc improve internal validity • Used GRADE framework to assess quality of evidence for each study improving internal validity • 2 authors independently screened all articles appropriateness of inclusion with disagreements decided by a final arbitrator	**Weaknesses** • Population of patients in retrospective studies vastly outnumber patients from RCTs • 81% of patients were from CRUSADE trial • Pain severity not reported in included studies • Dose and route of administration of morphine not reported in many trials • Medications that may inhibit clopidogrel effectiveness not reported • CYP 2C19 polymorphisms not addressed • Sensitivity analysis is not consistent with pooled analysis and subgroup analysis • High risk of bias in 2 of the 5 RCTs and all but one observational trial • Combined data from RCTs and observational trials introduces several confounders
Take Away Summary	Morphine associated with higher in-hospital mortality and MACE although since sensitivity analyses are inconsistent with this finding, the data is not strong. Platelet reactivity is significantly increased 1-2 hours after morphine administration in patients with ACS.	

Conclusion and Recommendation

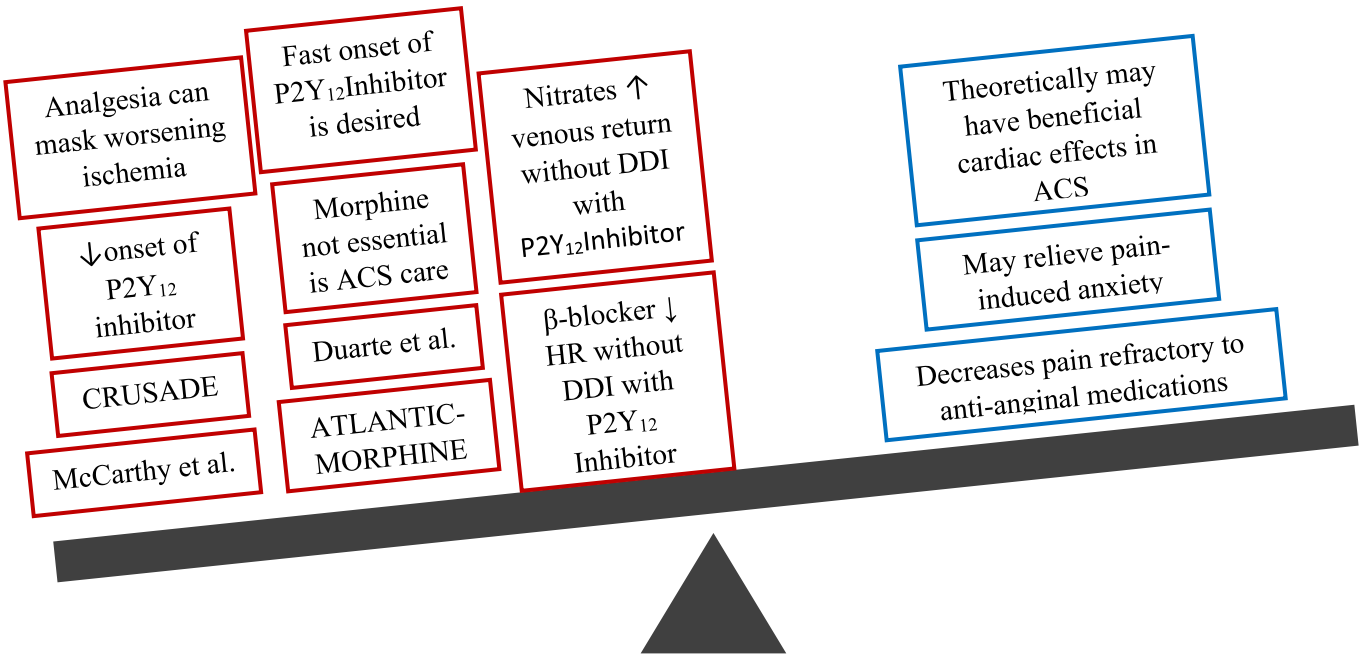
Summary of Literature:[33-37]

Study	ACS Population	$P2Y_{12}$ inhibitor	Conclusion	
CRUSADE	NSTE-ACS	clopidogrel	↑ Mortality, MI, cardiogenic shock, & CHF	
ATLANTIC-Morphine	STEMI	ticagrelor	↓ TIMI 3 Flow in culprit artery	
			↑ GP IIb/IIIa inhibitor use	↑ bleeding
McCarthy et al.	NSTE-ACS & STEMI	clopidogrel & ticagrelor	↑ infarct size	↑ hospital stay
			Trend towards ↑ mortality in NSTE-ACS	No effect on STEMI
Duarte et al.	NSTE-ACS & STEMI	mostly clopidogrel & ticagrelor; some prasugrel	↓ $P2Y_{12}$ effect within 2 hours of morphine use	
			↑ MACE	↑ mortality

Final Recommendation:

- Evidence does **NOT** support the safe use of morphine for pain relief in ACS.
- Morphine should **NOT** be recommended routinely for ACS, especially in patients receiving clopidogrel or ticagrelor prior to PCI according to current evidence.
- There is insufficient evidence to make a recommendation for morphine use in ACS in patients receiving prasugrel.
- Theoretically, morphine may be used safely in patients receiving cangrelor as it IV and therefore avoids drug interaction. However, more research must be conducted to determine safety.

Pros versus Cons of Morphine Use in ACS:



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