<table>
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<tr>
<th>Worksheet author(s)</th>
<th>Date Submitted for review: Jan 28 2010</th>
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<tbody>
<tr>
<td>Michelle Welsford</td>
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**Clinical question.**

ACS-19 – 1A: In patients with non-ST elevation ACS in prehospital and emergency department settings (P), does the use of clopidogrel or newer oral antiplatelet agents, (prasugrel, ticagrelor) (I) compared with standard management (ie. no prehospital or ED use of clopidogrel or compared to clopidogrel or new tienopyridines) (C), improve outcome (eg. chest pain resolution, infarct size, ekg resolution, survival to discharge, 30/60 d mortality) (O)?

ACS-19 – 2A: In patients with STEMI and fibrinolysis in prehospital and emergency department settings (P), does the use of clopidogrel (I) or newer oral antiplatelet agents, (prasugrel, ticagrelor) (I) compared with standard management (ie. no prehospital or ED use of clopidogrel or compared to clopidogrel or new tienopyridines) (C), improve outcome (eg. chest pain resolution, infarct size, ekg resolution, survival to discharge, 30/60 d mortality) (O)?

ACS-19 – 3A: In patients with suspected STEMI and PCI in prehospital and emergency department settings (P), does the use of clopidogrel or newer oral antiplatelet agents, (prasugrel, ticagrelor) (I) compared with standard management (ie. no prehospital or ED use of clopidogrel or compared to clopidogrel or new tienopyridines) (C), improve outcome (eg. chest pain resolution, infarct size, ekg resolution, survival to discharge, 30/60 d mortality) (O)?

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

Therapy

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

Revision

**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).**

- **Medline (OVID):** 
  
  ![Clopidogrel or plavix or Prasugrel).m_titl.] AND [Myocardial infarction/ OR Angina, Unstable/ OR acute coronary syndrome.mp. OR STEMI.mp.]; limit to human = 308 (1996 to July week 5 2008) then (1980 to 1996) then (July week 5 2008 to Sept week 4 2008)

- **EMBASE (OVID):**
  
  ![Clopidogrel or plavix or prasugrel). m_titl. ] AND [Myocardial infarction/ OR myocardial ischemia/ or Angina, Unstable/ OR coronary thrombosis/ OR myocardial reperfusion/ OR chest pain/ OR acute coronary syndrome.mp. OR STEMI.mp. OR angioplasty.mp. OR heart catheterization.mp. OR percutaneous coronary intervention.mp. OR primary angioplasty.mp. ] ; limit to human

- **COCHRANE Central Register of Controlled Trials (OVID):** 
  
  ![Clopidogrel or plavix or Prasugrel).mp.] AND [Myocardial infarction/ OR Angina, Unstable/ OR acute coronary syndrome.mp. OR STEMI.mp.]; 135 (to 3rd quarter 2008)

- **ECC EndNote Library (24 March 08):**
  
  "Clopidogrel" [81]
  "Prasugrel" [0]

- **Pubmed "Prasugrel" [112]

And hand reference searches of key articles

- **State inclusion and exclusion criteria**

  Inclusion: Therapy trials, ACS, STEMI or Non-STEMI only;
  Exclude Abstract only, animals

  Number of final references in worksheet: 37.
### Summary of evidence

#### Evidence Supporting Clinical Question

**Question 1 – Non-STEMI ACS; Clopidogrel, Prasugrel, Ticagrelor, or Ticlopidine**

<table>
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<th>Level of Evidence</th>
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<tr>
<td><strong>Good</strong></td>
<td>CURE / Yusuf 2001 (C, D)</td>
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<td>Murphy 2008 (D)</td>
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<td>Morrow 2009 (E)</td>
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**Level of evidence**

A = Survival/mortality hospital discharge  
B = Survival/mortality 30 days  
C = Composite: death, reinfarction, stroke  
D = Other composite outcome  
E = Other clinical outcome  
F = Platelet activity

#### Evidence Supporting Clinical Question

**Question 2 – STEMI managed with lysis; Clopidogrel, Prasugrel, Ticagrelor**

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A = Survival/mortality hospital discharge  
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D = Other composite outcome  
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F = Platelet activity

#### Evidence Supporting Clinical Question

**Question 3 – STEMI managed with PPCI; Clopidogrel, Prasugrel, Ticagrelor**

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**Level of evidence**

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E = Other clinical outcome  
F = Platelet activity
### Evidence Neutral to Clinical question

**Question 1 – Non-ST-elevation ACS; Clopidogrel or Prasugrel**

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<td>JUMBO / Wiviott 2005 (B, D)</td>
<td>CREDO / Steinhubl 2002 (D)</td>
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**Level of evidence**

1. A = Survival/mortality hospital discharge
2. B = Survival/mortality 30 days
3. C = Composite: death, reinfarction, stroke
4. D = Other composite outcome
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### Evidence Neutral to Clinical question

**Question 2 – STEMI managed with lysis**

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**Level of evidence**

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### Evidence Neutral to Clinical question

**Question 3 – STEMI managed with PPCI**

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**Level of evidence**

1. A = Survival/mortality hospital discharge
2. B = Survival/mortality 30 days
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## Evidence Opposing Clinical Question

**Question 1 – Non-ST-elevation ACS**  
**Question 2 – STEMI managed with lysis**  
**Question 3 – STEMI managed with PPCI**  
(NONE)

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- F = Platelet activity
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Clopidogrel:

Dual antiplatelet therapy with clopidogrel added to ASA, has shown evidence of benefit across the spectrum of moderate-to-high risk ACS patients. Those with STEMI managed with fibrinolysis and those with ACS managed with planned PCI have the greatest evidence of benefit. Clopidogrel’s onset of action is over hours but can be partly accelerated with higher loading doses. Active platelet inhibition is variable with some patients having a genetically-related poor response.

The CURE study randomized over 12,000 moderate to high risk ACS patients (without STEMI) to clopidogrel (300 mg load and 75 mg daily) or placebo and showed benefit. The Budaj 2002 post-hoc analysis of CURE showed the benefit was similar in low, moderate, and high risk groups, but the truly low-risk group was so small as to make the analysis weak for the low-risk group. Across all of these trials, the truly low risk ACS may not have been recruited into these trials (select higher risk to increase event rate and have a greater chance of showing a treatment effect). Therefore, the true balance of effectiveness and safety of clopidogrel in the low risk or possible, but not confirmed ACS, has not yet been determined.

The COMMIT trial showed benefit in STEMI patients either not being reperfused or receiving fibrinolysis. The multi-centre Chinese study, included over 45,000 STEMI patients randomized to receive 75 mg daily of clopidogrel (no loading dose) or placebo. Reduction in combined end-point (death, MI, stroke) and reduction in all mortality was found.

The CLARITY study was a double-blind RCT of clopidogrel (300 mg load and 75 mg daily) in > 3000 STEMI patients receiving fibrinolysis that also showed benefit to addition of Clopidogrel to ASA/anticoagulants and fibrinolysis.

Although several studies have shown benefit to Clopidogrel administration to ACS patients with planned PCI, there are no RCTs of Clopidogrel use for STEMI patients managed with primary PCI. However, three non-randomized trials of patients with STEMI and PPCI have shown benefit to clopidogrel (Lev, Zeymer 2006, Zeymer 2008 1). Similarly, another study that focused on planned PCI days after fibinolysis for STEMI (PCI-CLARITY) can be extrapolated to indicate that Clopidogrel is likely beneficial for STEMI patients prior to primary PCI.

There appears to be increased bleeding risks associated with clopidogrel use across most of the studies although the increase in major/fatal bleeding is small and did not appear to offset the benefit in the study populations. It is important to understand that most of these studies excluded patients that might be at higher risk of bleeding and so a careful risk assessment would need to occur with each patient. Additionally, it is generally known that Clopidogrel can increase bleeding in patients undergoing CABG, and thus the medication is ideally stopped for 5-7 days prior to CABG, if possible.

Optimal dosing of clopidogrel may not yet be known. Many of the studies have used a loading dose of 300 mg (although the COMMIT trial omitted the loading dose) and a maintenance dose of 75 mg. There is some evidence that a loading dose of 600 mg or even 900 mg may have larger benefit and a meta-analysis of several RCTs and non-randomized studies using higher doses showed a benefit. However, the risks of these higher doses in all subgroups have not been fully elucidated. Additionally, several newer studies on dosing of clopidogrel have focused on individualizing dosing regimens by measuring platelet responsiveness.

In a CLARITY substudy that involved over 200 patients (Verheugt 2007) who received pre-hospital thrombolysis, similar benefits were seen with prehospital administration of clopidogrel (300 mg load), with no significant increase in early major bleeding. This study demonstrated the feasibility, safety, and benefit of early prehospital administration of clopidogrel in STEMI patients.

Although clopidogrel is commonly used for STEMI patients managed by PPCI, this has not been directly studied in a RCT. Evidence is primarily from extrapolation of patients with non-STEMI ACS managed with elective PCI. One systematic review (Vlaar) attempted to answer the question. This study compared different studies of PPCI in STEMI patients where they did or did not also receive clopidogrel. Since these studies’ main goals were other therapies, the studies are quite heterogeneous. Despite taking some of these differences into consideration, the differences found may still be partly due to differences between the studies rather than the clopidogrel alone. However, the treatment effect is similar to that found in RCTs of clopidogrel use in STEMI managed with lysis and non-STEMI ACS patients, therefore,
there is reason to believe that the treatment effect may be genuine. Found statistically significant benefit in TIMI flow, mortality (OR 0.57), and death/reinfarction.

Prasugrel:

Prasugrel in a novel thienopyridine, which inhibits platelet activation and aggregation via the same ADP receptor pathway as Clopidogrel. It may have a more consistent and pronounced platelet inhibitory effect that may not have the same differential genetically-determined response. It has a shorter onset of action that clopidogrel (within 30 minutes, before Clopidogrel onset) which may be beneficial in the patient who undergoes unplanned / emergent PCI. The possible greater platelet inhibitory effect comes at a cost of associated greater major bleeding.

One double-blind RCT (LOE 1), and 4 additional subgroup/reanalysis (LOE 1-2), have studied the effect of Prasugrel compared to Clopidogrel in patients with ACS. In non-STEMI patients and patients with STEMI >12 hours after onset of initial symptoms, the loading dose was administered after angiography indicated coronary anatomy suitable for angioplasty in non-STE ACS. In STEMI ≤ 12 hours after onset of initial symptoms, the loading dose was given prior to the coronary angiography. 3 of the 4 LOE 1 studies showed benefit in combined endpoints and both LOE 2 studies showed benefit in combined endpoints. The benefit came at a cost of increased minor and major bleeding in the total population studied. Post-hoc exploratory analysis identified risk factors associated with a higher rate of bleeding with prasugrel: age ≥ 75 years, presence of a previous stroke or transient ischemic attack and body weight < 60 kg. In the prespecified subgroup analysis of STEMI patients, there was no difference in major or minor bleeding. This could however be due to the smaller population analyzed and to differences in base-line characteristics with less patients with high-risk profile for bleeding. The benefit of prasugrel compared to clopidogrel in this study (and reanalyses) may have been accentuated or solely due to the timing of administration and the quicker onset of action of prasugrel in comparison.

Since administration of this drug was only after the anatomy was known in non-STEMI and STEMI > 12 hours after onset of initial symptoms in this one trial (and reanalyses), there is NO evidence of its use in the ED or prehospital in these patients. It is unknown whether there would be added benefit and/or harm by administration prior to arrival at the cath lab. Further studies are needed to determine if there is any benefit to administration of Prasugrel in the prehospital or Emergency Department setting in these subgroups. Also, studies need to determine the best dose of Prasugrel and to determine if there are easily identified subgroup of patients that would benefit from this medication despite the increased bleeding risk. In the subgroup of STEMI ≤ 12 hours after onset of initial symptoms, the loading dose was administered before the coronary angiogram was performed, in a hospital setting. Extrapolation to a pre-hospital or emergency department setting therefore seems acceptable. However, despite the absence of difference of bleeding complications in the pre-specified STEMI sub-group, it seems reasonable to avoid prasugrel in patients with risk factors for bleeding identified in the total population (age ≥ 75 years, body weight < 60 kg, past history of transient ischemic attack or stroke).

There is no research on the administration of prasugrel to patients undergoing fibrinolysis for STEMI.

Prasugrel is a relatively new medication with promising results. Its role and usefulness in the ED and prehospital setting is not yet known in non-STEMI and STEMI > 12 hours patients and cannot be adequately extrapolated to these settings without further research. Whether or not administration of clopidogrel should be withheld in the ED and prasugrel administered in the PCI lab MAY be considered. If prasugrel is administered in the ED department, it should be avoided in patients with risk factors for bleeding with prasugrel ((age ≥ 75 years, body weight < 60 kg, past history of transient ischemic attack or stroke). Combination of loading and maintenance doses of clopidogrel and prasugrel have not been studied. Harmonization of pre-hospital, emergency department, interventional cardiology and coronary care unit treatment protocols are necessary to avoid combinations of prasugrel and clopidogrel in the same patient.

Ticagrelor:

There is one study (Wallentin 2009 NEJM p. 1045) on this novel medication which is a reversible direct platelet antagonist via the ADP receptor. Its onset of action may be quicker and its action may be more consistent. A large double-blinded randomized controlled trial compared ticagrelor to clopidogrel in patients with high-risk ACS (STEMI or high-risk non-STEMI). Nearly 40% had STEMI, just over 40% had non_STEMI and only just over 15% had unstable angina. None of the patients had planned fibrinolysis. Primary end point: death from vascular causes, MI, or stroke; secondary end-points include other combined endpoints as well as mortality, stroke, stent thrombosis, and bleeding. In this group of over 18,000 patients, they found reduction in combined end point and in mortality with only a marginal increase in bleeding, a small increase in dyspnea and a small relative rise in creatinine.
Acknowledgements:
Nil

Citation List

(1-37)

Non-STEMI ACS; clopidogrel; This registry trial compared those patients with NSTEMI who didn't undergo PCI who received or didn't receive early clopidogrel. Non-randomized, did not match controls so poorer quality. Demonstrated lower inhospital mortality without increased risk of major bleeding. Primary outcome: inhospital mortality (A) Other outcomes (E): other inhospital events: postadmission MI, death or MI, cardiogenic shock, heart failure, stroke, major bleeding (any), non-CABG major bleeding, CABG major bleeding, RBC transfusion (any), non-CABG RBC transfusion; also Adjusted mortality
LOE 2; fair quality; supporting.


Non-STEMI ACS (undergoing PCI) & STEMI (PPCI); (must receive PCI); prasugrel. Secondary subgroup analysis of the TRITON RCT on Prasugrel compared to Clopidogrel. Looked at the loading dose vs maintenance dose by somewhat arbitrarily defining the time at before and after 3 days. Found benefit of Prasugrel in both phases, but bleeding risk only in maintenance phase. Primary outcome: composite death, MI, stroke; secondary during study period: 0-3 and after 3 days primary; 30 and 90 days primary composite, composite death, MI, urgent revasc, stent thrombosis; composite death, MI, stroke or rehospitalization d/t cardiac ischemia;
LOE 5 (not in emerg) quality poor (subgroups (not all ACS), secondary analysis), supporting (prasugrel over clopidogrel).


Level 1, fair quality (post-hoc subgroup analysis), good quality; supporting. nonSTE ACS; clopidogrel; Post-hoc analysis of CURE trial (RCT). Well-designed analysis. Validated TIMI risk score in their population. Clopidogrel found effective in reducing primary endpoints in patients with all levels of risk for ACS. However, low risk group very small (TIMI risk 0-1 was approx 5%) as this study was designed to enroll mod-to high risk patients. Thus, may still not be applicable to truly low-risk patients. primary outcome: composite CV death, MI, stroke

LOE 2 (Level 1 initial study, but this study non-randomized), quality poor (post-hoc, and not all ACS patients), supportive. Post-hoc analysis without randomized control of TARGET trial evaluating tirofiban vs abciximab; clopidogrel given to all but did posthoc analysis of whether clopidogrel given before vs after, showing benefit of clopidogrel. Primary outcome: death, MI, revascularization (30 days); secondary: composite 6 months and 1 year; and each individual of death MI and RV at 30 days, 6 months, and 1 year.


LOE 1, Good Quality (Best), Supportive. STEMI (lysis and no reperfusion); clopidogrel (and 2x2 design to also assess metoprolol). This is a very large (45,852 patients) multi-centre RCT double-blind study of patients in China with STEMI randomized to clopidogrel 75 mg (within 24 h of STEMI or LBBB) or placebo - no loading dose. All patients also received ASA and other treatments at discretion of MD: lysis in 54%, anticoag 75%. Primary outcome = composite of death, reinfarction, or stroke; and death from any cause. Excluded PPCI, but could have PCI afterwards (3%). Found benefit for clopidogrel for both primary outcomes, no diff in major bleeds, but small increase in minor bleeds. Included patients over 70 (26%) Absolute reduction in mortality of 0.6 % (7% relative reduction). Reduction in combined endpoint of 0.9% (9% relative reduction) found in all 3 parts of mortality, reinfarction, and stroke). Benefit seen across those receiving lysis, and those not reperfused. Primary outcome: 1: composite death, reinfarction, or stroke; and 2: death from any cause during the treatment period (average 14 days but up to 28 days). Clopidogrel does not appear to significantly increase major or minor bleeding in the short term, but long-term use may be different. Because only followed to d/c or 28 days and average stay of 14 days, may have had larger event rate and larger difference if followed out to 30 days for all patients (including those discharged). Also, if loading dose used, may have seen greater and/or earlier difference, but perhaps greater bleeding. No difference in other safety events looked at: cardiogenic shock, heart failure, presumed cardiac rupture, V Fib, other cardiac arrest and pulmonary embolus. Subgroup analyses may not be true, but did show that the benefit emerged very early (in the first and second day post treatment). There may also be a greater benefit for those treated early (within 6 hours of onset). Final conclusion: benefit and no apparent harm.


post-hoc analysis of ACUITY study on non-STE ACS investigating the influence of use of clopidogrel prior to CABG vs no clopidogrel; found improvement in 30 day combined end point without significantly greater (but trend) bleeding. Thus supports concept of upstream clopidogrel prior to PCI
LOE 3, quality fair, supportive


LOE 2, good, supportive;
Dose of 600 mg was superior to 300 mg; admin before PCI was superior to after


Level 5 evidence, fair quality, neutral. Post-hoc analysis of CURE trial. Not specifically powered to demonstrate independent treatment effect for the primary endpoints among patients proceeding to CABG. In particular, inadequate power to demonstrate post-operative effect of clopidogrel. Significant benefits seen with administration before CABG and PCI extending into post-operative period. Excess bleeding risk for those on clopidogrel before CABG was not statistically significant. However, most patients stopped clopidogrel > or = 5 days before CABG. Consideration of the duration of effect on platelets in the context of consistent increased bleeding risk and trend towards increased re-operation rates due to bleeding for patients with acute coronary syndrome taking clopidogrel within 5 days before CABG suggests real, "modest" excess risk. This is significant in the face of an inadequately powered study. This study doesn’t directly relate to the PICO question, and doesn’t relate to the first 4 hours in the ED/prehospital, but is important to realize that if the STEMI / ACS patient goes on to CABG, the clopidogrel should be stopped.


LOE 2; post-hoc analysis of CLARITY-TIMI 28 found benefit to preadmin of clopidogrel in those receing lysis who went on to PCI for STEMI, lysis LOE 2, supportive, fair for STEMI, PPCI LOE 5, supportive, fair


171 STEMI patients undergoing PPCI
retrospective non-randomized comparison
given 300 or 600 mg clopidogrel before the angiography
the 600 mg dose statistically improved 30 day mortality, MI, urgent revascularization or stroke
LOE 2, supportive of 600 mg dose, fair

prospective non-randomized study (> 1000 patients) of clopidogrel vs ticlopidine in STEMI managed by PCI

clotdogrel had more recurrent ischemia in hospital and at 30 days and more moderate to severe bleeding at 30 days with similar rate of stent thrombosis. 

LOE 2, supportive (for ticlopidine), fair


before/after study of different dosing regimens for clopidogrel in patients receiving PCI.
approx 50% were stable angina, 25% NSTE ACS and 25% STEMI
600 mg load then 150 mg for 14 days vs 300 mg load then 75 mg
showed small but statistically significant improvement in composite deathm MI or stent thrombosis with nonsignificant small increase in bleeding

LOE 3, supportive (of higher dosing), fair (mixed group)


LOE2, poor quality, supportive (or receiving Clopidogrel before PPCI). Non-randomized prospective trial of STEMI patients who undergo PPCI and comparing clopidogrel before PCI vs after PCI. Overall supportive, but groups not the same and didn’t keep track of dose of clopidogrel. Results not strong in support of giving clopidogrel before Primary PCI. Primary Outcome : TMG 3 flow at end of PCI and 30/60 death, reinfarction, stent thrombosis, revascularization, and 60 d composite (death, reinfarction, or revascularization)


LOE 1 (meta-analysis of RCT and non-randomized); quality fair (some non-RCTs); supportive of higher dose. Clopidogrel; non ACS and some non-STEMI ACS patients (small proportion were ACS). Primary outcome: 30 day death, MI; secondary endpoints: recurrent ischemia, bleeding. Supportive 30 day mortality and little increase (non-significant) in major bleeding. OASIS 7 is ongoing study that will answer this question more definitively for ACS patients.

Level 1 LOE, good quality, supportive. Multicenter double-blind RCT, adequately powered trial conducted in tandem with the CURE trial using common patient population, treatment arms and primary outcomes. ACS patients with planned PCI (not emergent, but done an average of 6 days after randomization); therefore, not applicable to acute therapy per se. Evidence of safety and statistically significant reduction in primary outcome events when Clopidogrel was used for pretreatment of ACS before PCI during the course of admission. Patients in the placebo group receiving open label Clopidogrel after PCI which may result in an underestimation of the measured treatment effect. Primary outcome: composite of 30 d CV death, MI, or revascularisation.


prespecified STEMI substudy of TRITON-TIMI 38
3534 patients presenting with STEMI were separately randomized to clopidogrel vs prasugrel in addition to everyone receiving ASA; 2438 were randomized prior to primary PCI (others were secondary). only 27-31% of patients received either study drug prior to PCI and thus may not be directly applicable to emerg setting
primary endpoint: composite of CVS death, MI, Stroke, follow-up to 15 months
the results were reported for all STEMI and those for primary PCI only. Although there was a statistically significant reduction in primary composite endpoint, MI, mortality, etc in the all STEMI group, there was only a trend to improvement in the composite outcomes for the primary PCI cohort. For the bleeding complications, there were no significant differences in major, minor or life-threatening bleeding in the all STEMI group (and PPCI group). There was a significantly lower rate of stent thrombosis in the all STEMI and PPCI cohorts.
manufacturer supported
LOE 5 (not ED); good quality; neutral (for PPCI)


subgroup analysis of TRITON-TIMI 38 (prasugrel vs clopidogrel in ACS (mostly non-STE ACS)
examining rate of MIs of different classifications finding reduction in most types of MI; this isn't new data, just focuses on one of the findings
LOE 5; poor quality; supportive for non-STE ACS


LOE 5 (not emerg), quality poor, supporting. TRITON post-hoc re-analysis looking at all adverse events, not just first episode; prasugrel Primary outcome: recurrent primary endpoint after initial non-fatal endpoint (CV death, MI, stroke).

Found sustained benefit of combined endpoints for prasugrel when with GP IIa/IIIb with similar increased bleeding
LOE 5 (not admin in emerg), quality fair (subgroup), supportive


LOE 5 (different patient population), quality fair, supportive. RCT of fewer than 350 patients in 2 centres (Italy). No STEMI/PPCI. Patient population included both stable angina and nonSTEMI (only 25% were ACS), therefore, uncertain if this is the same treatment effect you would see in patients exclusively with NSTEMI ACS. Outcomes: combined end point 4% vs 12% (difference due mostly to periprocedural MI). There was a 50% reduction in MI rate.


Level 1 LOE, Good Quality, Supportive. Multi-centre RCT, of clopidogrel added to lysis/ASA/heparin for STEMI. There were 3491 patients, 18-75, who presented < 12 h after onset of CP with STEMI in 23 countries. All received lysis, ASA, some heparin, planned angio (day 2-8). STEMI anterior 41%.

Clopidogrel 300 loading followed by 75 daily with placebo control. Primary outcome: composite of occluded infarct-related artery on angio, or cath, or recurrent MI before angio. Showed benefit to clopidogrel mostly in TIMI flow and small reduction in recurrent MI at 30 days. V. Low overall mortality (3%) with no reduction in clopidogrel group. Therefore, the “positive” findings of this study is a benefit in a “surrogate” marker without increase in harm. Other endpoint at 30 days: death CV causes, recurrent MI, or stroke (non statistically significant reduction), had to add recurrent ischemia leading to urgent revascularization to find benefit at 30 days. Bleeding similar including post CABG. Trend towards greater major (v. little) and minor bleeding, but not statistically significant. Note that this only applies to the < 75 age group and thus safety in > 75 not established. This study was not powered to find a mortality benefit, and none seen (COMMIT was powered for this). This study had a surprisingly low event rate (and mortality rate) which may have resulted in the mandated angiography and PCI days 2-8. Those that did receive PCI were allowed to use open-label Clopidogrel (total of 55% of the patients). Thus overall event rates and mortality lower than in studies that did not mandate angio. (COMMIT did not have mandated angio and did have higher event rates). Exclusions: prior Clopidogrel (7 days), GP IIb/IIIa prior to angio; contraindication to lysis, plan to perform angio within 48 hours, cardiogenic shock, prior CABG, and higher dosing of UFH or LMWH. Authors report industrial sponsorship and conflicts.


LOE 1, good quality, supportive. Subgroup analysis of CLARITY trial of those STEMI patients initially receiving lysis/ASA/heparin +/- clopidogrel and later cath +/- PCI (day 2-8). Positive combined endpoints, this study does not look at primary or emergent PCI but rather PCI after routine cath 2-8 days later, thus any benefit can only be extrapolated, because 2+ days of therapy before PCI is very different than receiving the first dose just a few hours ago. Likewise, the periprocedural risks are different for PPCI and PCI done on days 2-8.


LOE 5 (extrapolate to ACS), quality fair, neutral (for pretreatment before PCI) and supportive (of long-term clopidogrel). Extrapolation of large, multi-center study of clopidogrel use in planned PCI (not only ACS), inadequately powered to study primary endpoints. No statistically significant benefits (trend) seen in patients pretreated with Clopidogrel > 6 hours before PCI. Primary endpoint: one year composite death, MI or stroke; and 30 day composite death, MI, revascularization


LOE 1, fair quality (relative small size), supportive. Subgroup prehospital study of CLARITY-TIMI 28 trial – trial of adding double blind clopidogrel to lysis, ASA, heparin for STEMI. Prehospital admin of Clopidogrel (216 patients) resulted in reduction of combined end-point without increased bleeding. Shows that admin of clopidogrel in the ambulance is feasible and that the benefit of administering clopidogrel extends to administering in ambulance (but did not compare that given in ambulance versus given in hospital). Primary endpoint: composite occluded IRA, death, or MI STEMI/Lysis; clopidogrel


LOE 2 (Systematic review of RCT and non-randomized studies to look at a non-randomized treatment); fair quality (heterogeneous studies); supportive. This systematic review attempts to answer the question of benefit of clopidogrel prior to PPCI in patients with STEMI. There are no randomized studies that answer this question so they compared different studies of PPCI in STEMI patients where they did or did not also receive clopidogrel. Since these studies’ main goals were other therapies, the studies are quite heterogeneous. Despite taking some of these differences into consideration, the differences found may still be partly due to differences between the studies rather than the clopidogrel alone. However, the treatment effect is similar to that found in RCTs of clopidogrel use in STEMI managed with lysis and non-STEMI ACS patients, therefore, there is reason to believe that the treatment effect may be genuine. Primary outcome: coronary artery patency before PPCI; Secondary end points: short-term mortality, composite of death or reinfarction,
and in-hospital major bleeding. Found statistically significant benefit in TIMI flow, mortality (OR 0.57), and death/reinfarction. Authors report no disclosures.


PLATO study: multicenter, double-blind, RCT of 18,624 ACS patients (high-risk non STE ACS and STEMI managed with Primary PCI (38%))
ticagrelor (180-mg loading dose, then 90 mg BID to clopidogrel (300-to-600-mg loading dose, then 75 mg daily) in addition to ASA ; 49% had already received clopidogrel load; treatment began within 5 hours of hospitalization so can correspond to ED but not prehospital treatment primary end point of composite of MI, CVS death, or stroke significantly reduced with ticagrelor compared to clopidogrel. Also significant reduction in other combined end points as well as MI alone and mortality alone (1.1% reduction) but not stroke. No substantially increased risk for overall major or life-threatening bleeding, but increased non-CABG fatal bleeding .
Ticagrelor was associated with greater dyspnea and ventricular pauses on holter similar to findings in dose-ranging previous studies
The drug is also apparently reversible (thus the lower CABG-related bleeding), making it safer when CABG is an option
manufacturer-sponsored study and was also part of executive steering committee
LOE 1, good quality, supportive of ticagrelor over clopidogrel


LOE 2, fair quality, neutral. This was a nonrandomized retrospective review of the loading dose of clopidogrel that showed those with a higher loading dose had a worse combined end point. There was no placebo or group that did not receive clopidogrel. Therefore, although this was a negative trial for the higher dose, it is a neutral study on the use or not of this medication. Primary endpoint: combined 60 d death, MI, stroke, or revascularization


LOE 5 (not in ED), quality fair, neutral for non-STE ACS
RCT double-blind. Dose-ranging randomized phase 2 trial of prasugrel compared to clopidogrel in elective PCI and ACS/PCI patients (randomized in cath lab after anatomy known). Major and minor bleeding non significantly increased. Efficacy nonsignificantly improved. Overall neutral trial. Primary outcomes: minor and major bleeding; efficacy outcomes: combined and individual 30 d death, MI stroke, recurrent ischemia, vessel thrombosis.


LOE 5 (not given in emerg); quality fair (subgroup); supportive. Subgroup analysis of large RCT of prasugrel compared to clopidogrel in patients with DM. Found relative benefit in combined endpoint greater than in non-DM patients without greater bleeding risk (AOT those without DM who do have greater bleeding). Primary outcome: combined CV death, MI, stroke; secondary: combined death, MI, stroke and TIMI major bleeding.

Subanalysis of TRITON-TIMI 38 trial. RCT prasugrel vs clopidogrel in those who underwent PCI stenting of mod-high risk ACS (not all ACS, only those stented, included UA, NSTEMI, STEMI). 12,000 + patients. primary endpoint: composite of cardiovascular death, non-fatal MI, or non-fatal stroke; other: stent thrombosis. Reduced both in bare-metal and drug-eluting stents

LOE 5 (not given in emerg), fair quality (subgroup), supportive.


Post-hoc analysis of CURE trial. To explore rapidity of onset of effects, the authors used the secondary composite outcome and included refractory or severe ischemia in addition to primary endpoints. During the first 24 hours, 20% RRR in primary outcome measures alone; 34% RRR in expanded composite (p < 0.003). Figure 2 Kaplan-Meier graph shows curves begin to diverge 2 hours after randomization. Unclear if effects in specific 0-4 hour time window are statistically significant. Need further study to elucidate this effect.
Level 1, poor quality, supportive.


Level 1, good quality, supporting study. The landmark CURE trial. Multi-center, adequately powered RCT of clopidogrel vs placebo in over 12,000 non-STEMI ACS patients (mod-high risk, had either positive biomarkers or new ischemic changes on ECG). Showed evidence to support efficacy of clopidogrel in association with aspirin to reduce events (composite endpoint of refractory ischemia, death from cardiovascular causes, nonfatal AMI, stroke) in non-ST elevation ACS. Increased risk of major bleeding. Benefit in primary outcome measures “within a few hours after randomization” with benefit seen by 24 hours after randomization. See Yusuf et.al., 2003 post-hoc analysis. Authors report industry sponsorship and conflicts.
Non-STE ACS, clopidogrel; primary outcome: composite: death, MI, stroke; first composite or refractory ischemia


LOE 3, quality fair; supportive. This retrospective study used registry data to compare those STEMI patients who either did or did not receive clopidogrel in the first 24 hours. Showed benefit in combined endpoint but increase in major bleeding.
STEMI patients: approx 28% no reperfusion, approx 29% lysis and 43% PPCI; clopidogrel; primary outcome: combined in hospital death, non-fatal reinfarction, not-fatal stroke


LOE 3, poor quality, supportive. Retrospective analysis with subgroup analysis of the addition of clopidogrel to ASA for STEMI patients that survived to d/c. Supportive but poor quality.
STEMI – lysis25%, PPCI (45%); primary outcome: 1 year mortality in those that survived to d/c

LOE 3, quality fair, supportive, Retrospective analysis of registry data on NSTEMI patients managed with ASA with Clopidogrel versus no clopidogrel; Showed benefit in combined endpoint but increase in bleeding; primary outcome: in hospital and 1 year mortality and combined death, MI, stroke