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

**Worksheet author(s)**

<table>
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<tr>
<th>Christian Spaulding</th>
<th>Date Submitted for review:</th>
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<tr>
<td>Ian Jacobs</td>
<td>14th June 2009; Updated 9th Feb 2010</td>
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### Clinical question.

ACS-19-1-B: In patients with non-ST elevation ACS in prehospital and emergency department settings (P), does the use of clopidogrel (or new tienopyridines, prasugrel)(I), compared with standard management (ie. no prehospital or ED use of clopidogrel) (C), improve outcome (eg. rate of infarction, survival to discharge, 30/60 d mortality) (O)?

ACS-19-2-B: In patients with STEMI and fibrinolysis in prehospital and emergency department settings (P), does the use of clopidogrel (or new tienopyridines, prasugrel)(I), compared with standard management (ie. no prehospital or ED use of clopidogrel) (C), improve outcome (eg. rate of infarction, survival to discharge, 30/60 d mortality) (O)?

ACS-19-3-B: In patients with suspected STEMI and PCI in prehospital and emergency department settings (P), does the use of clopidogrel (or new tienopyridines, prasugrel)(I), compared with standard management (ie. no prehospital or ED use of clopidogrel) (C), improve outcome (eg. rate of infarction, survival to discharge, 30/60 d mortality) (O)?

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

**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?

Spaulding: I have received speaker’s fees from Lilly and Sanofi (less than $ 10 000 yearly)

Jacobs: Nil

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

**PubMed:** up to November 12 2009: prasugrel (252); clopidogrel and acute myocardial infarction (738); clopidogrel and acute coronary syndrome (913); ticagrelor (54)

**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]

And hand reference searches of key articles, and personnel collection of manuscripts

### State inclusion and exclusion criteria

**Inclusion:** Therapy trials, ACS, STEMI or Non-STEMI only;

**Exclude:** Abstract only, animals

### Number of articles/sources meeting criteria for further review:

253 articles reviewed, 22 considered for the consensus on science statement
# Summary of evidence

## Evidence Supporting Clinical Question

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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- *Italics = Animal studies*
**Evidence Neutral to Clinical question**

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**Evidence Opposing Clinical Question**

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CLOPIDOGREL:
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.

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. This 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.

There appears to be increased bleeding risks associated with clopidogrel use in most 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. The issue of increased bleeding in patients receiving Clopidogrel and undergoing coronary artery bypass grafting has been extensively debated. A recent substudy analysis of the ACUITY trial has shown that Clopidogrel administration before catheterization in patients with NSTE-ACS requiring CABG is associated with significantly fewer 30-day adverse ischemic events without significantly increasing major bleeding, compared to withholding clopidogrel until after angiography. These findings support the American College of Cardiology/American Heart Association guidelines for upstream clopidogrel administration in all NSTE-ACS patients, including those who subsequently undergo CABG.

Optimal dosing of clopidogrel has been studied in the CURRENT OASIS trial. A loading dose of 600 mg of clopidogrel followed by 150 mg daily for one week and then by 75 mg daily was superior to a loading dose of 300 mg followed by 75 mg daily. In a pre-specified subgroup analysis of the Horizons trial, the use of a loading dose of 600 mg significantly reduced the rate of major cardiac events compared to a loading dose of 300 mg. 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.

The use of clopidogrel in patients with ACS aged ≥ 75 years of age has not been studied in a dedicated randomized trial. In the early studies on clopidogrel in NSTEMI ACS and in studies on STEMI treated by thrombolytic therapy, this subgroup was excluded. In the more recent trials such as TRITON TIMI 38, HORIZONS and CURRENT OASIS, these patients were included however specific substudies on patients...
aged ≥ 75 years of age is lacking. The prognosis of patients aged ≥ 75 years of age with STEMI is poor, mostly because these patients are not managed effectively. It therefore seems acceptable to administer clopidogrel in patients aged ≥ 75 years of age except in STEMI treated with thrombolysis, where the risk/benefit is unknown. The ideal dose in this group has not yet been determined (75-600mg)

**Prasugrel:**
Prasugrel in a novel thienopyridine, which inhibits platelet activation and aggregation via the same ADP receptor pathway as Clopidogrel. One double-blind RCT (Wiviott 2008), and 4 additional subgroup/reanalysis 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 STEMI ≤ 12 hours after onset of initial symptoms, the loading dose was given prior to the coronary angiography. There was a benefit in combined end-points. 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 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. 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**
Ticagrelor is the first reversible oral P2Y12 receptor antagonist.12 Unlike the thienopyridines, ticagrelor is not a prodrug and does not require metabolic activation to inhibit the P2Y12 receptor. Furthermore, ticagrelor has favorable pharmacokinetics and pharmacodynamics, including rapid peaking of plasma levels (1.5-3 hours) and rapid onset of antiplatelet effects (within 2 hours). The interindividual variability of response is low.12 Importantly, the agent's half-life is 7 to 8 hours; and the antiplatelet effect is low 48 hours after the last dose. This reversibility might offer greater flexibility for surgical procedures. On the other hand, it may be a disadvantage in relation to possible poor compliance.

Ticagrelor was assessed in a large randomized trials on patients with STEMI and NSTEMI ACS and compared to clopidogrel. The drugs were given before PCI. Treatment with ticagrelor as compared with
clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. There was no heterogeneity in a subgroup analysis of patients aged >75 years of age.

Acknowledgements:

**Citation List**


Level 3 Fair.


Level 2. Fair. Clinical end-points but no randomization.


Level 1. Fair. Post-hoc analysis of CURLY trial. Well-designed analysis. Validated the TIMI risk score in their population. Clopidogrel found effective in reducing primary endpoints as outlined in CURE trial in patients with all levels of risk for ACS. No information on pre-hospital use


Level 1, good. Comparison between clopidogrel and aspirin.


Level 1. Fair Small trial with both clinical and platelet reactivity end-points demonstrating the value of a loading dose of 600 mg of clopidogrel in patients with NSTEMI treated by coronary stenting.

Level 2 Fair. Good appraisal of CABG with pretreatment with clopidogrel

Level 1. Fair Post-hoc analysis of CURE trial. Not specifically designed to demonstrate independent treatment effect for the primary endpoints among patients proceeding to CABG. 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, there was an increase of re-operation rates due to bleeding if clopidogrel was taken within 5 days of clopidogrel. Important findings in clinical practice: if all patients are to receive pre-hospital clopidogrel, some patients will be sent for CABG after coronary angiogram. If CABG must be performed within 5 days of clopidogrel administration, there will be an increase of re-CABG due to bleeding complications.

Level 1 Fair. Small trial with clinical end-points. Limited to patients with drug eluting stents

Level 3 Fair. Study on database.

Level 2 Fair. Non randomized comparison

Level 2 Fair. Subgroup analysis of a randomized trial. Only patients who receive bivalirudin.

Level 2 Fair Metaanalysis
Level 1. Good. Multicenter, adequately powered trial conducted within the CURE trial using common patient population, treatment arms and primary outcomes. Statistically significant reduction in primary outcome events when Clopidogrel was used for pretreatment of ACS treated by PCI during the hospital stay. Some patients in the placebo group receiving open label Clopidogrel resulted in an underestimation of the measured treatment effect.

Level 1. Fair. Pre-defined subgroup analysis of the TIMI 38 study on patients with acute MI and primary PCI. Demonstrates the effectiveness of prasugrel over clopidogrel. No increase in bleeding which contrasts with the increase in bleeding in the TIMI 38 study in subgroups (> 75 years of age, low BMI, previous CVA)

Level 1. Fair. Study based on platelet function which tested three clopidogrel loading doses. Clearly shows that the effect of clopidogrel is time dependant and that higher loading doses (600 mg, or even 900 mg) are more effective. Limited by the absence of clinical end-point.

Level 1. Fair. Randomized study in PCI patients (stable and unstable, excluded STEMI). Clear benefit of high loading doses of clopidogrel.

Level 1. Fair. Post-hoc analysis of CURE trial. Reduction in primary outcomes when clopidogrel is added to aspirin regardless of aspirin dose. Evidence to support low doses of aspirin: doses > 100 mg increase bleeding risk, with no benefit on efficacy.

Level 1. Good. Randomized trial in patients with STEMI treated by fibrinolytic therapy. Patients randomized to clopidogrel or no clopidogrel. Highly significant reduction in major adverse events with no increase in bleeding. Patients over 75 years of age excluded.

Level 1. Good. Large, multicenter, adequately powered to study primary endpoints. No difference between patients receiving pre-treatment with clopidogrel or not. However, in a pre-specified subgroup analysis, there was a reduction of 38.6% of major adverse events in patients receiving clopidogrel more than six hours before PCI. Major data favoring early administration of clopidogrel in pre-hospital and emergency room settings.

Level 1.Good. Randomized trial demonstrating the superiority of prasugrel on clopidogrel in patients with ACS. Increase of bleeding complications in patients aged > 75 years of age, previous CVA, low BMI. No information on pre-hospital or emergency department use.

Level 3 Poor. Small study with biological end-point. Neutral to the question: 300 mg or 600 mg

Level 1. GoodMulticenter randomized controlled trial, which clearly proves the benefit of adding clopidogrel to aspirin in NSTEMI. Reduction of a composite endpoint of refractory ischemia, death from cardiovascular causes, nonfatal AMI, stroke.) Increased risk of major bleeding not statistically significant. An early benefit can be seen a few hours after randomization.

Level 1. Fair.Post-hoc analysis of CURE trial. To explore rapidity of onset of effects, the authors included refractory or severe ischemia in addition to primary endpoints. During the first 24 hours, a 20% RRR in
primary outcome measures alone; 34% RRR in expanded composite (p < 0.003) were noted. The effect appears 2 hours after randomization.