RCT
Potential PURL Review Form
PURL Jam Version
PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]


C. First date published study available to readers: 11/1/2017

D. PubMed ID: 28510646

E. Nominated By: Jim Stevermer

F. Institutional Affiliation of Nominator: University of Missouri

G. Date Nominated: 5/22/2017

H. Identified Through: Evidence Updates

I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon

J. Nomination Decision Date: 5/31/2017

K. Potential PURL Review Form (PPRF) Type: RCT

L. Assigned Potential PURL Reviewer: Corey Lyon

M. Reviewer Affiliation: University of Colorado

A. Abstract: AIMS:
Newer P2Y12 blockers (prasugrel and ticagrelor) demonstrated significant ischaemic benefit over clopidogrel after acute coronary syndrome (ACS). However, both drugs are associated with an increase in bleeding complications. The objective of the present study was to evaluate the benefit of switching dual antiplatelet therapy (DAPT) from aspirin plus a newer P2Y12 blocker to aspirin plus clopidogrel 1 month after ACS.

METHODS AND RESULTS:
We performed an open-label, monocentric, and randomized trial. From March 2014 to April 2016, patients admitted with ACS requiring coronary intervention, on aspirin and a newer P2Y12 blocker and without adverse event at 1 month, were assigned to switch to aspirin and clopidogrel (switched DAPT) or continuation of their drug regimen (unchanged DAPT). The primary outcome was a composite of cardiovascular death, urgent revascularization, stroke and bleeding as defined by the Bleeding Academic Research Consortium (BARC) classification ≥2 at 1 year post ACS. Six hundred and forty six patients were randomized and 645 analysed, corresponding to 322 patients in the switched DAPT and 323 in the unchanged DAPT group. The primary endpoint occurred in 43 (13.4%) patients in the switched DAPT group and in 85 (26.3%) patients in the unchanged DAPT (HR 95%CI 0.48 (0.34-0.68), P < 0.01). No significant differences were reported on ischaemic endpoints, while BARC ≥ 2 bleeding occurred in 13 (4.0%) patients in the switched DAPT and in 48 (14.9%) in the unchanged DAPT group (HR 95%CI 0.30 (0.18-0.50), P < 0.01).
CONCLUSION:
A switched DAPT is superior to an unchanged DAPT strategy to prevent bleeding complications without increase in ischaemic events following ACS.

B. Pending PURL Review Date: 5/17/2018

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?
   - 322 in switched DAPT group
   - 323 in unchanged DAPT group

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
   - Single center RCT in Marseille France 2014-2016
   - Inclusion is admission for ACS requiring early PCI within 72 hours, and treatment with ASA and newer P2Y12 drug (prasugrel, and ticagrelor)
   - PCI inclusion criteria for patients with unstable angina or non-ST-elevation MI were ischemic symptoms defined as chest pain at rest or de novo exercise induced angina and either ST-segment deviation of 1 mm or more, elevated levels of a cardiac biomarker of necrosis or prior history of coronary artery disease. Patients with a negative troponin of lack of myocardial necrosis markers were classified as unstable angina. Patients with ST-elevation MI who underwent primary PCI within 12 hours after the onset of symptoms were enrolled.
   - Exclusion: history of intracranial bleeding, contraindication to use of aspirin, clopidogrel, prasugrel, or ticagrelor; major adverse event (ischemic or bleeding event) within a month of ACS diagnosis; thrombocytopenia (platelet concentration lower than 50 109/L); major bleeding (according to the Bleeding Academic Research Consortium (BARC) criteria) in the last 12 months; long term anticoagulation (contraindication for newer P2Y12 blockers) and pregnancy

C. Intervention(s) being investigated?
   - At 1 month patients received a single tablet FDC of aspirin 75 mg plus clopidogrel 75 mg (switched DAPT).

D. Comparison treatment(s), placebo, or nothing?
   - continue with the standard regimen of aspirin plus newer P2Y12 blocker (unchanged DAPT)

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
   - 1 year

F. What outcome measures are used? List all that assess effectiveness.
   - composite of cardiovascular death, urgent revascularization,
stroke and bleeding as defined by the Bleeding Academic Research Consortium (BARC) classification ≥ 2 at 1 year post ACS.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Endpoints at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Switched DAPT</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>43 (13.4%)</td>
</tr>
<tr>
<td>Any ischaemic event</td>
<td>30 (9.3%)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>28 (8.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>All bleedings</td>
<td>30 (9.3%)</td>
</tr>
<tr>
<td>Bleeding BARC ≥ 2</td>
<td>13 (4.0%)</td>
</tr>
<tr>
<td>TIMI major</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>9 (2.8%)</td>
</tr>
<tr>
<td>TIMI minimal</td>
<td>20 (6.2%)</td>
</tr>
</tbody>
</table>

NNT: 2.4

H. What are the adverse effects of intervention compared with no intervention?
   a. No major events noted

I. The study addresses an appropriate and clearly focused question.
   (select one) Well covered
   Comments: PLATO TRITON- MI

J. Random allocation to comparison groups:
   (select one) Well covered
   Comments: methods/limitations

K. Concealed allocation to comparison groups:
   (select one) Well covered
   Comments: methods/limitations

L. Subjects and investigators kept “blind” to comparison group allocation:
   (select one) Well covered
   Comments: methods, was open label trial and addressed

M. Comparison groups are similar at the start of the trial:
   (select one) Well covered
   Comments: table 2

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of
bias. (select one)  Adequately addressed
Comments: difference in new anti-platelet agents (between rather than vs clopidigrel)

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
   (select one)  Well covered
Comments: BARC score seems validated Ori Ben-Yehuda, Björn Redfors
Journal of the American College of Cardiology May 2016, 67 (18) 2145-2147; DOI:
10.1016/j.jacc.2016.03.505

P. Are patient oriented outcomes included? If yes, what are they?
   Yes, major bleeding, MI, death, morbidity

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
   a. 1 patient refused change, seems unlikely to affect results

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
   - Limited due to low level of patient loss/heterogeneity etc.

S. If a multi-site study, are results comparable for all sites?
T. n/a

U. Is the funding for the trial a potential source of bias? If yes, what measures were taken to
   ensure scientific integrity?
   - Publicly funded

V. To which patients might the finding apply? Include patients in the study and other patients to
   whom the findings may be generalized.
   - ACS patients, overall seems relatively generalizable  Any patient with ACS and
   stent on DAPT therapy

W. In what care settings might the finding apply, or not apply?
   - ED/inpatient, pcp follow up

X. To which clinicians or policy makers might the finding be relevant?
   - Family docs etc.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]
Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:

A. DynaMed excerpts

Dual antiplatelet therapy (DAPT) duration with aspirin and a P2Y12 inhibitor  
o Give for at least 12 months (Strong recommendation).
o Consider > 12 months in patients who have tolerated DAPT without bleeding complication and/or who are not at high bleeding risk (Weak recommendation).
o Consider discontinuation of P2Y12 inhibitor therapy after 6 months in patients who develop either high risk of bleeding or who have significant overt bleeding (Weak recommendation).
o Continue P2Y12 inhibitor therapy (clopidogrel) for minimum of 14 days (Strong recommendation) and ideally for at least 12 months in patients treated with fibrinolytic therapy.
o Consider use of risk score (such as DAPT or PRECISE-DAPT) to evaluate risks and benefits of different DAPT durations (such as > 1 year) (Weak recommendation).


C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

Continue DAPT, newer agents preferred for at least 6 months post MI with PCI using DES. No mention of changes.

D. UpToDate excerpts:

The risk of coronary artery stent thrombosis and its consequences of myocardial infarction (MI) or death are diminished by the use of dual antiplatelet therapy (DAPT) with aspirin and a platelet P2Y12 receptor blocker compared with the use of aspirin monotherapy. (See ‘Duration’ above and “Coronary artery stent thrombosis: Incidence and risk factors”, section on ‘Comparison of DES and BMS’.)

Updated 8/2017
For stable patients treated with either drug-eluting or bare metal intracoronary stents (DES/BMS) who are not at high bleeding risk and who do not have planned noncardiac surgery within one year, we recommend aspirin and a platelet P2Y₁₂ receptor blocker for at least 6 to 12 months rather than a shorter treatment duration (Grade 1B). (See 'Duration' above.)

Clopidogrel is the preferred P2Y₁₂ receptor blocker and the dose of clopidogrel is 75 mg daily. We suggest aspirin 75 to 100 mg daily, rather than higher doses. (See 'Agent and dose' above.)


F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Start clopidigrel and ASA for DAPT post DES for stable CAD, no change or mention of newer agent

G. Other excerpts (USPSTF; other guidelines; etc.)

ACC guidelines:

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Newer antiplatelet agent over clopidigrel.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. Validity: Are the findings scientifically valid? 1 (extremely well)

B. If A was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

Updated 8/2017
C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?

1 (extremely well)

D. If C was coded 4, 5, 6, or 7, please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?

1 (definitely a change from current practice)

F. If E was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

   a. Active assessment of DAPT for patients following up with pcp to ensure change to clopidigrel

G. **Applicability to a Family Medical Care Setting**: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention?

1 (definitely could be done in a medical care setting)

H. If G was coded as a 4, 5, 6, or 7, please explain.

I. **Immediacy of Implementation**: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market?

1 (definitely could be immediately applied)

J. If I was coded 4, 5, 6, or 7, please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**: Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

1 (definitely clinically meaningful or patient oriented)

L. If K was coded 4, 5, 6, or 7 please explain why.
M. In your opinion, is this a pending PURL? 1 (definitely a pending PURL)

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.