ALPIC2012

Advanced Learning on Platelets & Thrombosis International Course

Antiplatelets in coronary artery by pass surgery

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Cardiac Surgeon

"I cannot teach anybody anything,
I can only make them think."

Socrates, 470-399bc

Antiplatelets and patient's journey

- From cardiologist to the cardiac surgeon
- From cardiac surgeon to the cardiologist
- TiP-CardiaS

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From cardiologist to the cardiac surgeon

- Low risk patient on single or dual antiplatelet therapy should stop therapy for 5 days prior to cardiac surgery.
- High risk patents on single or dual antiplatelet therapy should proceed to surgery accepting a higher risk (2-3x) of bleeding complications.
- Patients on Ticagrelor or Prasugrel can possibly proceed safely with surgery 1-2 days after the last dose.
- 91% of patients on Clopidogrel with ADP-induced aggregation of less than 40% (or more than 60% inhibition) can expect an increased CABG-related bleeding and transfusion requirements.

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From cardiac surgeon to the cardiologist

I would like your opinion…

Patient 51 years old presented with LMS and two vessels with complex lesions and was offered CABG with LIMA to OM and RIMA to LAD.

After the successful surgery would your recommend:

- Aspirin 80mg/d
- Clopidogrel 75mg/d
- Combination of Aspirin/Clopidogrel 100/75mg/d
- Ticagrelor 90mgx2/d
- Prasugrel 10mg/d

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No Evidence!

Cardiac surgery

- 50 years of modern history
- Millions of CABGs
- Antiplatelet therapy used over the years:

- Clopidogrel
- Combination of the two

Recommendations

Aspirin should be given postoperatively to all patients without contra-indications after coronary artery bypass grafting in order to improve the long-term patency of **vein grafts**.

N Engl J Med. 1982 Jul 8;307(2):73-8.
Circulation. 2004 Oct 5;110(14):e340-437 & 2005 Apr 19;111(15):2014.
Chest. 2008 Jun;133(6 Suppl):776S-814S.
Eur J Cardiothorac Surg. 1993;7(4):169-80.
Interact Cardiovasc Thorac Surg. 2003 Dec;2(4):427-30.
Eur J Cardiothorac Surg. 2008; 34: 73—92
Canad. J Cardio 2011; 27: S1–S59

What about the arterial grafts?

- There is no evidence to promote the use of Aspirin after coronary artery bypass grafting to improve the patency of arterial grafts.

- However, Aspirin may be recommended on the basis of improved survival of patients in general who have atherosclerotic disease.

How much Aspirin?

- The dose should be 150 — 325 mg
  (or 75 – 165mg if you are Canadian!)
- Studies show a trend towards maximal benefit with 325 mg/day in the first year.
- …but we usually prescribe it at 80-100mg!

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When to give Aspirin?

- After CABG: there is a trend towards maximal benefit of aspirin the sooner it is given postoperatively
  - The optimal strategy may be to give aspirin at 6 h or when bleeding has ceased, although the largest risk reduction happens when aspirin is given at 1 h *(…however, we often give it the following morning!)*
  - There is no benefit giving Aspirin if started more than 48h postoperatively.

- After tissue aortic valve replacement and in the absence of other indications for anticoagulation, antiplatelet therapy alone is adequate. *(….at least in Europe)!*

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What about Clopidogrel?

- Has yet to be proven superior to Aspirin.
- It is an acceptable alternative to Aspirin for the optimisation of graft patency after CABG.

J Am Coll Cardiol. 2011 Mar 8;57(10):1202-9
Circulation. 2004 Oct 5;110(14):e340-437 & 2005 Apr 19;111(15):2014

Combination of Aspirin & Clopidogrel

- Associated with:
  - An adjusted 50% relative reduction of in-hospital mortality.
  - No reductions in ischemic or thrombotic events.
- May further improve the patency of veins & radials.
- Patients having CABG after ACS should be considered for dual antiplatelet therapy for a period of 9—12 months.
- CABG patients with coronary stent in situ should continue Clopidogrel if the stented vessel has not been grafted.

Am Heart J. 2010 Dec;160(6):1178-84.
J Am Coll Cardiol. 2010 Nov 9;56(20):1639-43.
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New antiplatelet agents & cardiac surgery

- Ticagrelor:
  - Has been used in patients post CABG
  - Can be used instead of Clopidogrel
  - Never been used in cardiac surgery as monotherapy
- Prasugrel:
  - Can be used instead of Clopidogrel
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Eur J Clin Pharmacol. 2010 May;66(5):487-96. Epub 2010 Jan 21.
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Prasugrel - National Institute of Clinical Excellence (NICE), United Kingdom

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I would like you to consider the following

The usage of antiplatelets in cardiac surgery is based on poor basic science and clinical data that often do not represent current practice.

CABG is an invasive procedure which also has:

- extensive collagen exposure & ischaemic –reperfusion
- a very high production of thrombin *(lasting for days),*
- high consumption of platelets *(lasting for hours or days),*
- high production of platelets *(lasting for hours or days),*
- an increase in the production of megakaryocytes *(lasting for hours or days),*
- activation of the fibrinolysis mechanism *(the magnitude of which is linked to the length of the operation and is logarithmically related to the time that the patients stays on cardiopulmonary support)*
- the use of very high doses of Heparin – Protamine

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- Aspirin has a half-life of only 20min.
- There are no clear evidence regarding the pharmacodynamic profile of Aspirin, Clopidogrel or Ticagrelor on patients after CABG.
- Aspirin, Clopidogrel and Prasugrel (unlike Ticagrelor) are pro-agents and their pharmacodynamic profile can be affected by:
  - absorption,
  - metabolism and
  - non-responsiveness
- Clopidogrel needs a loading dose or 5d to achieve levels.
- There are no data of the percentage of platelet inhibition post CABG surgery in relation:
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“There's only one corner of the universe
you can be certain of improving,
and that's your own self”

Aldous Huxley

TiP-CardiaS

TiP-CardiaS study

Ticagrelor, Platelets and Cardiac Surgery Study

To investigate the pharmacodynamics, safety and efficacy of the new antiplatelet agent Ticagrelor on patients after CABG surgery in a multicentre, international setting.

TiP-CardiaS study

The aim of this study will be to achieve an over 60% platelet inhibition, within the first 24 hours from the end of CABG surgery and to maintain this level of platelet inhibition for one - to - six - to - twelve months by using a simple, reproducible and cost-effective protocol of Ticagrelor administration, without any compromise on patients safety.

TiP-CardiaS study

- Phase II, single arm, prospective, interventional study.
- 50 patients (powered at 30).
- 90mg Ticagrelor, x2/d without loading dose.
- Inclusion criteria
  - All comers: all patients who are in need for a nonemergency, first time CABG surgery, following a recent NSTEMI or unstable angina.

TiP-CardiaS study

Exclusion criteria, patient who:

- have undergone a STEMI and need to proceed with CABG surgery
- are in need for an emergency CABG
- are in need for a redo CABG
- are in need for a CABG in combination with any other kind of surgery
- have been on antiplatelets for less than 5 days prior to CABG, other than Aspirin
- are on Warfarin or Dabigatran for less than 5 days prior to CABG
- suffer from COPD or conduction problems
- have a platelet count of less than 120.000 prior to CABG
- are less than 55Kg in weight
- have a Creatinine level of more than 1,20
- bleed more than 5ml/Kg/h for the first three or more hours postoperatively
- require reoperation for bleeding within the first 24 postoperative hours
- have a postoperative stroke, myocardial infarction, sepsis or acute renal failure (Cr>2.0)

TiP-CardiaS study

The three key dimensions for research with direct translation to clinical practice will be to confirm that after CABG the dose of Ticagrelor 90mg, x2/d:

- Is safe (assessed by postoperative bleeding).
- Can inhibit over 60% of platelets at any time after CABG.
- The dose has the capacity to maintain a platelet inhibition above 60% at all times, within the first year after CABG.

TiP-CardiaS study

- The side dimension for research, with direct or indirect clinical translation will be:
  - The need for repeated dosage of Ticagrelor.
  - The capacity of Ticagrelor to inhibit megakaryocytes.
  - Postoperative bleeding complications.
- The side-line research with indirect clinical translation will be:
  - Effectiveness on secondary prevention of MASE and graft occlusion at one year (cardiac death, CT angiography).
  - Compliance to the medical treatment with Ticagrelor on platelet inhibition at six months and one year post CABG.

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TiP-CardiaS study

The necessary blood samples will be collected at following seven prearranged times:

- preoperatively (P0),
- immediately postoperatively (P1),
- twelve hours postoperatively (P2),
- three (P3) and six days (P4) postoperatively,
- at three months postoperatively (P5) and
- at one year postoperatively (P6).

TiP-CardiaS study

The proposed laboratory methods of assessing the platelet function are:

- Platelet aggregation.
- Assessment of platelet adhesion (shear stress).
- Platelet-mediated thrombin generation.
- Platelet membrane protein expression.
- Platelet-leukocyte conjugates.
- Platelet-associated and/or secreted specific microRNAs.
- Evaluation of megakaryocytic functionality (number, volume, specific megakaryocyte-derived microRNAs).
- Determination of various gene polymorphisms.

Behind the argument between “superlative” and “cost-effective” lie differences of opinion about the purpose of science.

TiP-CardiaS is based on the belief that it is the job of science to at least think of serving society and not to generate knowledge as an abstract good, with unpredictable benefits to the society that pays for it.

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TiP-CardiaS is based on the belief that it is the job of science to at least think of serving society and not to generate knowledge as an abstract good, with unpredictable benefits to the society that pays for it.

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Thank you very much for your attention

The real voyage of discovery consists
not in seeking new landscapes but in having new eyes.
Marcel Proust