Round Table: “Antithrombotic therapy beyond ACS”

Antiplatelet and anticoagulant drugs for prevention of restenosis / reoclusion following peripheral endovascular treatment

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Peripheral Transluminal Angioplasty and Stenting

...rises more and more with time
...it’s about to replace open surgery in most vascular beds
PTA and Stenting has many advantages...

- **Minimal** invasive approach
- Ability to treat the **high-risk** patients
- Ability to treat **poor out-flow** lesions
- **Shorter** hospital stay
- Revascularization using the **native arteries**
  - No prosthetic grafts
  - No harvesting of useful veins
...but also some disadvantages and limitations

- Radiation and contrast media exposure
- Reduced long term patency
- More re-interventions
- Need for more intensive follow-up
Cost-effectiveness

• No reliable data so far

• It mainly depends on re-interventions

دير prevention of restenosis / reoclusion
Platelet activation

Always during peripheral PTA

... even after just an angiography!

Buchholz AM et al., Thrombosis Research, 2003
Platelet adhesion

- Is an important step in the development of neo-intima hyperplasia and subsequent re-stenosis

- In the site of stenting there is an increase in platelet deposition

Cassar K et al., Eur J Vasc Endovasc Surg, 2003
Platelet aggregation

Platelet recruitment and adhesion at the site of injury

Platelet activation and aggregation
We do need antiplatelet action during and after peripheral PTA and stenting.
Peripheral Arterial Disease
Angioplasty and Stenting
Antithrombotic therapy in peripheral PTA

- Few studies guide clinicians regarding type and duration of antithrombotic therapy following such procedures.

- Current practice is very heterogeneous and often is based on indirect evidence from studies in patients undergoing coronary stenting.

Chest 2012; 141: e669S-e690S
Antithrombotic therapy in peripheral PTA

• There are no RCTs comparing antithrombotic agents post-PTA with stent placement

• Indeed, it remains unclear whether PTA with stent placement is superior to PTA alone with respect to patient-important outcomes

• Nevertheless, stenting is performed frequently!!

Chest 2012; 141: e669S-e690S
Basic and acceptable principle

- We need antiplatelet therapy during and after peripheral PTA and Stenting !!
• **Discontinuing** antiplatelet therapy **before** the procedure?

• In any case: **NO !!**
  - Minimal invasive procedures
  - High-risk CV patients
  - Probability of acute thrombosis at the site of the lesion
Questions to be answered

- Is there a need for **more intensive therapy**?
- If there is, **what it should be**?
- ... and for **how long**?
• It looks **reasonable** to consider the **combination**
of two antiplatelet drugs during and after
peripheral PTA and Stenting

... **but**

**Data are lacking !!**
Dual antiplatelet therapy in PTA

- The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) study was started in the US to evaluate the efficacy and safety of this dual therapy after femoropopliteal PTA.
- Unfortunately, the study was stopped because of insufficient randomization numbers.
- Many patients are already treated off-label with clopidogrel and aspirin.
- Physicians were uncomfortable with patients receiving aspirin monotherapy after PTA.

*Cohrane Database Syst Review 2005*
Dual antiplatelet therapy in PTA

- Dual therapy with **aspirin** (100 mg/d) indefinitely and **clopidogrel** (75 mg/d) for 4 weeks after the **intervention** is often adopted worldwide

*Tepe et al. N Eng J Med 2008*
The usual clinical practice up to date

• **Dual combination therapy** with
  - **aspirin** (100 mg/d) and
  - **clopidogrel** (75 mg/d)

  for 1-3 months after peripheral PTA and Stenting
The main question remains un-answered

Dual or single antiplatelet therapy after peripheral PTA and Stenting?

What the recent Guidelines tell us about?
Despite low-quality evidence regarding thienopyridines in patients undergoing PTA with stent placement for PAD, many interventionists provide dual antiplatelet therapy for 1 to 3 months post-PTA, particularly if a stent is placed in a small peripheral vessel.

The rationale for this practice is based on the results from coronary artery stenting trials.

Chest 2012; 141: e669S-e690S
ACCP is skeptical about extrapolating these data to all patients with PAD given differences in the risk of stent thrombosis (lower in stenting of largercaliber peripheral arteries compared with smaller coronary arteries), difference in stent types, and differing outcomes related to stent thrombosis (limb ischemia vs MI)

Given that dual antiplatelet therapy is associated with an increased risk of major bleeding compared with single antiplatelet therapy

_Chest 2012; 141: e669S-e690S_
9th ACCP recommendation

- 7.1. For patients undergoing peripheral artery percutaneous transluminal angioplasty (PTA) with or without stenting, we recommend long-term aspirin (75-100 mg/day) or clopidogrel (75 mg/day) (Grade 1A). For patients undergoing peripheral artery PTA with stenting, we suggest single rather than dual antiplatelet therapy (Grade 2C).

Chest 2012; 141: e669S-e690S
• 7.1. Comment

• Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a potential increased risk of bleeding are likely to choose to use dual antiplatelet therapy.

Chest 2012; 141: e669S-e690S
Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. (Level of Evidence: A)

The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk (Level of Evidence: B)

In line with recommendations for patients with coronary heart disease, an intermittent administration of dual antiplatelet therapy (aspirin plus clopidogrel) may be considered for patients undergoing stent implantation or drug-eluting balloon angioplasty of femoropopliteal or infrapopliteal arteries. (Level 5; Grade D)

• After prosthetic bypass or endovascular revascularisation, ASA or ASA combined with dipyridamole, should be given daily at low dose (50 to 300 mg) to lower the incidence of bypass or angioplasty occlusions (Level 1b; Grade B).

• Additional use of thienopyridine (clopidogrel) may be beneficial without increasing the risk of major bleeding. (Level 2b; Grade C).

Antiplatelets vs oral anticoagulants in PTA

- Aspirin 50 to 330 mg, started before femoropopliteal endovascular treatment, appeared to be the most effective and safest strategy.

- Reduced the incidence of re-occlusion at 6 and 12 months when compared with no therapy or vitamin K antagonists.

*Cohrane Database Syst Review 2005*
Questions to be answered

• Is there a need for a **loading dose**?

• If there is, **when**? ... and **how**?

  - Before the procedure?
  - After the procedure?
  - What drug and in what dose?
Loading Antiplatelet Dose in PAD patients

A loading dose of Clopidogrel (300mg) inhibits platelet activation in PAD patients as early as 2 hours


... a decade later

Data are still lacking !!
Questions to be answered

• What about of the use of GP IIb/IIIa inhibitors during and after the procedure?

• If there a need to use them?
  ➢ In which cases?
One randomized study (98 patients -103 limbs with long-segment femoropopliteal occlusions), demonstrated significant benefit in patients receiving abciximab, improving patency and functional outcome.

Dorffler-Melly Jet al. Radiology 2005

However...

More data are needed!!
Other considerable issues

- The *indications* of PTA and Stenting in peripheral vessels are rapidly changing
  ➢ *more and more total occlusions now treated*  
  ➢ *longer lesions*  
  ➢ *subintimal technique, remote endarterectomy*  

thus... *more atherothrombotic surface !!
Long peripheral PTA and Stenting
The use of Drug Eluting Stents (DES) and Drug Eluting Balloons (DEB) in peripheral interventions

• DES initial use in tibial arteries
  
  *Siablis D, et al., J Endovasc Ther, 2007*

• DEB in femoropopliteal lesions

  *Tepe G, et al., NEJM, 2008*

➢ Better results?

➢ Increased risk for acute thrombosis?
Other considerable issues

- Expanding use of covered stents in peripheral vessels
  - No data from the coronaries
  - No data at all !!!

- Do we need intensive antiplatelet therapy ?
- Do we need anticoagulants ?
- Can we adapt data from surgical prosthetic grafts ?
Abdominal Aortic Aneurysm
Endovascular repair

- Patients with AAA should be on low-dose aspirin and this should be continued through the perioperative period (Level 3b, Recommendation C)

Resistance to anti-platelet therapy

• It is well known that some PAD patients show resistance to ASA
  Matsagas et al, Ann Vasc Surg 2002

• Recently has been stated that some cardiovascular patients have resistance to Clopidogrel
  Papathanasiou et al, Hellenic J Cardiol 2007

↓ should we evaluate patients before peripheral interventions for resistance to antiplatelet drugs?
Carotid Artery Disease

Carotid Artery Stenting
Carotid Artery Stenting (CAS)

- The risk of acute thrombosis could become **disabling** or **even fatal**
- After procedure **embolization** could lead to serious neurologic complications

**We need intensive antithrombotic therapy**

**We have to define what it would be**
Dual or single drug antiplatelet therapy for CAS?

- Neurological complication
  - 75 mg aspirin + 24h Heparin: 24 patients
  - 75 mg aspirin + loading dose 300 clopidogrel 6-12 h before: 23 patients
    - 25% vs 0%

- Bleeding disorders

McKevitt et al. Eur J Vasc Endovasc Surg 2005
Dual or single drug antiplatelet therapy for CAS?

Was there a difference in antiplatelet therapy?
There were many significant differences overall but, as for antiplatelet treatment ...

SAPPHIRE trial *required* DUAL antiplatelet therapy

While

EVA-3S trial *only recommended it* (17% before and 14.6% after CAS)
Antiplatelet therapy for CAS

Current Guidelines
ESVS Guidelines for CAS

- CAS should be performed under **dual antiplatelet treatment** with **aspirin** and **clopidogrel**
  Grade A

- Dual antiplatelet treatment should start before CAS and continue for 3 months after stenting
  Grade C

Before and for a minimum of 30 days after CAS, dual-antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) is recommended (Level of Evidence: C)

What about loading dose before CAS?

- There is **not sufficient evidence** for a loading dose of Clopidogrel

<table>
<thead>
<tr>
<th>Reference</th>
<th>Loading dose Clopidogrel</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush et al. Ann Vasc Surg 2003</td>
<td>150 mg X2 when starting</td>
<td>Not a Clinical Trial – Observed data</td>
</tr>
<tr>
<td>Bhat et al. J Invas Cardiol 2001</td>
<td>300mg (none before)</td>
<td>Heparin or IIb/IIIa inhibitor used too</td>
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And about GP IIb/IIIa inhibitors?

- The adjunctive use of GP IIb/IIIa fibrinogen receptor antagonist may further reduce periprocedural ischemic events in patients undergoing CAS
  - In a non-randomized study of 128 patients receiving adjunctive abciximab, there were fewer major ischemic events
  - There was 1 delayed intracranial hemorrhage in the abciximab-treated patients

More questions waiting for answers ...

- Do we need a loading dose with clopidogrel before CAS?
  - What is the proper dose (300mg or 600mg)?
  - How early before the procedure?
  - Or maybe after the procedure?

- How long the dual therapy would last after CAS?
  - 1 month, 3 months, further on?
Antiplatelet therapy seems to be a cornerstone in endovascular treatment of patients with peripheral and carotid artery disease.

An amount of Knowledge has been added during the last two decades.

but unfortunately ...

there are still many questions waiting for an answer
In Conclusion ...

- We do need **intensive antiplatelet therapy** during and after peripheral and carotid **endovascular interventions**

- We are lacking of **reliable** data to develop **evidence based guidelines** in many subjects

and at the same time ...

we are performing these operations more and more frequently in the every day practice
We have to develop guidelines for optimal antiplatelet therapy during and after peripheral and carotid PTA and Stenting.

Even if these will be based in Grade C (small studies) and Grade D (expert opinions) recommendations and also adapting data from the coronaries.
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