ALPIC 2012

Advanced Learning on Platelets & Thrombosis International Course

Organized by: the University of Ioannina

Under the auspices of: the Hellenic Cardiological Society, the Mediterranean League Against Thromboembolic Diseases

Round Table: *"Antithrombotic therapy beyond ACS"*

Antiplatelet and anticoagulation treatment of patients undergoing carotid and peripheral artery angioplasty

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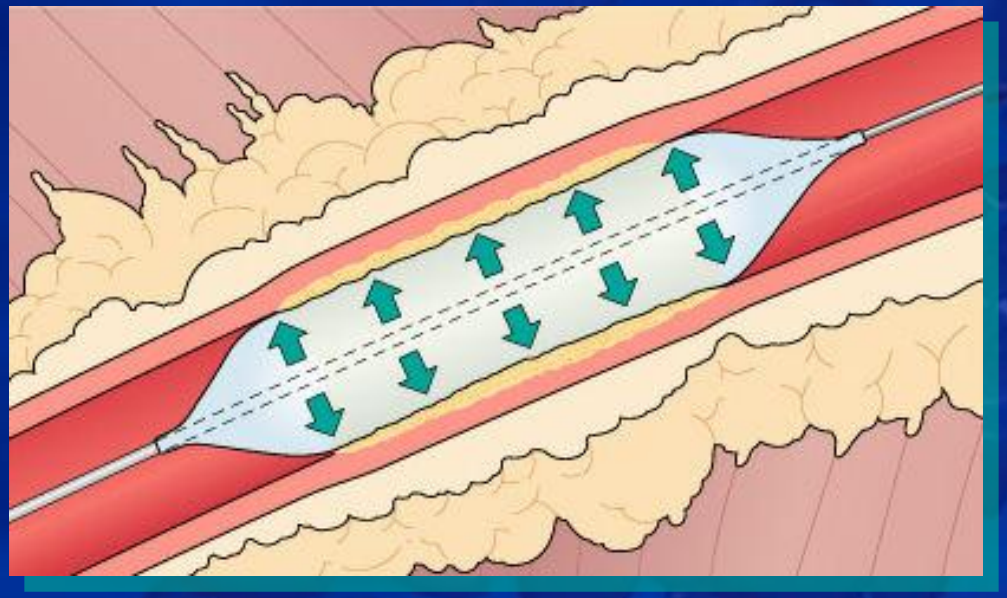
Peripheral Artery Disease

Angioplasty and Stenting

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

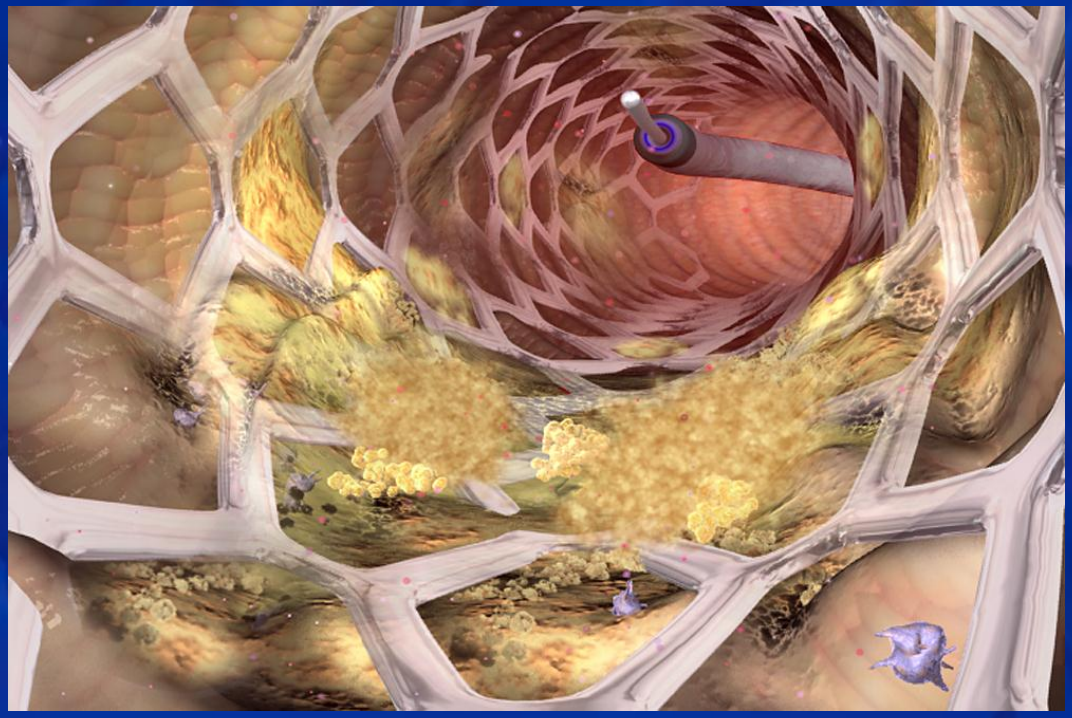
- **No reliable data so far**
- **It depends on re-interventions**

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

Fact

We do need antiplatelet action

during and after

peripheral PTA and stenting

8th ACCP

- Aspirin should be used before and after PTA of the peripheral arteries to reduce the incidence of periprocedural thromboembolic events

Grade 1C

CHEST 2008; 133:815S–843S

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

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 randomisation 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

Tepe et al. N Eng J Med 2008

Questions to be answered

- 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 lession

Questions to be answered

- Is there a need for more intensive therapy ?
- If there is, what it should be ?

… and for how long ?

Questions to be answered

- It looks reasonable to consider the combination of two antilpatelet drugs during and after peripheral PTA and Stenting

… but

Data are lacking !!

Current guidelines

- 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)

Rooke TW, et al. J Am Coll Cardiol. 2011; 58: 2020-45.

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

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

Matsagas et al, Clin Appl Thromb Hemost, 2003

… almost 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 ?

GP IIb/IIIa inhibitors in peripheral PTA and Stending

- 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

Although…

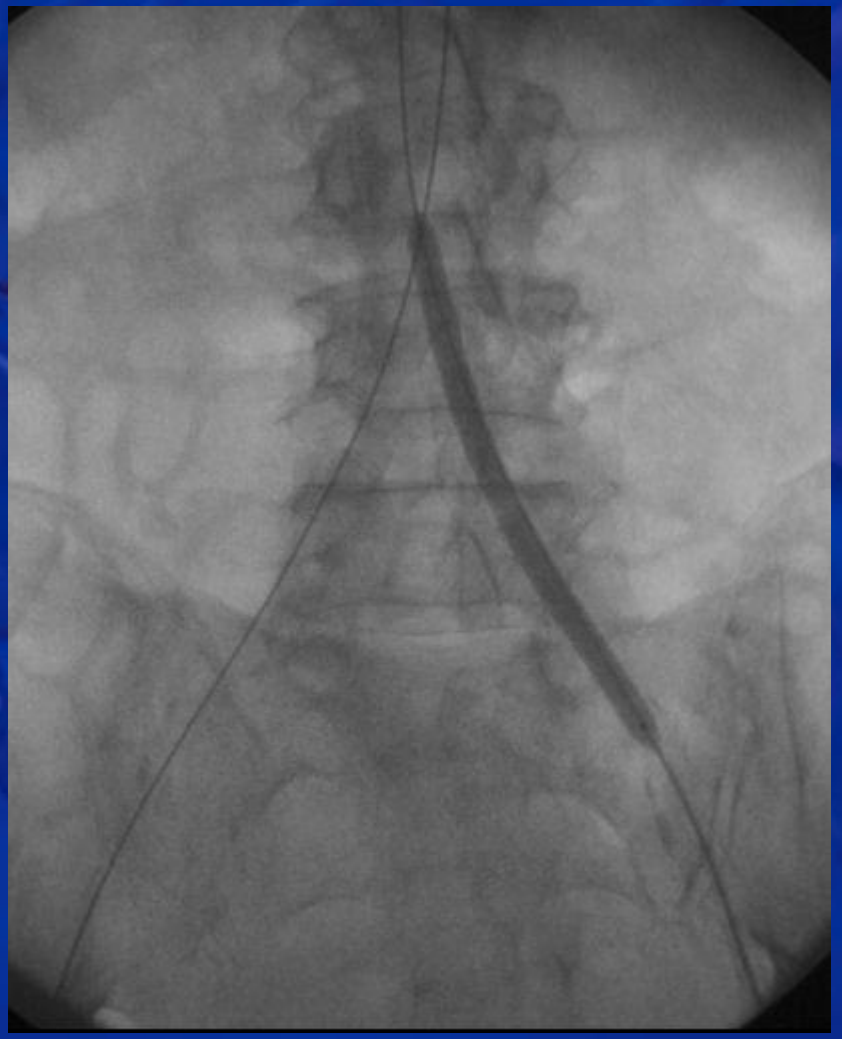
More data are needed !!

Other considerable issues

- **The indications of PTA and Stenting in peripheral vessels are rapidly changing**
- **TASC (2000) → TASC II (2007) → still 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) in peripheral interventions

- **Initial use in tibial arteries**

Siablis D et al., J Endovasc Ther, 2007

- **Better results ?**
- **Increased risk for acute thrombosis ?**

Other considerable issues

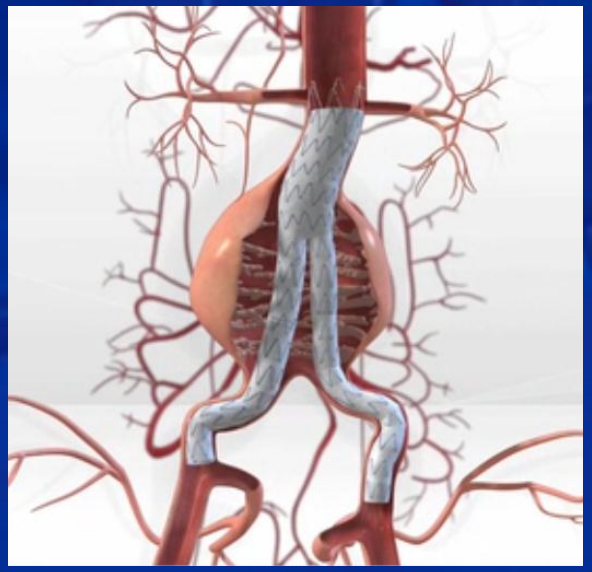
- **Expanding use of covered stents in peripheral vessels**

  - ***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)



F.L. Moll, et al. Eur J Vasc Endovasc Surg 2011; 41: S1-S58.

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?

75 mg aspirin + 24h Heparin	Vs	*75 mg aspirin + loading dose 300 clopidogrel 6-12 h before*

- Neurological complication  *25% vs 0%*
- Bleeding disorders 

McKevitt et al. Eur J Vasc Endovasc Surg 2005

Dual or single drug antiplatelet therapy for CAS?

SAPPHIRE trial  **CAS**

EVA-3S trial  **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

- 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

Liapis C, et al. ESVS Guidelines 2009

What about loading dose before CAS?

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

Reference	Loading dose Clopidogrel	Comments
Bush et al. Ann Vasc Surg 2003	150 mg X2 when starting	Not a Clinical Trial – Observed data
Bhat et al. J Invas Cardiol 2001	300mg (none before)	Heparin or IIb/IIIa inhibitor used too

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 nonrandomized study of 128 patients receiving adjunctive abciximab, there were fewer major ischemic events
  - There was 1 delayed intracranial hemorrhage in the abciximab-treated patients

Kapadia SR, et al. Stroke 2001

More questions waiting for answers …

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

- How long the dual therapy would last after CAS ?
  - 1 month, 3 months, further on ?

In Conclusion …

- ✓ **Antiplatelet therapy seems to be a cornerstone in treating patients with peripheral and carotid artery disease**

- ✓ **A lot 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 interventions, especially endovascular ones

- ✓ 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 in the every day practice

In the meanwhile …

- ✓ 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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