M.E.E.T.
Cannes, June 16, 2006
The silent revolution of Interventional Pharmacology
Overview of interventional pharmacology

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Heart Center Bogenhausen, Munich
Targets of interventional pharmacology?

• The (systemic) disease

• The target lesion

• The interventional procedure
Clinical Manifestations of atherothrombotic vascular disease

- Ischaemic stroke
- Transient ischaemic attack
- Myocardial infarction
- Angina pectoris (stable, unstable)
- Sudden death
- Intermittent claudication
- Critical limb ischaemia, gangrene, necrosis

Manifestations of aortic disease

Renal insufficiency
Cardiovascular multimorbidity (MM) in pts. with coronary (CAD) and peripheral artery disease (PAD)

Adapted from P. Lanzer Z Kardiol 93, 2004
# Carotid disease and CAD (complex vascular disease)

- In CAD pts, significant carotid stenosis occurs in 30-50%
- In pts with Carotid stenosis, CAD occurs in 20-30%
- Stroke with CABG without carotid stenosis 1-3%
- Stroke with CABG with >70% carotid stenosis 6-20%
- Stroke with simultaneous ACVB/CEA 4-12%
Objectives of Medical Tx in Chronic vascular disease and for Interventional Tx

- Prevent cardio/cerebrovascular events (Stroke)
- Slow progression of stenosis, induce regression
- Prevent plaque rupture
- Prevent periprocedural thrombosis / emboli
- Prevent early postinterventional vessel/stent occlusion
- Establish safe environment for endovascular techniques
- Achieve long term target vessel patency (prevent restenosis)
- Treat acute ischemic & non-ischemic interv.complications
- Prevent bleeding complications
- Avoid interference with tx for comorbidity
Challenges of Comorbidity & older Age

- Increased procedural cardiovascular risk with interventional & surgical therapies
- Reduced prognosis post invasive procedures
- Complex procedural challenges including peri/post procedural care & logistics, e.g.:
  - hemodynamics, cardiac and neurological risks
  - renal function
  - bleeding risks
  - risks of interventional pharmacological tx and combination tx (anticoag., antiaggregation)
  - risks of intercurrent non-vascular morbidity/therapy
The target lesion...embolic risks

Segmented ring stent (Nitinol) in ICA

Plaque protrusion

Angiographically successful stenting
Morphologies of the target.....

Mobile thrombus

Ulcerative & thrombotic

Spontaneous dissection
The procedure: vascular & structural heart disease interventions

Complex coronary, carotid & mitral valvular intervention therapy in an elderly patient in 2 sessions

- Circumflex stenting
- Carotid stenting
- Mitral balloon valvuloplasty
Unstable Angina: 3 VD, LIMA to LAD
Supraaortic disease: left subclavian artery 90% limiting flow to LAD via a.mammaria graft, retrograde flow from LAD
History: H.S. 61 J / S/p multiple PTCA and stents, ACS with hypertensive crisis. Highgrade right RAS

Treatment: PTA mit Cutting Balloon. Duplex: no stenosis. BP without medication 110/90 mmHg
Complex vascular patient:
3 vessel coronary disease
2 x PTCA, severe PAD - “below the knee“
..PTA after PTCA
Interdisciplinary treatment:
Structural heart disease & stroke (neurocardiology)

Embolus in PFO / ASD

Female with thrombotic venous disease

Interventional PFO closure

Isch 07
Aorta-Stentgraft Implantation (mit TEE)
Restenosis

Case 1

Case 2
Current strategies of medTX postintervention**

Incidence of restenosis  antiaggregation Tx

? > 25% ?  Dual antiagg longterm?

3 - 6 %  Dual antiagg 2-4 mos, monotx longterm

10 - 30%  Dual antiagg 3-12 mos*,monotx longterm

5 - 30%  Dual antiagg < 6 mos, monotx longterm

10 - 25%  Dual antiagg < 3 mos, monotx longterm

25 - 70%  Dual antiagg < 6 mos, monotx longterm

10 - 50%  Dual antiagg longterm

* varies with stent type (DES)  ** varies with comorbidity
The 2 breakthroughs...

Local concepts:

**STENT**

- Active drug coating - Rapamycin, Paclitaxel, EPC capture
- Embolic protection,

Systemic concepts

**Med. Tx**

- Clopidogrel & ASS
- IIB/IIIA
- Direct antithrombins
- Concomitant medical tx

Fig 1. Charles Stent (1845-1901), an English dentist who lent his name to a tooth mold (bottom) and more recently to endoluminal scaffolding devices.
Reduction of Coronary Restenosis

at what price...?
Drug dependency? Life long? Bleeding?...

balloon 50%
BMS 25%
Better BMS 15%
DES <10%

Type, intensity & duration of dual drug antiaggregation / AC

1985 → 2007
Risk factors for Stent Thrombosis
Subgroup Analysis

Milan/Siegburg Experience

- Unstable angina: 1.3%
- Thrombus: 2.0%
- Diabetes: 2.6%
- Unprot. left main: 3.2%
- Bifurcation: 3.5%
- Renal failure: 5.5%
- Prior brachyRx: 8.7%
- Premature Plavix d/c:
Mid Term Human Pathology Sirolimus Eluting Stents Findings from Different Coronary Arteries in the Same Patient

BMS 24 Months after Deployment

Cypher 16 Months after Deployment

G. Guagliumi et al, Circulation 2003; 107:1340
Comparison of Various BMS and DES In Rabbit Iliac Arteries at 28-days
BASKET LATE
(late clinical events related to late stent thrombosis at 1 year after discontinuation of Clopidogrel)

No diff in TLR
LAST:
2.6% in DES
1.3% in BMS

M.E. Pfisterer, ACC 2006
Drugs in atherosclerotic vascular disease

- Traditional risk factor recognition & intervention
- Medical Tx of
  - hypertension (ACEI, AT1 blockers, diuretics, β-blockers, Ca-antagonists
  - hyperlipidemia (statins)
- Passivation of vulnerable plaque / regression
  (statins, dual antiplatelet tx post stroke (CARESS), ACEI, Statins, restitution of endothelial function ..???)
- Antithrombotic management (ASS 100-125mg, Clopidogrel 75mg alone (CAPRIE), ASS + Dipyridamole 75mg x3(post stroke,ESPRIT study), ASS 100 mg + Clopidogrel 75mg in complex sympt.pts (ChARISMA)+post stent (CLASSICS),

  Coumadin: comorbidity requiring anticoagulation (e.g.AF, valvular D)
Drug Categories in Peri-Interventional Pharmacology

- Antithrombotic drugs
  - antithrombin
  - antiplatelet
- Hemodynamic drugs
- Antiallergic drugs
- Renal protective drugs
Interventional pharmacology:

antithrombotic drugs: antiplatelet

- **Aspirin**: irreversible inhibition of cyclooxygenase, (reduction of thromboxane) independent of dosage
- **Dypiridamole**: modulation of cyclic AMP / benefit in combination with ASS over ASS alone in stroke prevention. Obsolete with coronary disease
- **Ticlopidine**: almost obsolete, burdened with adverse effects (neutropenia)
- **Clopidogrel**: adenosine monophosphate receptor antagonist, irreversible action. Post stenting in combination with ASS. Monotherapy in selected cases (ASS intolerance or resistance)
- **Glycoprotein IIb / IIa** receptor antagonist: selective use in carotid stenting, acute thrombus associated situations, periprocedurally (*Abciximab, Tirofiban*)
Pretreatment with antiplatelet agents

<table>
<thead>
<tr>
<th></th>
<th>starting ≥ 4 days before intervention: 100-325mg daily</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>starting ≤ 3 days: loading dose = 325mg oral or 500-1000mg i.v.</td>
</tr>
<tr>
<td></td>
<td>starting periprocedurally: 1000 mg i.v.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>starting ≥ 4 days before intervention: 75 mg daily</td>
</tr>
<tr>
<td></td>
<td>starting ≤ 3 days: loading dose 300-600 mg</td>
</tr>
<tr>
<td></td>
<td>starting ≤ 24 hours: loading dose 600 mg</td>
</tr>
<tr>
<td></td>
<td>starting periprocedurally: short term antiaggregation by GP IIb/IIIa (TIROFIBAN)</td>
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*600mg loading dose achieves full antiplatelet effect after 2 hrs*
*300mg loading dose achieves full effect after 6 hrs*
Interventional pharmacology:

**antithrombotic drugs: antithrombins**

- **Indirect thrombin inhibitors:**
  - UF heparin: bolus tx periprocedurally, „unstable plaque“, acute ischemic situation
  - LMW Heparins: by inactivation of factor Xa, no control by ACT, extended periprocedural tx

- **Direct thrombin inhibitors:**
  - Hirudin: alternative to UF Heparin in HIT (PTT control)
  - Bivalirudin: inhibition of circ&clot-bound thrombin (ACT control, reduction in bleeding vs UF Hep + IIb / IIIa in CAD, REPLACE study)

- **Anticoagulants: Coumadin or Warfarin**
  - for increased thromboembolic risks from cardiac sources
  - no routine role in interventional pharmacology

- **Thrombolytics: specific tPA / unspecific Streptokinase:**
  in ischemic stroke naturally occurring or periinterventionally if thrombotic problem identified (selective administration)
Rationale for IIb/IIIa blockers

• Periprocedural inhibition of platelet aggregation & adhesion (short duration) at target lesion / plaque, stent, catheters, filter devices, and during prolonged interventions
• Substitute / bridging for Clopidogrel loading
• Risk reduction in pts with chronic clopidogrel tx and emergent PCI
• Improvement of microcirculation at balanced bleeding risk (Albers JAMA 2000, Clark JAMA 99)
Increasing evidence for IIb/IIIa blockers in cerebrovascular disease (adjunctive to lysis, alternative to heparin)

Adams AJC 2000, Furlan AJNR 97, Calais DMW 2001
Bliden JACC 2007
### Selective periprocedural antithrombotic tx

<table>
<thead>
<tr>
<th>Antithrombotic</th>
<th>Details</th>
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</table>
| **Standard - heparin** | - Starting bolus: weight adjusted 80-100 IU/kg  
  *(ACT goal 2 min post bolus: 250-300 sec, if combined with GP IIb/IIIa: 200-250 sec)*  
  - only in selective cases subsequent tx: 12-18 IU / kg / hour  
  *(PTT goal 60-80 sec)* |
| **Tirofiban** | Restore trial:  
  - initial bolus and single bolus: 10ug / kg  
  - only in selective cases subsequent tx: 0.15ug / kg / min  
  for a duration of > 12 hours |
| **Eptifibatide** | - initial bolus or single bolus: 0.135-0.180ug / kg  
  - only in selective cases subsequent tx: 0.5 - 2 ug / kg / min  
  for a duration of > 12 hours |
| **Abciximab** | - rare indications: acute periprocedural thrombotic complication -  
  - weight adjusted „coronary“ dosing |
Differential Tx with IIb / IIIa antagonists?

Inhibition and restoration of aggregation

- Abciximab
- Eptifibatide
- Tirofiban

10 min ~ 10 min > 20 min

Liu AHA 2000
Keriakes AJC 1999

Meet 07
Specific procedure related pharmacology

- Pretreatment
  - antithrombotic: ASS and Clopidogrel
  - renoprotective: hydration, contrast sel, metformin discon., Theophylline*, Accetylcysteine, Fenoldopam (dopamin 1 rec agonist)
  - antiallergic: Methylprednisolon, H1 Anthistamins, H2 Blocker,

- Intraprocedural
  - antithrombotic: Heparin UF / Bivalirudin
  - antiplatelet: IIb / IIIa antagonist (short acting)
  - hemodynamic: Atropin / Dopamin / Suprarenin (Epinephrine)
  - anti-spasm: selective i.art. Nitroglycerin 200ug, Ca antag
  - rescue: lytics: tPA for identified thrombus

- Posttreatment
  - antithrombotic: ASS and Clopidogrel, select. Heparin
  - hemodynamic: Dopamin / Suprarenin (select), Ca-Antag.in Hypertension
  - Anticoagulation: special clinical indications (cardiac)

- hyperperfusion syn: diuretics, BP control, β Blocker, Clonidin, sumatriptan**?

*Huber 2001, **Liu. Schröder 2001
Hyperactivation of Sinus Caroticus reflex by carotid dilatation: acute asystole & hypotension, followed by prolonged hypotension.

Degree of cardioinhibitory & vasodepressive reactions vary.
Hemodynamic Tx

- **Atropin**: i.v. treatment or prevention of vagal mechanism induced bradycardia & hypotension
- **Vasopressor agents** (with persistent hypotension)
  - **Dopamine**: peripheral vasoconstriction / positive inotropy (specific β1 and α receptor activation)
  - **Suprarenin / Epinephrine**: heart rate increase & inotropy (unspecific α, β1 and β2 activation)

  *cave*: excessive effects with risks of intracerebral bleeding, hyperperfusion sx and myocardial ischemia (coronary pts)

- **Antihypertensives periprocedural**: Ca Antagonists, Nitrates; in Hyperperfusion syndrome: β Blocker, Clonidin, no vasodil
# Hemodynamic tx pre and periprocedurally

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
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</table>
| atropin     | **Prophylactic** use prior to dilatation **at bifurcation**: 1.0 mg  
Tx of periprocedural hypotension: 1.0-2.0 mg |
| dopamine    | - Low dose (<2ug/kg/min): dopamine receptors (*splanchnicus area*)  
- Intermediate dose (2-5ug/kg/min): cardiac β1-receptors and α-receptors, *minor vasoconstriction*  
- high dose (>5ug/kg/min): *progressive vasoconstriction*  
-initial bolus: 0.5 - 1.0 ml = 2.5-5.0mg *(ampoule: 250mg/50ml)*  
-subsequent tx: > 1.0 ml/min depending on hemodynamics |
| epinephrine | Initial test dose: 0.01 - 0.04 ug / kg / min,  
followed by titrated dosing |
| suprarenin  | *(ampoule: 250mg/50ml)* |
Special clinical situations

- **Imminent vascular / other surgery post CAS**
  - if possible, postpone > 3 weeks for dual antiaggregation tx
  - if planned immediate surgery (< 1-2 days):
    periprocedural antiaggregation with IIa/IIIb Tirofiban (short acting until < 6 hrs of surgery
  - coronary bypass surgery possible under dual antiaggregation
  - always: balanced risk assessments

- **Indications (preexisting) for anticoagulation (usually cardiac)**
  - Atrial fib: 8-12 weeks dual antiaggr + anticoag (INR @ 2)
  - mechanical valves: antiaggr monotherapy w clopidogrel (8-12 weeks) + anticoag (INR @ 3)

*depending on individual risk assessment bleeding vs. thrombotic event*

Karjalainen EHJ 2007
Specific device related targets of interventional pharmacology

• Emboli
• Vasospasm
• Protection systems
• Stent designs
• Drug elution from stents
• Restenosis (post stent, post CEA)
Arterial spasm with wires / filters
Risk of low or no flow or spasm or thrombus?

Pharmacological therapy: i.a. Nitro 200mcg, Verapamil 500mcg i.a., flush, IIB / IIIa?
Clinical issues in interventional pharmacology 2007

- Variability in clopidogrel response - recognition?
  (80% of pts with events are low responder = risk x 4))
- Low response to clopidogrel - management?
- Pts w chronic clopidogrel tx - reload for PCI?
- Bridging of dual antiplatelet tx
- Bridging of oral anticoagulation
- Strategy post intervention in pts with indication for oral anticoagulation - combined OAC/antiplatelet tx

Ish meet 2007
Heterogenous antiplatelet effects with Clopidogrel 75mg and ASS 100mg > 1 month

Angiolillo, JACC 2007; 49:1505
Mechanisms leading to variability of response to Clopidogrel

Genetic factors
- polymorphisms of receptors & enzymes

Suboptimal Clopidogrel response

Cellular factors
- up/down regulation of receptors & enzymes

Clinical factors
- poor compliance
- underdosing
- poor absorption
- drug interactions
- acute coronary syndromes
- diabetes
- elevated body mass index

Isch meet 07
after Angiolillo JACC 2007
### „Unresolved“ pharmacological issues I

- **Antiplatelet drug allergy** *
  - Aspirin allergy: desensitization
    (in < 4h, 1-5mg ASS, dose doubling every 30min, up to 80-100mg)
- **Aspirin resistance (> 5-75%)**
  - lack of practical assay
  - Option: use of Clopidogrel or dual drug (only valid for PCI?)

- **Clopidogrel resistance/variable low response (> 10-30%)** *
  - associated with higher cardiovascular event rate post PCI
  - lack of practical assay
  - **Option**: 600mg loading dose, 150mg/die, triple antiplat.Tx
    (with Cilostazol = Phosphodiesterase III blocker), or GP IIB / IIIa
  - in pts on chronic clopidogrel tx: reloading with 300mg or 600mg

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Bridging of antithrombotic therapy for surgical / interventional procedures

• Rationale: pts with indication for oral anticoagulation or dual platelet antiaggregation therapy or both have higher periprocedural risk of thromboembolic and/or bleeding events than pts without the need for such antithrombotic therapy - therefore it exists a need for strategies to bridge

• Oral anticoagulation (VKA)
• Antiaggregation therapy (Clopidogrel & ASS)

• ...or to combine both tx for limited duration
## Risk profiles for thromboembolism and bleeding

<table>
<thead>
<tr>
<th>High (&gt;10% / year w/o anticoagulation)</th>
<th>Low (&lt;4% / year)</th>
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<tbody>
<tr>
<td>- mechanical heart valve</td>
<td>- AF without risk factors</td>
</tr>
<tr>
<td>- mitral valve repair &lt; 3 months</td>
<td>- biolog heart valves &gt; 3 months</td>
</tr>
<tr>
<td>- AF w ischemic event, HF, thrombus</td>
<td>- mitral valve repair &gt; 3 months</td>
</tr>
<tr>
<td><strong>Intermediate (4-10% / year)</strong></td>
<td></td>
</tr>
<tr>
<td>- Primary DVT / PE &lt; 1 year</td>
<td></td>
</tr>
<tr>
<td>- biolog heart valves &lt; 3 months</td>
<td></td>
</tr>
<tr>
<td>- AF + Diabetes / hypertension / elderly</td>
<td></td>
</tr>
<tr>
<td><strong>Low (&lt;4% / year)</strong></td>
<td></td>
</tr>
<tr>
<td>- secondary DVT / PE &gt; 1 year</td>
<td></td>
</tr>
<tr>
<td>- dental surgery</td>
<td></td>
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<tr>
<td>- polypectomy / endoscopy</td>
<td></td>
</tr>
<tr>
<td>- TEA</td>
<td></td>
</tr>
<tr>
<td>- complex interventional / stent procedure</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High</th>
<th>Low</th>
</tr>
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<tbody>
<tr>
<td>- heart surgery</td>
<td>- dental surgery</td>
</tr>
<tr>
<td>- aneurysm surgery</td>
<td></td>
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<tr>
<td>- major vascular surgery</td>
<td></td>
</tr>
<tr>
<td>- neurosurgery</td>
<td></td>
</tr>
<tr>
<td>- major intraabdominal / cancer surgery</td>
<td></td>
</tr>
<tr>
<td>- complex orthopedic surgery (hip/knee)</td>
<td></td>
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<tr>
<td>- transurethral prostate resection</td>
<td></td>
</tr>
<tr>
<td>- biospy / puncture in non-compr. tissue</td>
<td></td>
</tr>
<tr>
<td>- angiography / selective interventions</td>
<td></td>
</tr>
</tbody>
</table>
Bridging of Tx with Vitamin K Antagonists for elective surgical / interventional procedure

After Bauersachs, Dtsch Arztebl 2007;104:A 1237

guidelines: Am Coll of Chest Physicians &
www.escardio.org and www.circulationaha.org

isch meet 2007
Studies on UF vs LMWH for bridging of oral anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>UFH (&gt; 300 pts)</th>
<th>LMWH (&gt; 3000 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bleeding</td>
<td>2 - 7%</td>
<td>2 - 4%</td>
</tr>
<tr>
<td>thromboembolic events</td>
<td>0 - 1%</td>
<td>0 - 1%</td>
</tr>
<tr>
<td>costs</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>Length of hospitalisation</td>
<td>longer</td>
<td>shorter</td>
</tr>
<tr>
<td>% pts in therapeutic range at day 2</td>
<td>&lt; 10%</td>
<td>&lt; 90%</td>
</tr>
</tbody>
</table>

Indications for VKA: AF, artificial heart valves, cerebral infarction, DVT, DCM
Surgery performed: cardiovasc, interv.procedures, orthopedic, endoscopic, dental

De Caterina EHJ 2007;28:880, Bauersachs Dtsch Arztebl 2007;104:A1237
Perioperative bridging of oral anticoagulation

• Avoid gap with insufficient AC
• Use bridge drugs with short half life (Warfarin/Coumadin)
• Conventional:
  titration of UFH (aPTT)
  = UFH & LMWH equally safe & effective, accepted general indication, but i.v administration

• Proposed:
  LMWH at therapeutic dosing
  lower HIT, lower cost, shorter hospitalization, no accepted indication
Bridging of dual platelet antiaggregation

ASS 100 mg/die

Clopidogrel Stop

Clopidogrel (Loading)

days: 5  4  3  2  1

Tirofiban

Tirofiban

6 hrs

surgery
Safety & efficacy of combined antiplatelet & anticoagulation Tx in pts with indication for anticoagulation

Complications during 12 mos FU with various drug combinations in pts under VKA (warfarin).
Prescribed drug combinations either ON or OFF at time of event

Warfarin needed for stroke prevention

Karjalainen EHJ 2007
„Unresolved“ pharmacological issues III

- Renal protection from contrast induced nephropathy:**
  - hydration pre / post intervention
  - minimization of contrast use
  - selection of contrast agent (non ionic, isoosmolar, dimeric = iodixanol)
  - Theophyllin (adenosin antagonist, 200 mg iv)
  - Fenoldopam (dopamin1 rec agonist) i.v.? or intrarenal selectively
  - Acetylcysteine??

- Carotid stenting:***
  - Hyperperfusion sy: BP control, β Blocker, Clonidin, no vasodil

Future Directions......

- Wider use of preventive measures
- Fast onset (more potent) antiplatelet drugs & antiplatelet drugs with less response-variability
- Recognition of low responsiveness to clopidogrel-&management of resistance
- Reversible ADP receptor Blockers
- Defining the role of IIb/IIIa
- Lysis and IIb / IIIa
- Local drug-on-stent concepts
Future directions I

The pharmacological revolution continues.....

- **Antiplatelet**
  more potent, fast onset, long duration, reduced response variability / resistance, reversible
  - **Prasugrel** (third generation thienopyridine), 10 x more potent
    (Trials: Jumbo-TIMI, TRITON, PRINCIPLE)
  - **AZD6140** (non-thienopyridine P2Y 12 receptor antagonist),
    more potent, less response variability
    (Trials: DISPERSE, PLATO)
  - **Cangrelor** (P2Y 12 receptor antagonist)
    (Trials: CHAMPION PCI and CHAMPION platform)

- Identification of drug resistance/high risk for events for a more tailored treatment strategy
Future directions II

*The pharmacological revolution continues*...

- **Anticoagulants**
  mainstay in cardiovascular therapy (permitted cardiac surgery, adjuvant in PCI, longterm Tx in various cv conditions)
  - shortcomings: bleeding, side effects not linked to AC, drug/food interaction (VKA), need for monitoring, poor acceptance

- **Novel developments:**
  simple fixed dosing, no food/drug interaction, no monitoring
  - pentasaccharides
  - orally active DTI (ximelagatran)
  - orally active F Xa inhibitors

*Isch meet 2007*
"To play it safe, I still take one aspirin every other day......"
Restenosis post Intervention:
Magnitude of the problem

- ? > 25% ?
- 3 - 6%
- 10 - 30%
- 5 - 30%
- 10 - 25%
- 25 - 70%
- 10 - 50%

Balloon / Stent
@ 12 mos

Isch 06
Pharmacologically failed interdisciplinary approach

*Lack of platelet inhibition*

*In bilateral stenting preceding CABG*

8 h post bilateral stenting & lack of continued antiaggregation. Aborted IIB/IIA bridging, but no Clopidogrel/ASS) due to planned urgent coronary bypass.
Challenges in Interventional pharmacology

- Systemic pharmacological concepts
- Safe acute antithrombotic procedural environment: Timely pretreatment/ periprocedural tx, dosing issues
- Resistance/Hyporesponsiveness to antiplatelet agents: recognition, dosing, alternative (multiple)drugs
- Long term patient tolerance to antiaggr.Tx
- Minimized bleeding risks & drug reversibility
- Anti-restenosis efficacy? (Statins for increase of EP cells?)

- Localized intravascular drug release concepts (DES):
  - minimized hypersensitivity to device, polymers, drugs
  - optimized pharmacokinetics
  - balance of LATE LOSS vs LAST
    at intermediate term antiaggregation tx
“Unresolved“ pharmacological issues

• **Antiplatelet drug allergy**

• **Antiplatelet drug resistance**
  - Aspirin allergy: desensitization
    (< 4h, 1-5mg ASS, doubled every 30min, up to 100mg)
  - Aspirin resistance (> 5-75%, assay?): use of Clopidogrel
  - Clopidogrel resistance (> 4-30%, assay?): 600mg loading, 150mg/die, triple antiplat.Tx (Cilostazol=Phosphodiesterase III blocker, IIB / IIIa) *

• **Renal protection from contrast induced nephropathy:**
  - hydration pre / post intervention
  - minimization of contrast use (non ionic, isoosmolar, dimeric = iodixanol)
  - Theophyllin
  - Fenoldopam (dopamin 1 rec agonist) selectively or i.v.**

• **Carotid stenting: Hyperperfusion syndrome**
  β Blocker, BP control, no vasodil**

***Schroeder
“Unresolved“ pharmacological issues

• **Antiplatelet drug allergy / resistance**
  - Aspirin allergy: desensitization
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  - Theophyllin
  - Fenoldopam (dopamin 1 rec agonist) selectively or i.v.**

• **Carotid stenting:**
  - Hyperperfusion syndrome: β Blocker, Clonidin, BP control, no vasodil**, Sumatriptan?

---

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