Treatment of ischaemic heart disease - coronary artery disease (CAD)

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Contents ...

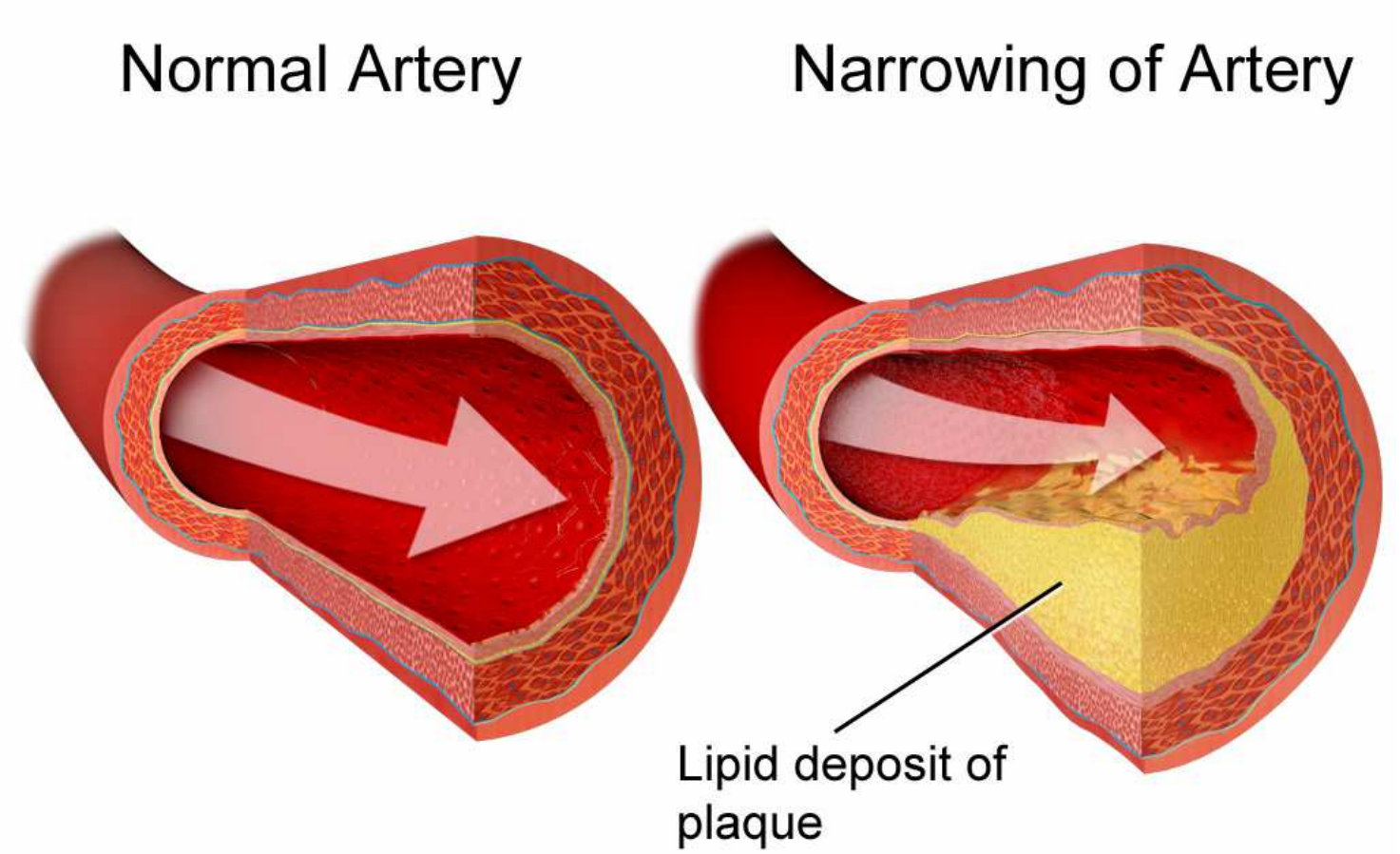
- What is „coronary artery disease“ ?
- What are the goals of treatment ?
- What kind of medication is required ?
- What are benefits and potential risks of CAD pharmacotherapy ?

What is „coronary artery disease“ ? (1)

- Defined with ischemia
  - Inbalance between oxygen demand and blood oxygen supply

- Major energy metabolic pathway
  - β-oxidation of fatty acids

What is „coronary artery disease“ ? (2)



- **ACUTE CORONARY SYNDROME**

  - MYOCARDIAL INFARCTION (STEMI, NSTEMI)

    - HIGH **CARDIOMARKERS**
    - **CORONARY VESSEL STENOSIS**
    - HIGH RISK OF CORONARY NECROSIS AND LATER COMPLICATIONS

- **ACUTE CORONARY SYNDROME**
  - UNSTABLE ANGINA
  - **SPASM OF CORONARY ARTERY**
  - CO-INCIDENCE OF CORONARY ATHEROSCLEROSIS AND CALCIFICATIONS
  - LOW DYNAMICS OF CARDIOMARKERS

What are the goals of treatment ?

- Improve the quality of life
- Improve patient prognosis

- Methods
  - Stop or slow down progress of atherosclerosis
  - Improve flow of ischaemic myocardium
  - Prevention of vascular thrombosis

Therapy of CAD

- Non-pharmacological
  - Lifestyle changes
- Pharmacological
  - Drug therapy
- Interventional procedures

Interventional procedures in CAD treatment

- THROMBOLYSIS – indication ?
- CABG – surgical revascularization

- **dPCI – direct percutaneous coronary intervention –** developement of novel antitrombotic therapy

- **Succesful treatment of CAD is coupled with high quality antitrombotic therapy**

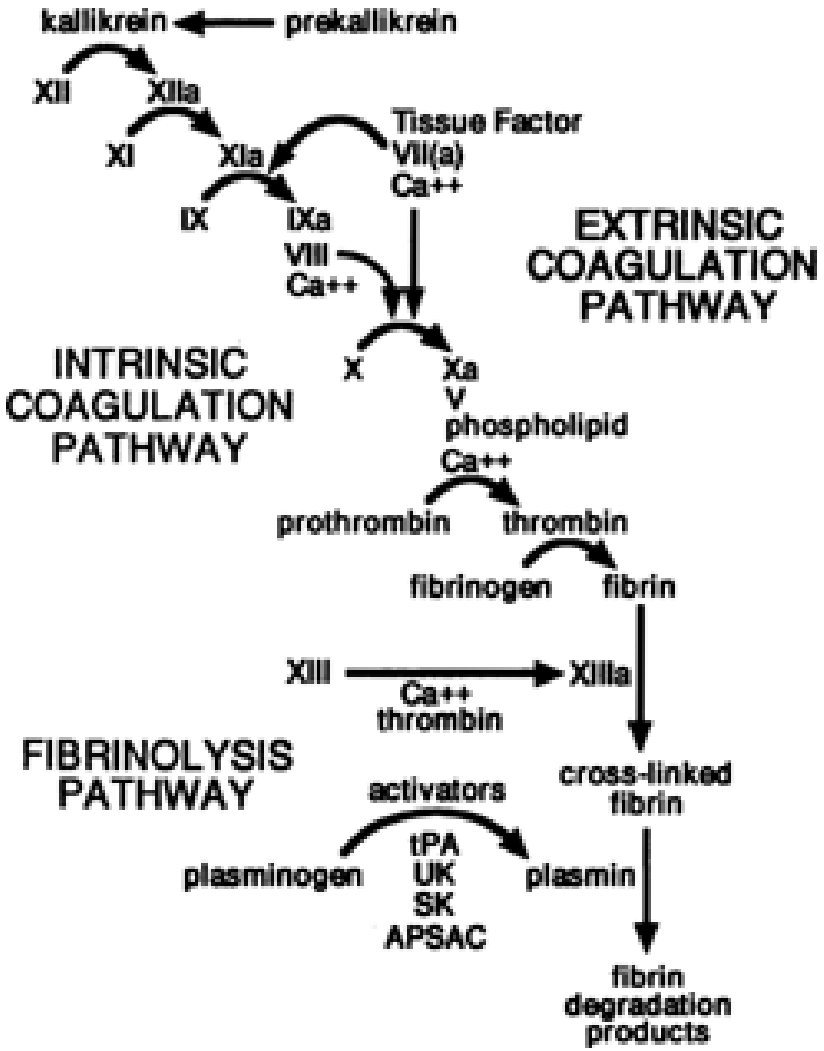
Thrombolysis in CAD treatment

- **Streptokinase**
  - Polypeptide (n=415) isolated from β-hemolytic *Streptococcus*
  - Antigenic potential
  - Administration coupled with antibody production

Thrombolysis in CAD treatment

- **Alteplase**
  - Recombinant tPa (tissue plasmin activator)
  - Without antigen potential
  - 10 mg bolus, 90 mg i.v. infusion
  - Less effective than PTCA

Thrombolysis in CAD treatment



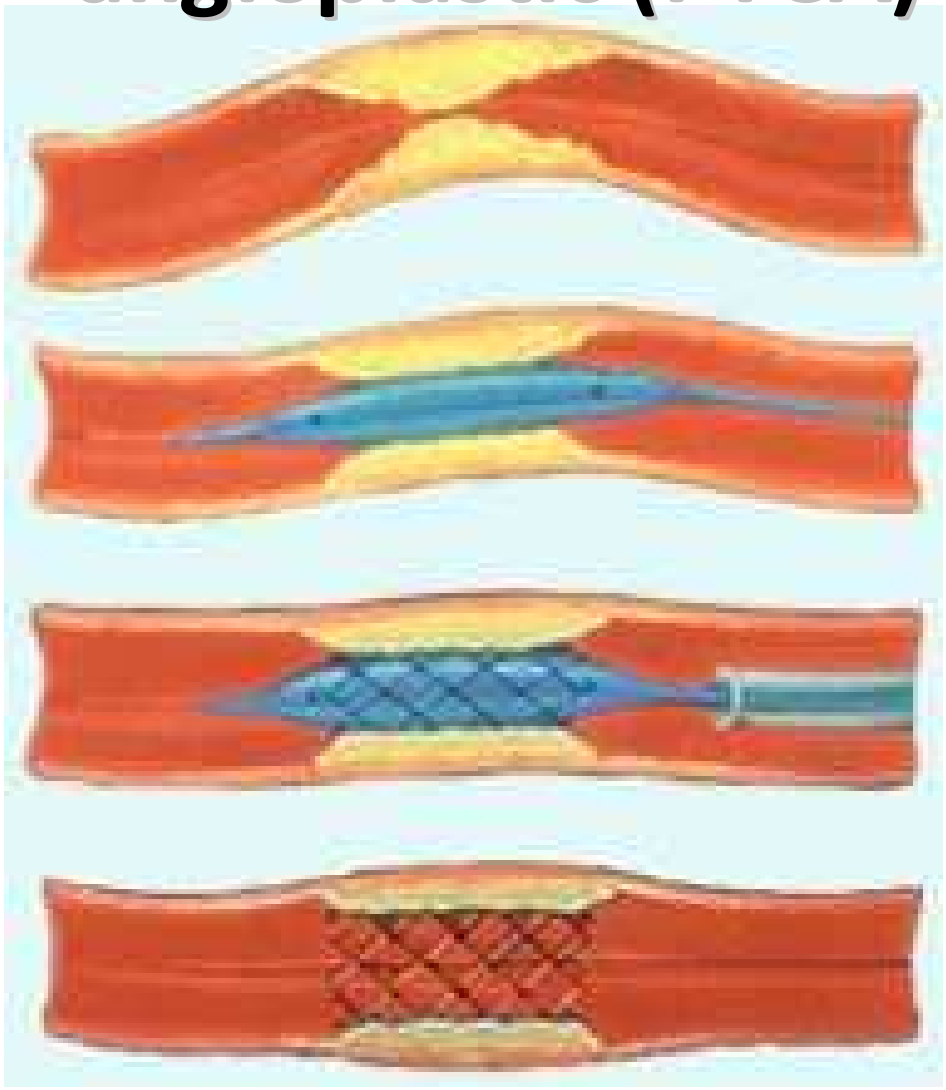
Cossum P.A., Baughman R.A.: Pharmacokinetics and metabolism of cardiovascular therapeutic proteins.

Thrombolysis indication

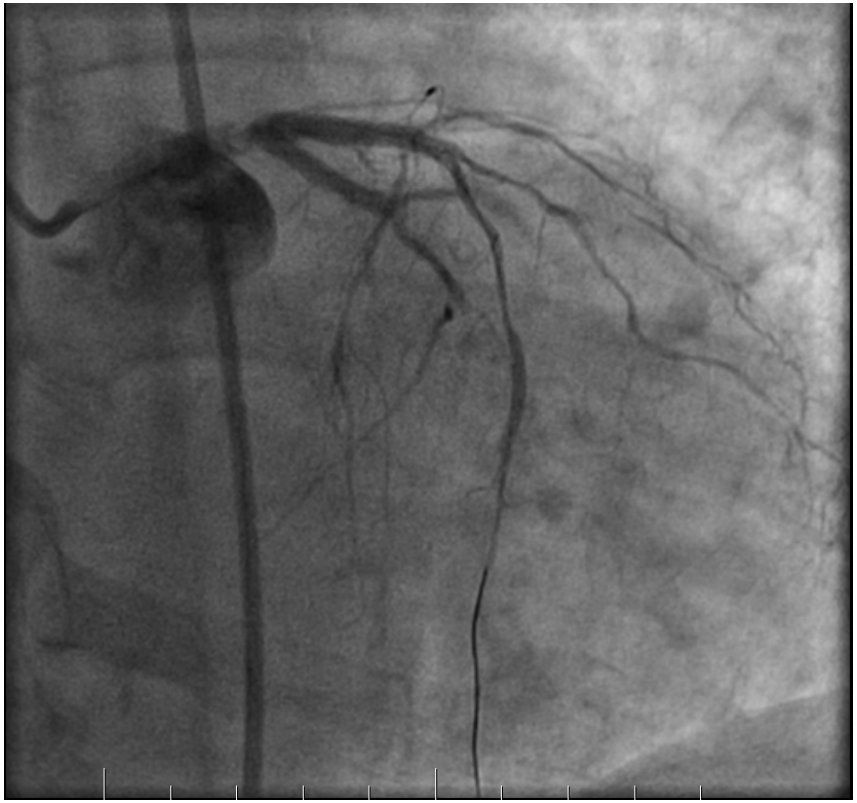
- Alteplase (**ACTILYSE)**
- Dubious prognosis
- Unavailability of CathLAB within 2 hrs of symptoms occur

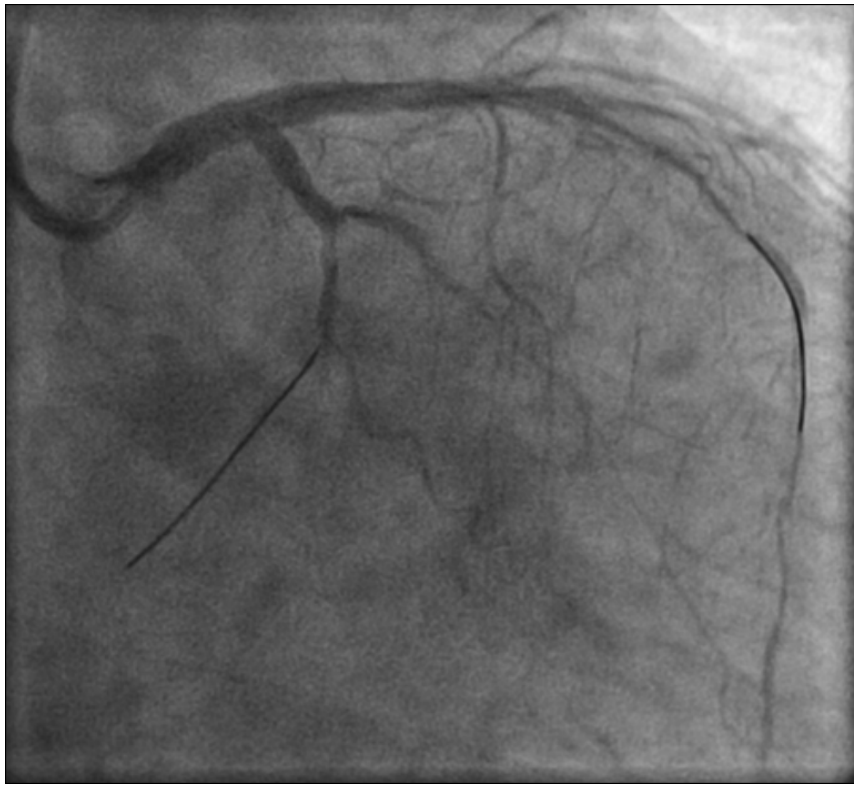
THROMBOLYTIC TREATMENT OF CAD IS OBSOLETE !

Percutaneous transluminal coronary angioplastic (PTCA)



ACS-stem intervention





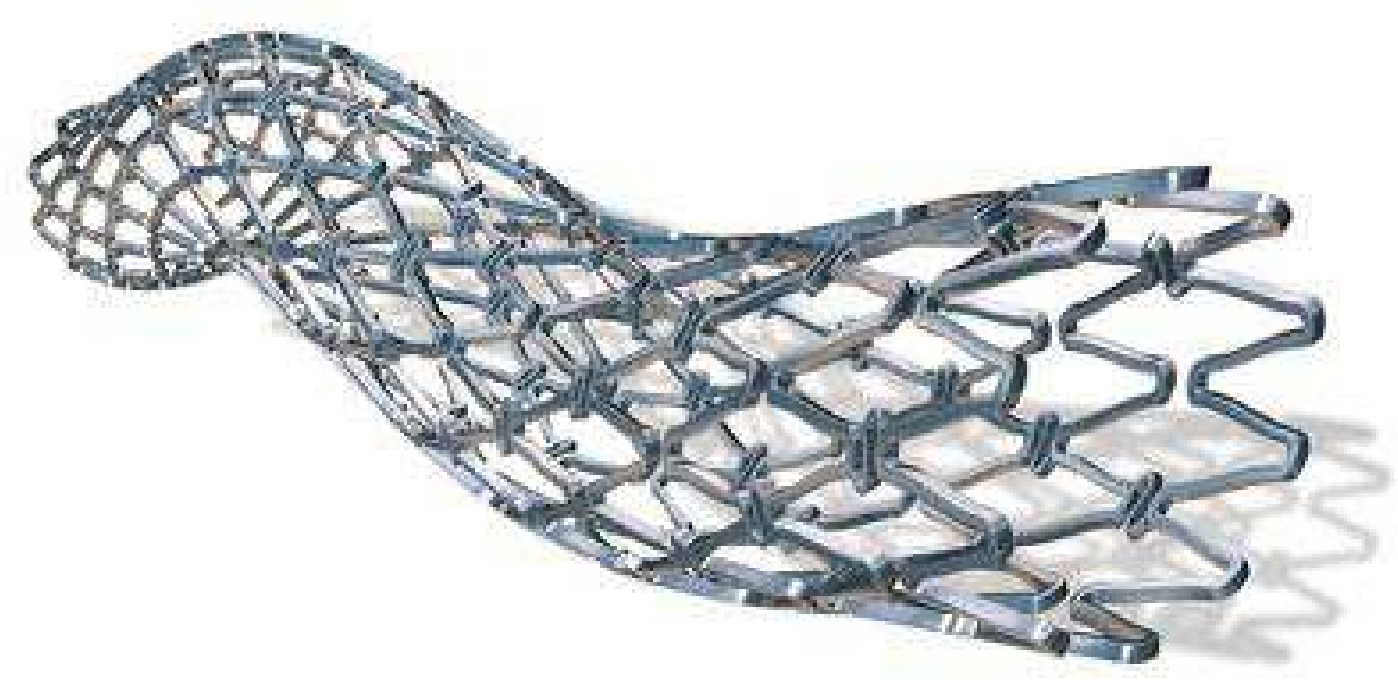
Percutaneous transluminal coronary angioplastic (PTCA)

- Interventional method determines
  - Duration of antiplatelet therapy (3-12 months)

- Too short
  - risk of stent thrombosis
- Too long
  - risk of bleeding and side effects

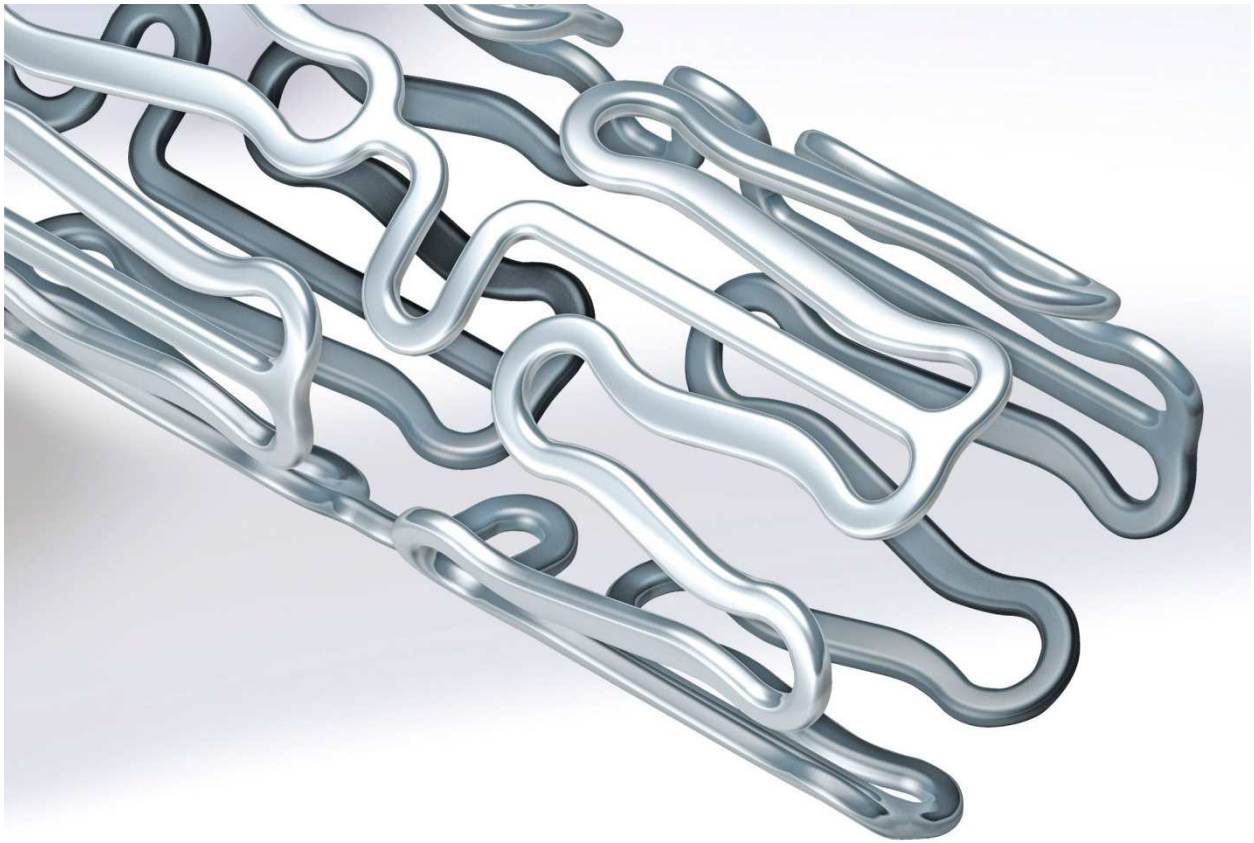
dPCI determines therapeutic strategy (1)

- **BARE-METAL STENT (BMS)**



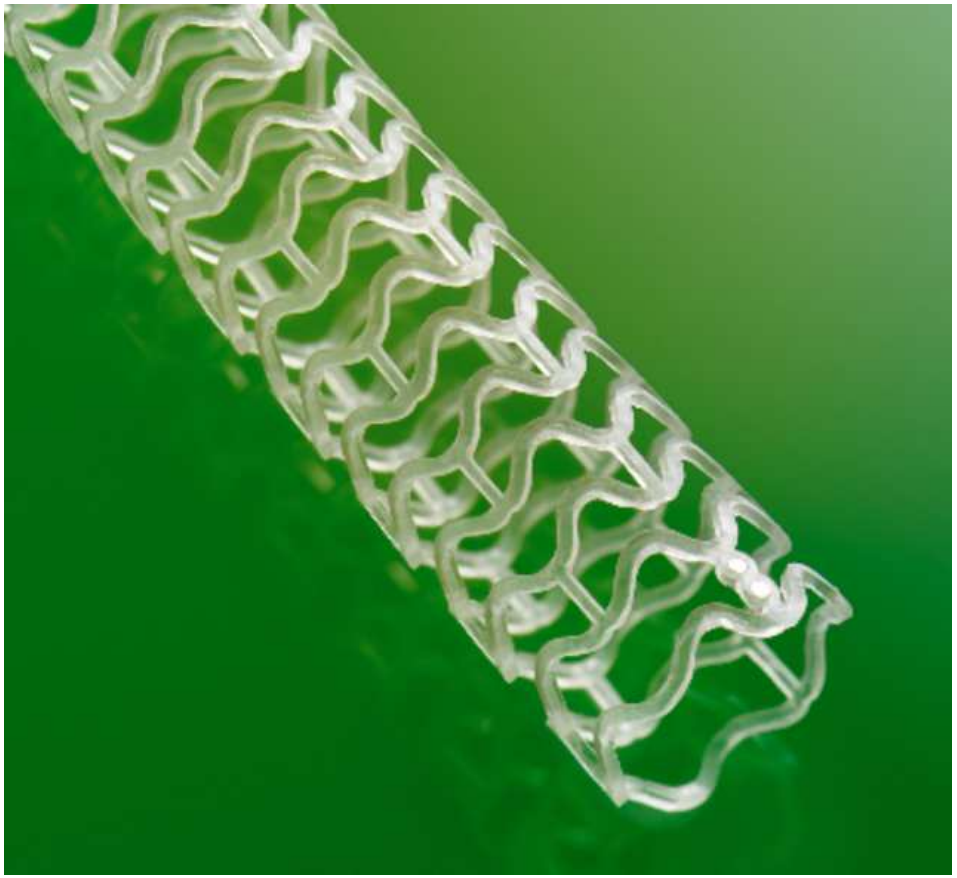
dPCI determines therapeutic strategy (2)

- **DRUG-ELUTING STENT (DES)**



dPCI determines therapeutic strategy (3)

- **CORONARY SCAFFOLD**



What kind of medication is required ? (1)

- **antithrombotic agents –dual antiplatelet therapy (DAPT)**

- β-blockers
- ACE – inhibitors (ARB)
- hypolipidemics

ACUTE PHASE TREATMENT

- HEPARIN BOLUS 70 – 100 IU/KG
- ANTITROMBIN III SUBSTITUTION NOT REQUIRED
- **EXCLUSIVELLY I.V. !!!!**

- **HEPARIN ACCELERATES PROTEOLYTIC REACTION OF ANTITROMBIN III 1000x**

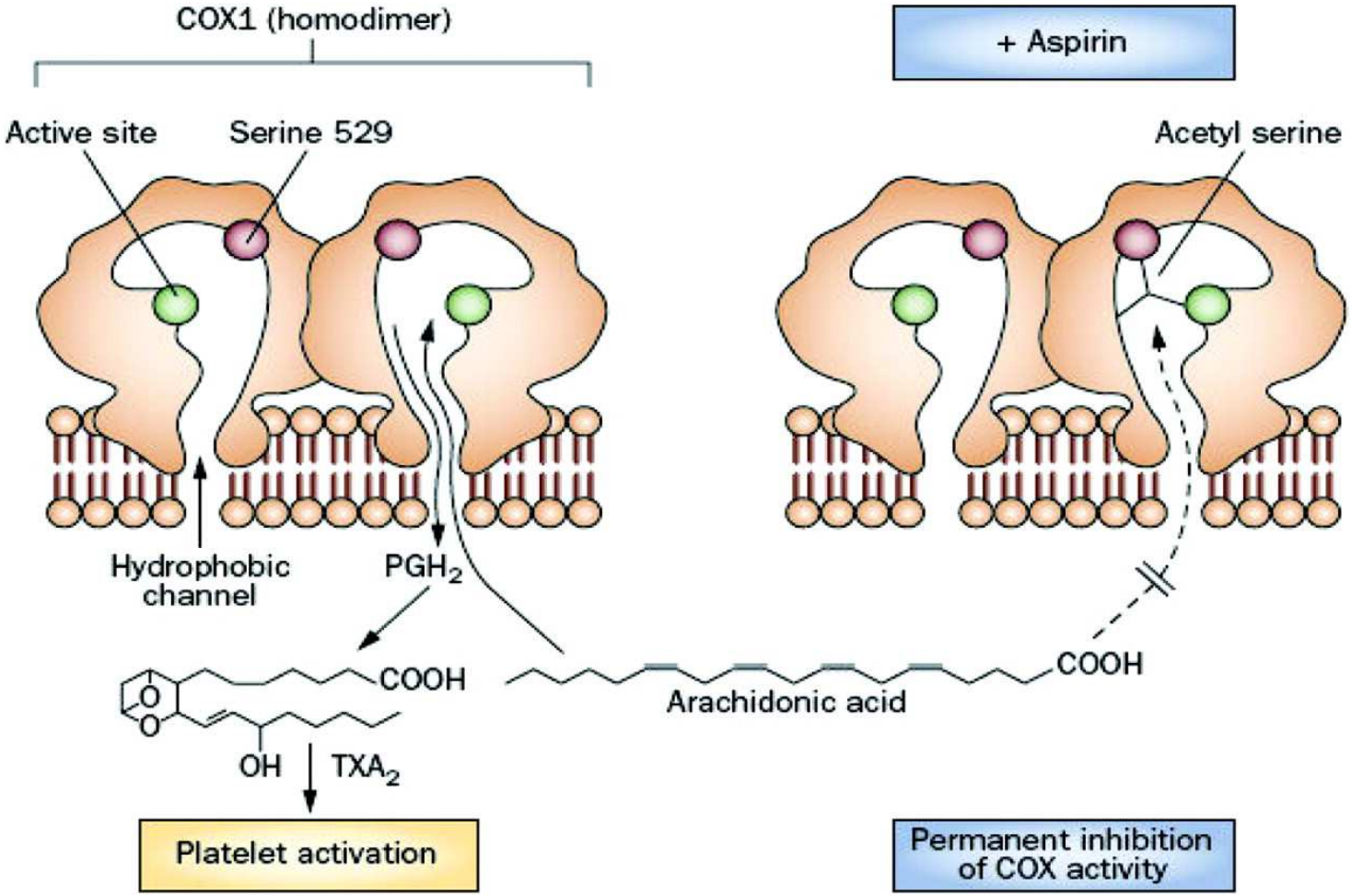
- Administration of **opiates** to reduce stenocardial pain

DAPT – mechanism of action

- **COX inhibition**
  - Aspirin (acetylsalicylic acid)
- **ADP receptor inhibition**
  - Clopidogrel
  - Prasugrel
  - Ticagrelor

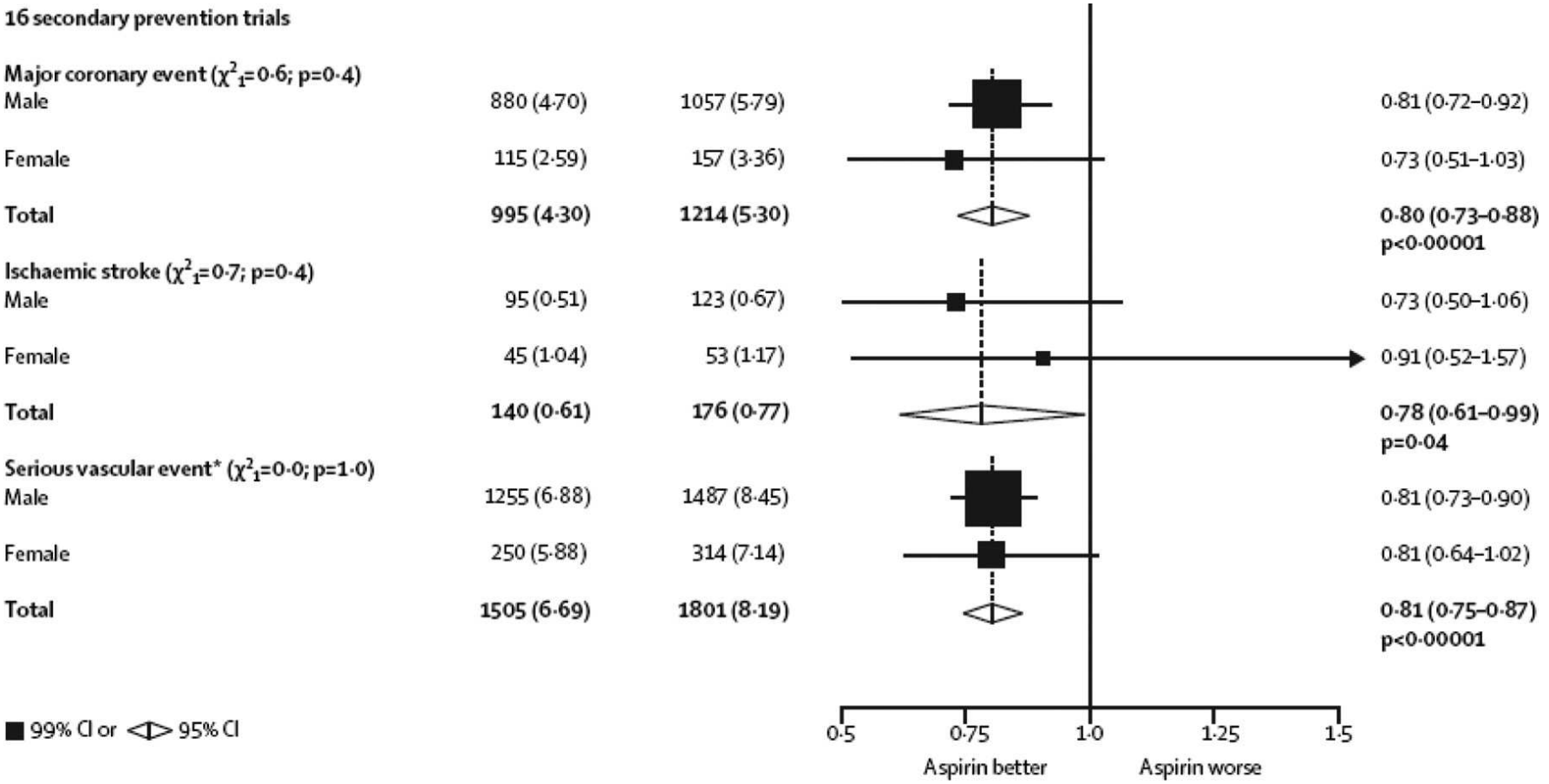
- **Drug resistance – risk of stent thrombosis**

Aspirin – mechanism of action



Valentin Fuster, and Joseph M. Sweeny *Circulation*. 2011;123:768-778

Selected outcomes in secondary prevention trials of aspirin by sex



Valentin Fuster, and Joseph M. Sweeny Circulation. 2011;123:768-778

Aspirin – side effects and risks

- GI tract toxicity; Nephrotoxicity
- Aspirin triggered encefalopathy (Reye syndrome)
- Aspirin-induced bronchospasm
- **Hypersensitivity and allergy**

- Primary and secondary prevention
- What dose ?

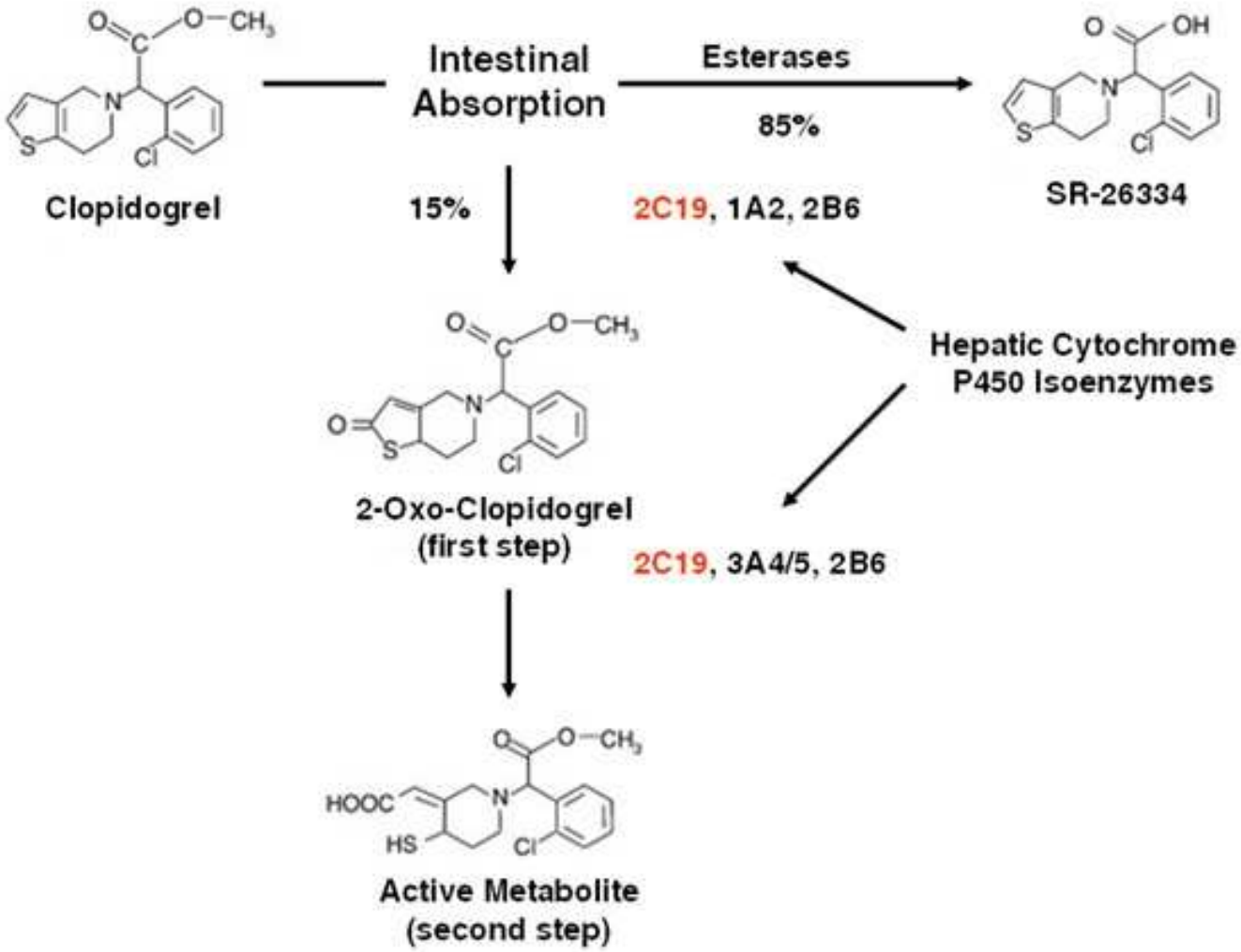
Clopidogrel

- Irreversibile inhibition of ADP-mediated platelet aggregation ($P2Y_{12}$ receptor)

- Loading dose 300 – 600 mg
- Maintenance dose 75 mg

- 30 % of patients are resistant to clopidogrel based DAPT

Clopidogrel is Metabolized in a Two-Step Process



Clopidogrel (2)

- Prodrug – necessary activation via
  - *p450 CYP 2C19 cytochromeoxidase*
- Resistance to Clopidogrel-based DAPT
  - Pharmacological interactions
  - Genetic predisposition

Clopidogrel – contraindications, adverse effects

- Severe hepatic insuficiency
- Active pathological bleeding (peptic ulcer bleeding, intracranial bleeding)

- Epistaxis, GIT bleeding, diarhea, trombocytopaenia, increased bleeding

DAPT resistance and therapy failure

- **<u>Genetic predisposition</u>**
  - Slow metabolizers *p450 CYP 2C19*
  - Fast metabolizers *p450 CYP 2C19*

- **MULTIPLATE method**

DAPT resistance and therapy failure (2)

- **Pharmacological resistance**
  - Pharmacokinetic drug interactions
  - **SSRI** (fluoxetin, fluvoxamine, paroxetine), **anticonvulsives** (carbamazepine, felbamate, topiramate), **PPI** (omeprazol)

- Therapy failure leads to **stent thrombosis !**
- Discontinuation of interfering drug or ...

ADP-inhibitor pharmacodynamic drug interaction

- NSAID use with DAPT leads to increase of bleeding complications
  - Epistaxis
  - CNS bleeding
  - GIT bleeding
- Avoid prescribing NSAID with DAPT !

PRASUGREL

- High ADP-receptor afinity
- Necessary conversion from prodrug to active metabolite
- Irreversibile inhibition of **$P2Y_{12}$ ADP-receptor**
- Onset of action : 30 MINUTES

- Loading and maintenance dose

EFIENT; LILLY

PRASUGREL - dosing

- Patients weight below 60 kg

- Elderly population (75 years and older)
  - Dose reduction to ½
  - Bleeding complications

PRASUGREL - restrictions

- Drug interactions (?)
  - NSAID, inducers and inhibitors of hepatic turn-over
- So far, none clinically relevant FK interactions (*p450 CYP 2C19* level)

- **Surgical procedures and discontinuation of DAPT based on prasugrel**

The NEW ENGLAND JOURNAL of MEDICINE

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Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

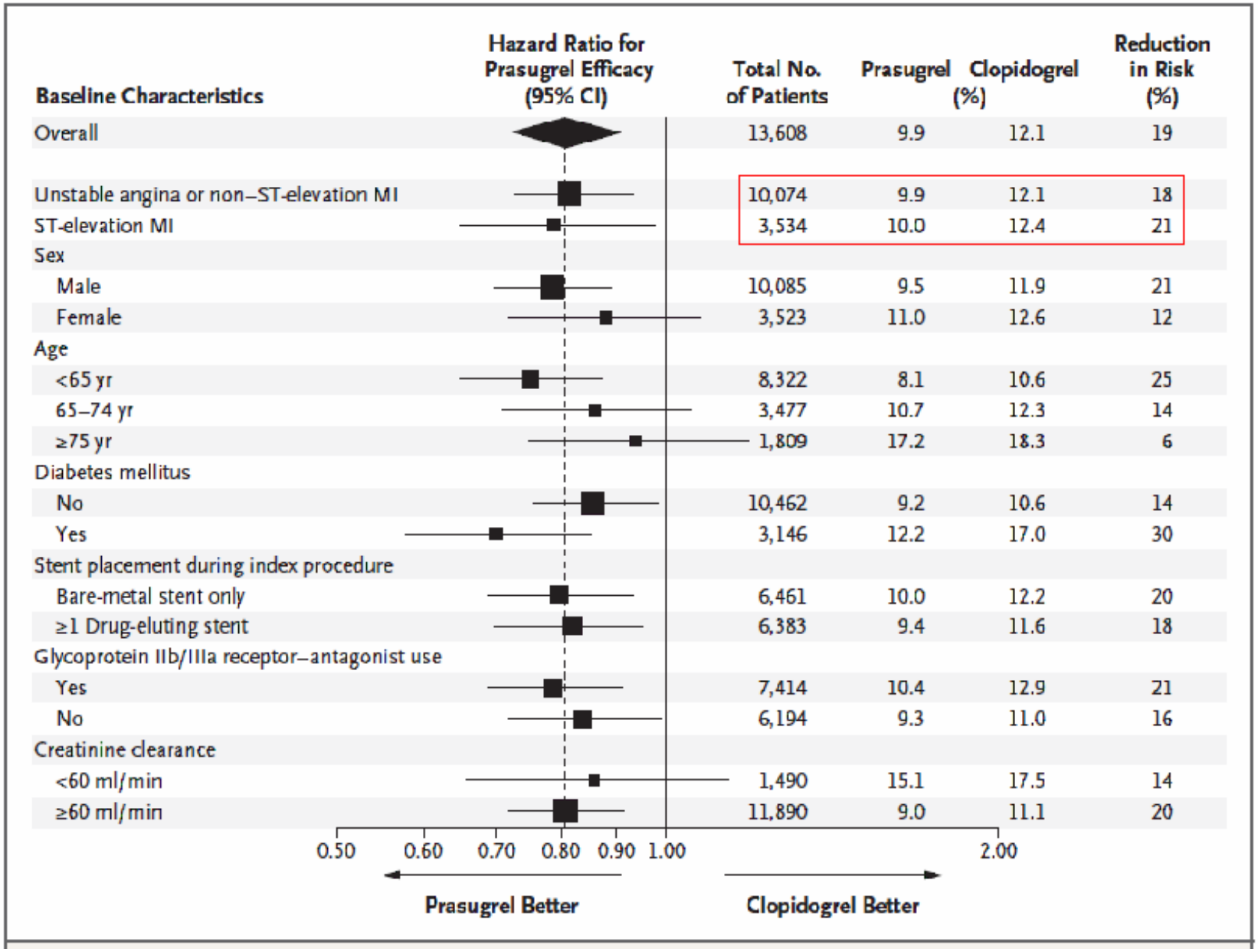
Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

TRITON-TIMI 38 TRIAL - EFFICACY

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

Wiviott S.D., et al.: Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes; *N Engl J Med* 2007;357:2001-15.



Wiviott S.D., et al.: Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes; *N Engl J Med* 2007;357:2001-15.

TRITON-TIMI 38 TRIAL – SAFETY

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

TICAGRELOR

- Direct **reversibile** inhibitor of ADP-mediated platelet aggregation (inhibition of $P2Y_{12}$ –ADP receptor)

- Native substance and metabolite are equipotent inhibitors

- **BRILIQUE; ASTRA ZENECA**

TICAGRELOR

- Onset of action within 1,5 hrs
- ↓ risk of major bleeding
- ↓ risk of stent thrombosis
- ↑ Adenosin mediated coronary vasodilatation

- No effect on incidence of stroke vs clopidogrel

Wittfeldt A. Et al.: Ticagrelor enhances Adenosine-induced coronary vasodilatatory responses in humans; J Am Soc Cardiol; 2013: 61;7

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

PLATO TRIAL-primary endpoints

Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22

Wallentin L. et al.: Ticagrelor versus Clopidogrel in patients with acute coronary syndromes; *N Eng J Med; 2009: 351;11*

PLATO STUDY – primary endpoints (2)

Stent thrombosis — no. of patients who received a stent/ total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

Wallentin L. et al.: Ticagrelor versus Clopidogrel in patients with acute coronary syndromes; *N Eng J Med; 2009: 351;11*

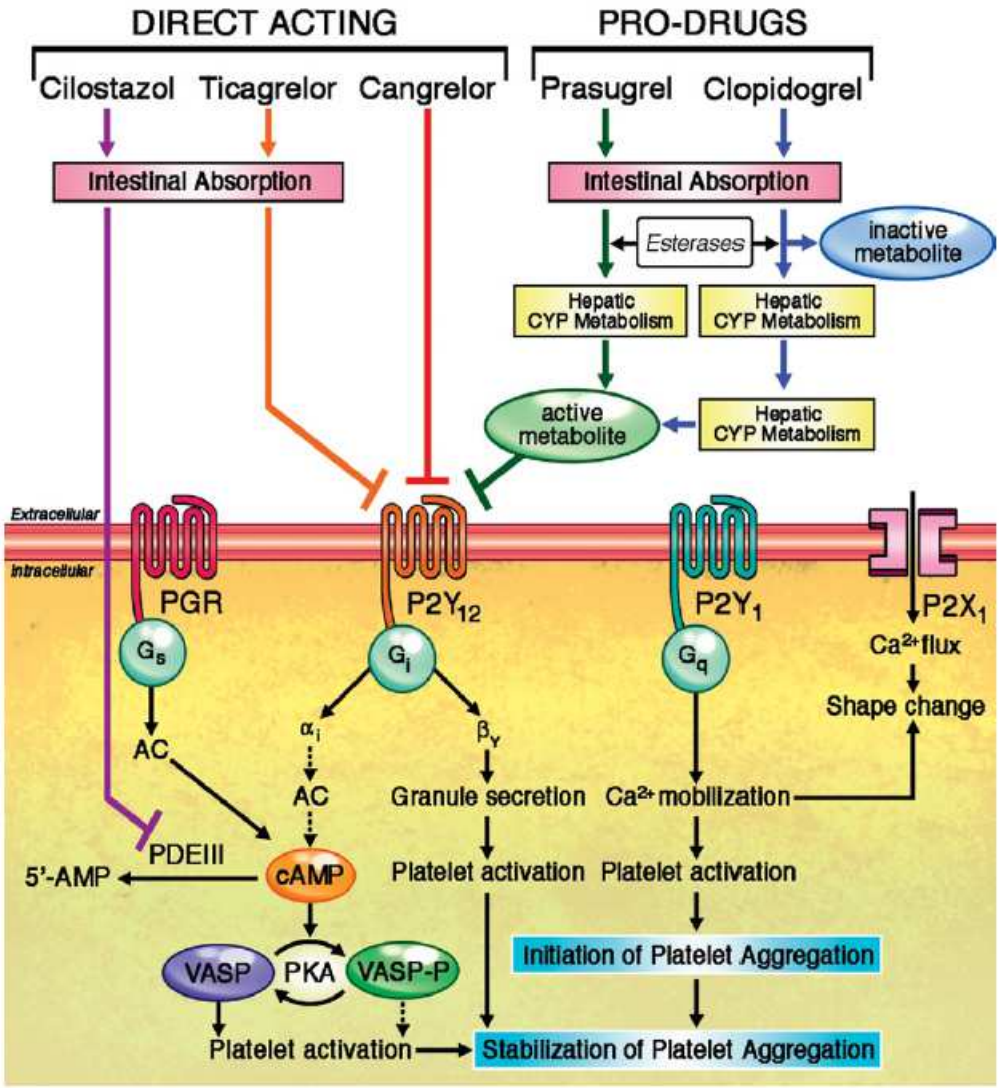
PLATO STUDY - safety

Table 4. Safety of the Study Drugs.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69

Wallentin L. et al.: Ticagrelor versus Clopidogrel in patients with acute coronary syndromes; *N Eng J Med;* 2009: 351;11

ADP-inhibitor comparison



Angiolillo D.J. et al.: Optimizing platelet inhibition in Clopidogrel poor metabolizers; JACC: Cardiovascular Intervention; 2011:4

What kind of medication is required ?

- antithrombotic agents –dual antiplatelet therapy (DAPT)

- **β-blockers**
- ACE – inhibitors (ARB)
- hypolipidemics

β-blockers

- competitive antagonists of β-adrenoreceptors
  - Myocardium
  - Kidneys
  - Brain
  - Liver
  - Bronchi

β-blockers (2)

- **clinical implications**
  - Decrease myocardium oxygen consumption
  - Decrease heart rate and increase flow
  - Prophylaxis of angina
  - Prevention of ischaemia-induced arrhytmias

β-blockers (3)

- Non-selective – **timolol, pindolol, propranolol**
- β_1-selective – **metoptolol, bisoprolol, betaxolol, nebivolol** (without ISA)
- β_1-selective – **acebutolol** (with ISA)
- Combined - **carvedilol**

ISA – intristic sympatomimetic activity

- Ability of β-blocker to act as **partial agonist** on β-receptor (acebutolol) and still act as an **antagonist** to epinephrin and norepinephrin in case of increased catecholamine activity

ISA – intristic sympatomimetic activity (2)

- Result
  - Effect simillar to endogenous stimuli (EPI,NOR to β-receptor)
  - **Depends on current state** of sympaticus activation

ISA – intristic sympatomimetic activity (3)

- Potential of benefit
  - Reducing vessel resistance in peripheral circulation
  - Reducing risk of resting bradycardia
  - Reducing risk of blood lipids imbalance

β-blockers (4)

- Adverse effects
  - Evocation of bronchospasm
  - Bradycardia
  - Hypoglycaemia
  - Fatigue

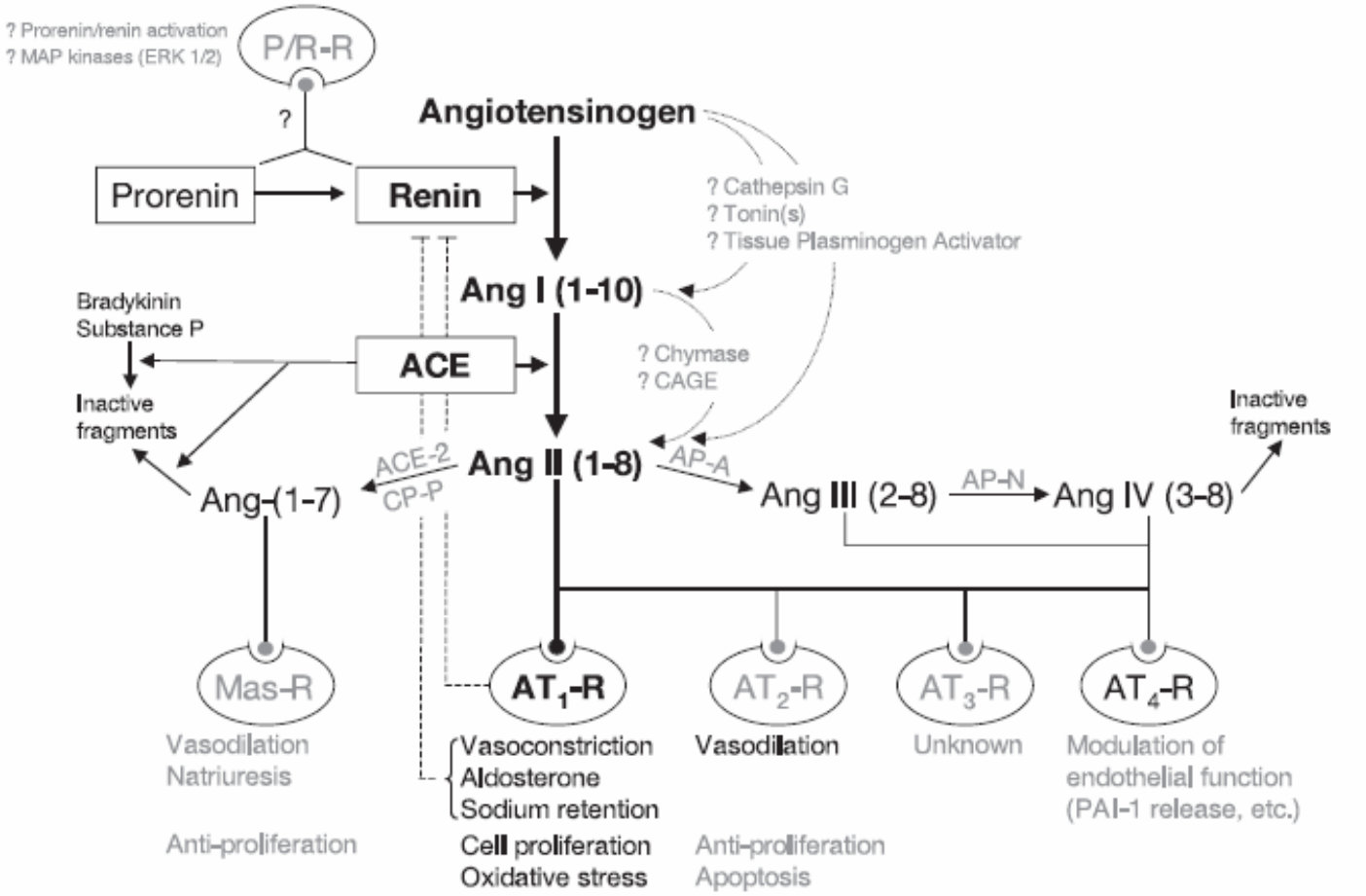
- Contraindications
  - AV block (2,3), asthma bronchiale, hypotension,

What kind of medication is required ?

- antithrombotic agents –dual antiplatelet therapy (DAPT)

- β-blockers
- **ACE – inhibitors**
- hypolipidemics

RAAS system and myocardial infarction – drug targets



Atlas S.A.:2007

Angiontensin-**C**onverting **E**nzyme (kininase II) **I**nhibitors – **basic properties**

	Captopril	Enalapril	Quinapril	Ramipril	Trandolapril
Zinc ligand	Sulfhydryl	Carboxyl	Carboxyl	Carboxyl	Carboxyl
Prodrug	No	Yes	Yes	Yes	Yes
t_{max} active drug, h	0.7–0.9	2–8	2	3	4–10
$t_{1/2}$ active drug, h	1.7	11	1.9–2.5, 25 terminal	Triphasic 4, 9–18, >50	15–24 terminal
Route of elimination	Kidney	Kidney	Kidney	Kidney	Kidney, liver
Dosage range, mg	6.25–300	2.5–40	5–80	1.25–20	1–8
F, %*	75–91	60	>60	50–60	70

Brown N.J., Vaughan D.E. 1998

What kind of medication is required ?

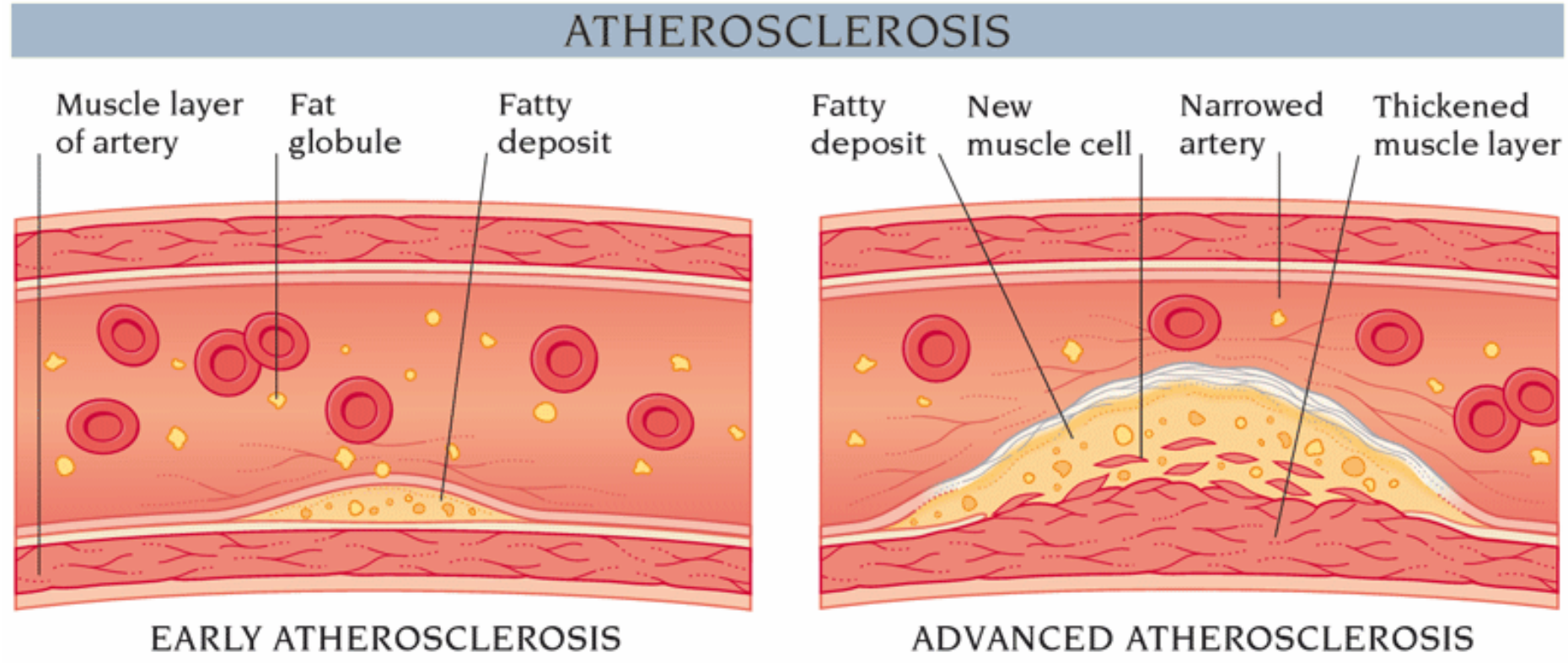
- antithrombotic agents –dual antiplatelet therapy (DAPT)

- β-blockers
- ACE – inhibitors
- **hypolipidemics**

Hypolipidemic therapy in CAD

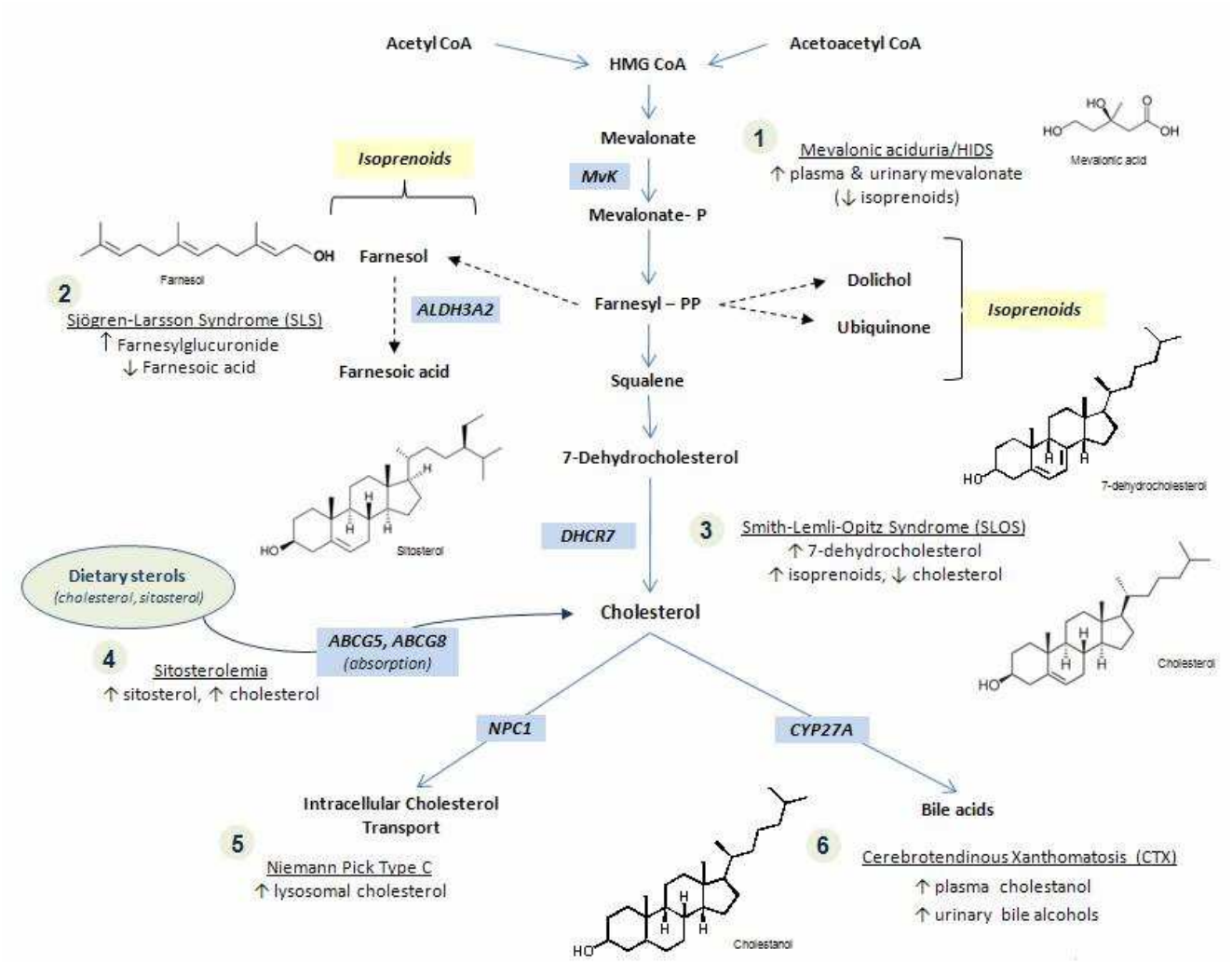
- **HMG-CoA-reductase inhibitors (statins)**
  - Fluvastatin
  - Simvastatin (4S; HPS)
  - Atorvastatin (MIRACL, ALLIANCE – high dose)
  - Rosuvastatin (JUPITER)
- **Drug interactions on hepatic metabolism !**

Hypolipidemic therapy in CAD



Higher dose – better treatment outcome

Hypolipidemic therapy in CAD – mechanism of action



Hypolipidemic therapy in CAD – pleiotropic potential of statins

- Improvement of endotelial function
- Antioxidant and antiinflamnatory properties
- Stabilization of atherosclerotic plaques
- Antitrombotic and neo-angiogenetic activity

Hypolipidemic therapy in CAD – side effects

- **Muscle pain and muscle dyscomfort**
- **In rare cases rhabdomyolysis**

- Hepatotoxicity
- Allergic reaction
- Glucose intolerance
- Neurologic side effects (headache, vertigo, ...)

Hypolipidemic therapy in CAD

Dose Conversion Table for Statins:

% LDL Reduction	LOVASTATIN (MEVACOR*)	PRAVASTATIN (PRAVACHOL*)	SIMVASTATIN (ZOCOR*)	LESCOL	LIPITOR	CRESTOR	VYTORIN
25-32%	20 MG	20MG	10MG	40MG	-	-	-
31-39%	40MG	40MG	20MG	80MG	10MG	-	-
37-45%	80MG	80MG	40MG	-	20MG	5MG	10/10
48-52%	-	-	80MG	-	40MG	10MG	10/20
55-60%	-	-	-	-	80MG	20MG	10/40
60-63%	-	-	-	-	-	40MG	10/80

*TRADE NAMES WITH AB EQUIVALENT GENERICS AVAILABLE

Hypolipidemic therapy in CAD – alternative treatment

- Fibrates – **fenofibrát, klofibrát**
  - **Elevated FFA, lowering VLDL particles**

- Inhibitors NPC1L1-protein – **Ezetimib**
  - **Fixed dose with statin (simvastatin)**

- Inhibitors proteinkinase SK-9 – **Evolocumab**
  - **In clinical trials for cardiovascular prevention**

- Thank you for your attention

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