Farmakoterapie akutního koronárního syndromu a ICHS

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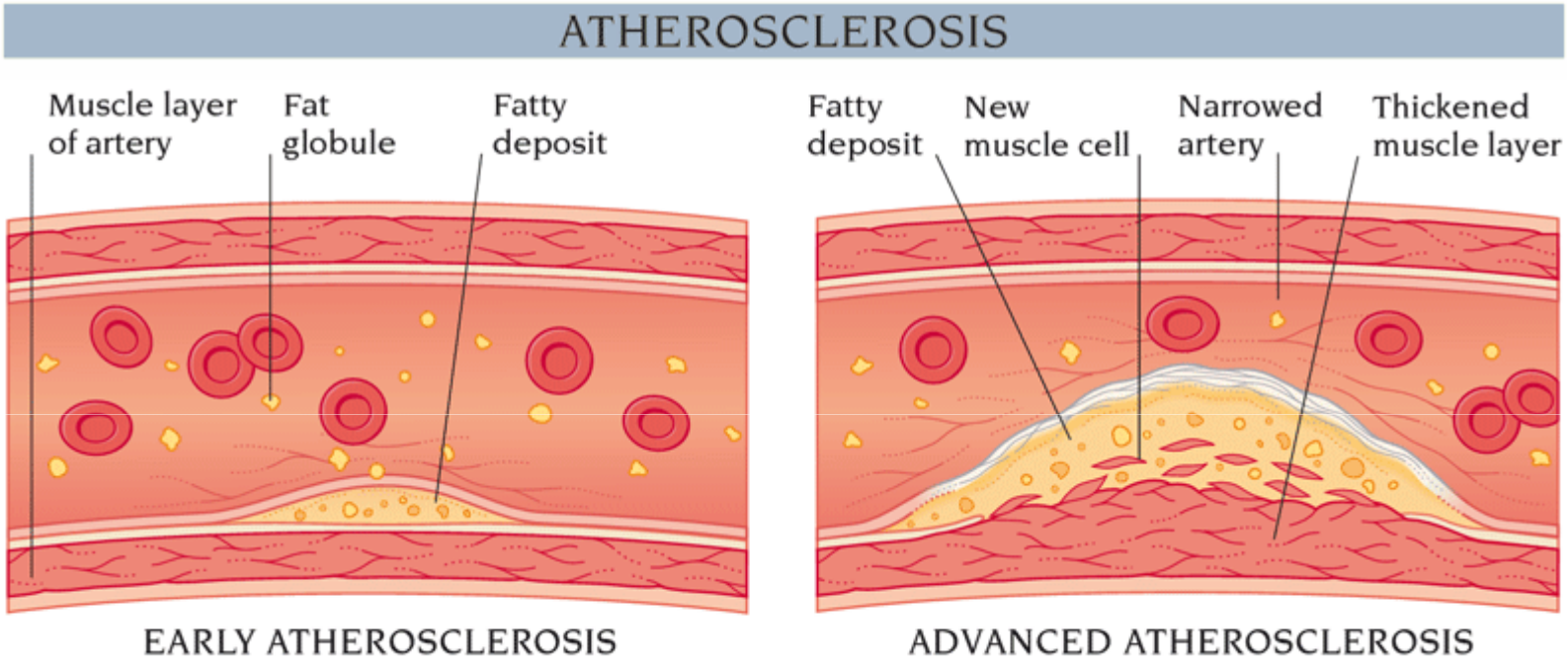
ČO JE CIEĽOM ZDELENIA ?

- STRUČNE O „AKS“ ?
- POSTUP LIEČBY

- BENEFITY A POTENCIÁLNE RIZIKÁ FARMAKOTERAPIE – evidence-based

- Na záver kazuistika ?

Ako vzniká AKS ?



- **<u>Komplikácie AKS</u>**
  - Ďalší AKS, iktus, angina pectoris
  - Renálna insuficiencia, zlyhanie srdca, arytmie, **náhla smrť**

- **AKUTNÝ KORONÁRNY SYNDROM**

  – INFARKT MYOKARDU (STEMI, NSTEMI)

    •VYSOKÁ **DYNAMIKA KARDIOMARKEROV**

    •**STENÓZA** LUMINU KORONÁRNEJ TEPNY

    •RIZIKO MYOKARDIÁLNEJ NEKRÓZY A NESKORŠÍCH KOMPLIKACIÍ

- **AKUTNÝ KORONÁRNY SYNDROM**

  – NESTABILNÁ ANGINA PECTORIS

    - **SPASMUS** KORONÁRNEJ TEPNY
    - PODIEL ATEROSKLEROTICKEJ STENÓZY+KALCIFIKÁCIE
    - DYNAMIKA **KARDIOMARKEROV** NÍZKÁ

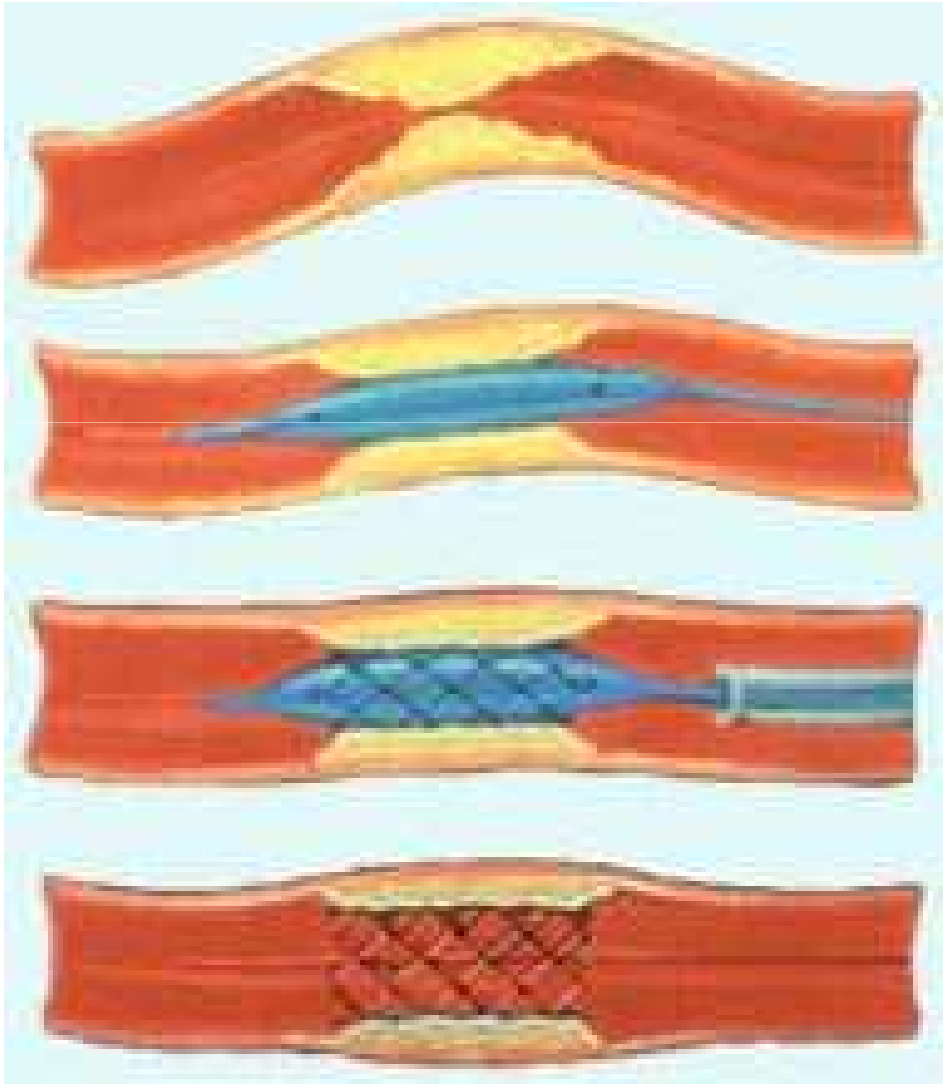
ZÁKLADNÉ TERAPEUTICKÉ POSTUPY U AKS

- TROMBOLÝZA – indikácia ?
- CABG

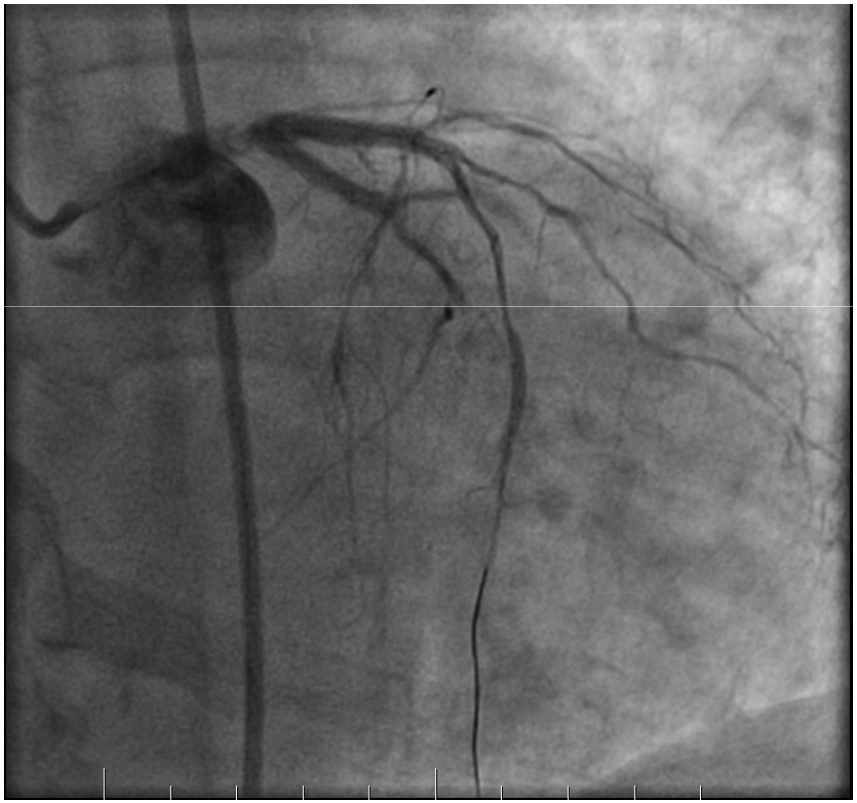
- **dPCI – direct percutaneous coronary intervention –** rozvoj modernej antiagregácie

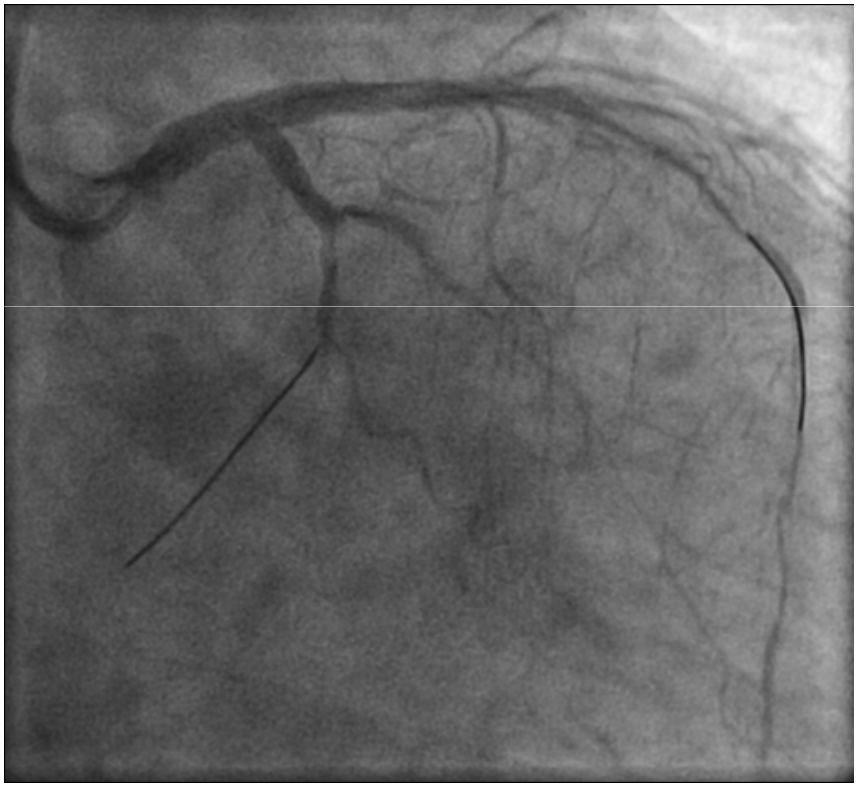
- **Základom úspešnej liečby AKS je kvalitná antiagregačná liečba**

DIREKTNÁ PERKUTÁNNA KORONÁRNA INTERVENCIA



dPCI na kmeni ACS





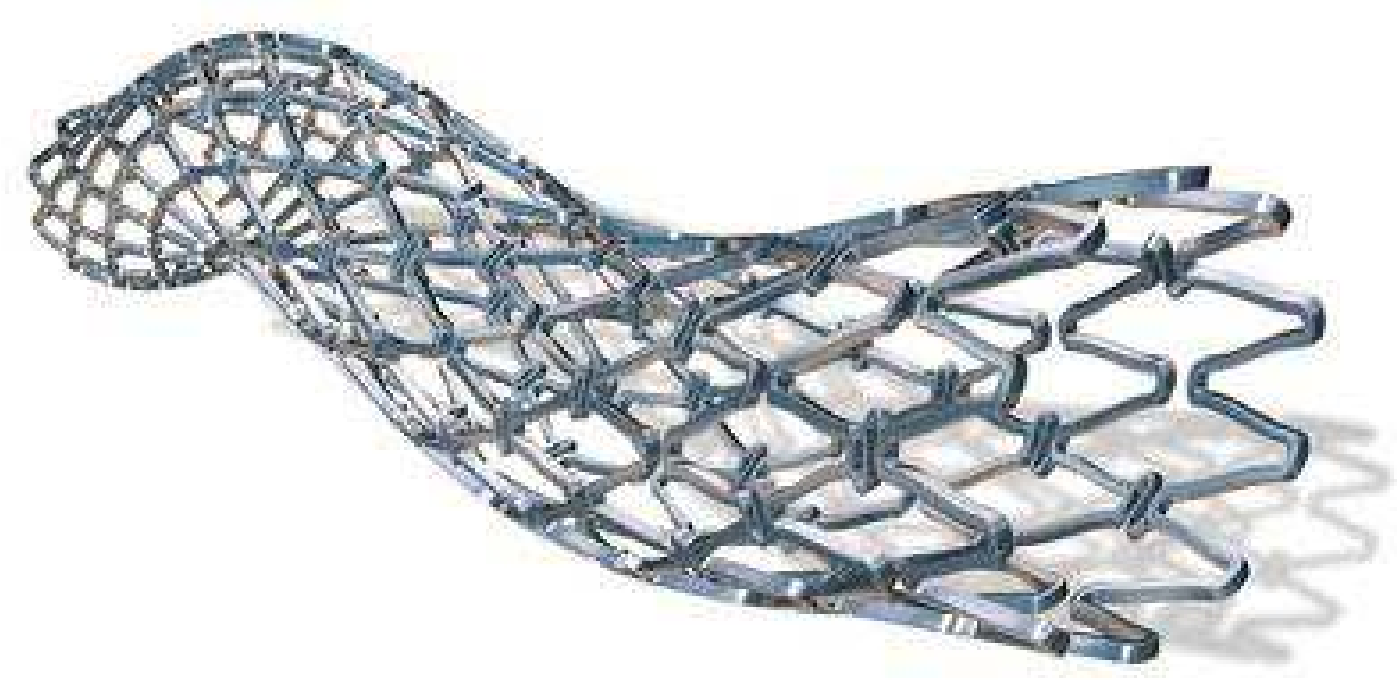
dPCI DETERMINUJE FARMAKOTERAPEUTICKÝ POSTUP

- **<u>TYP ANTIAGREGÁCIE</u>**
  - Dual therapy
  - Triple therapy ? – u komplikácií AKS

- **<u>DĹŽKU ANTIAGREGÁCIE</u>**
  - 3-12 MESIACOV
  - Trvale ?

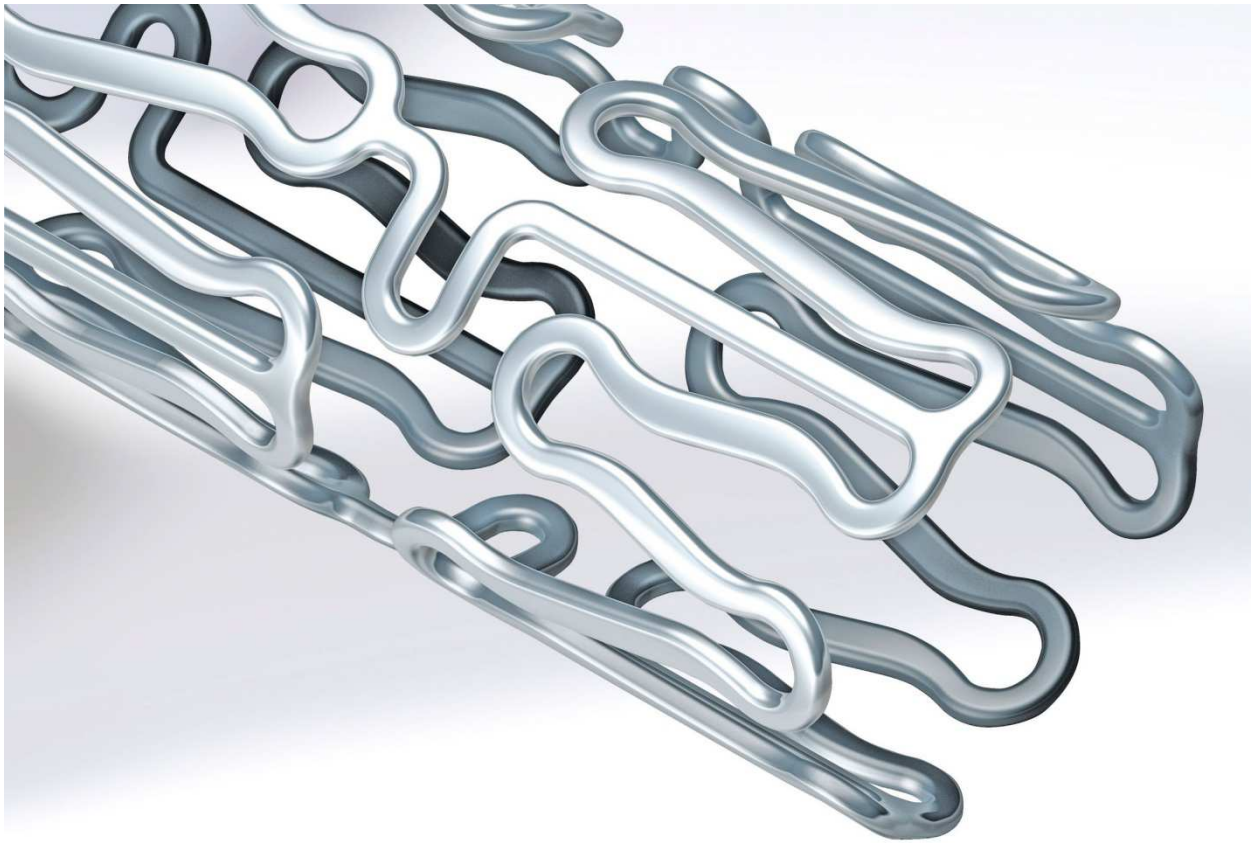
dPCI DETERMINUJE FARMAKOTERAPEUTICKÝ POSTUP (1)

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



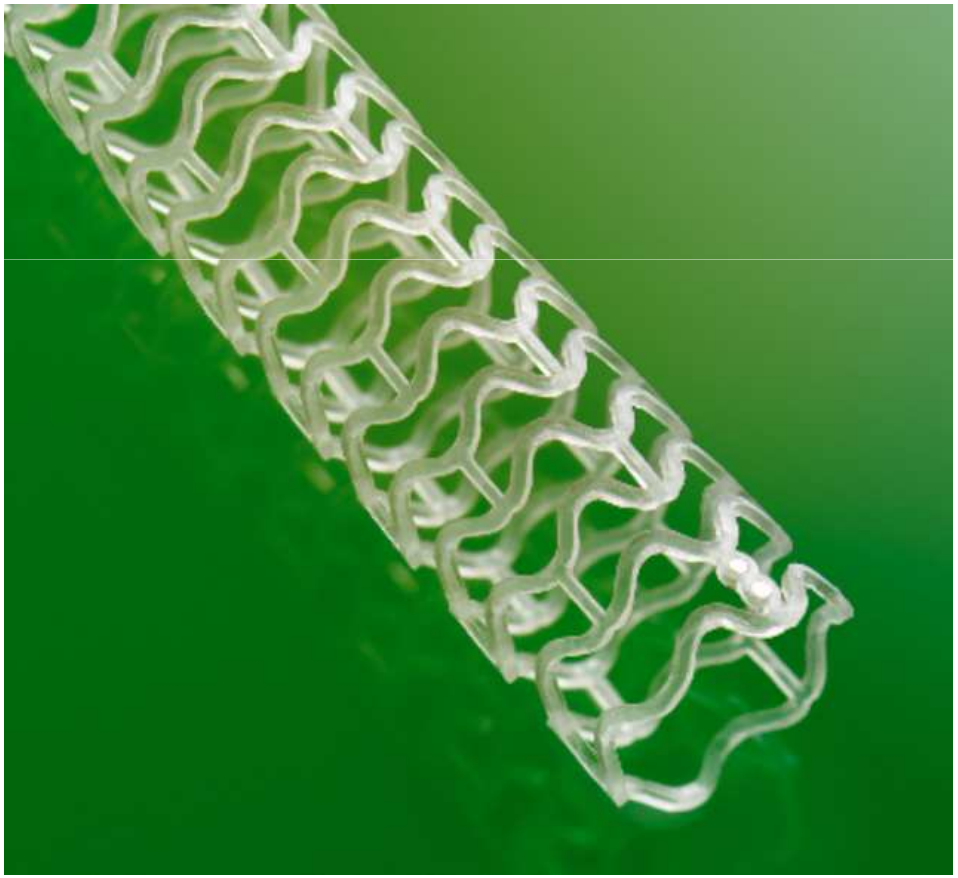
dPCI DETERMINUJE FARMAKOTERAPEUTICKÝ POSTUP (2)

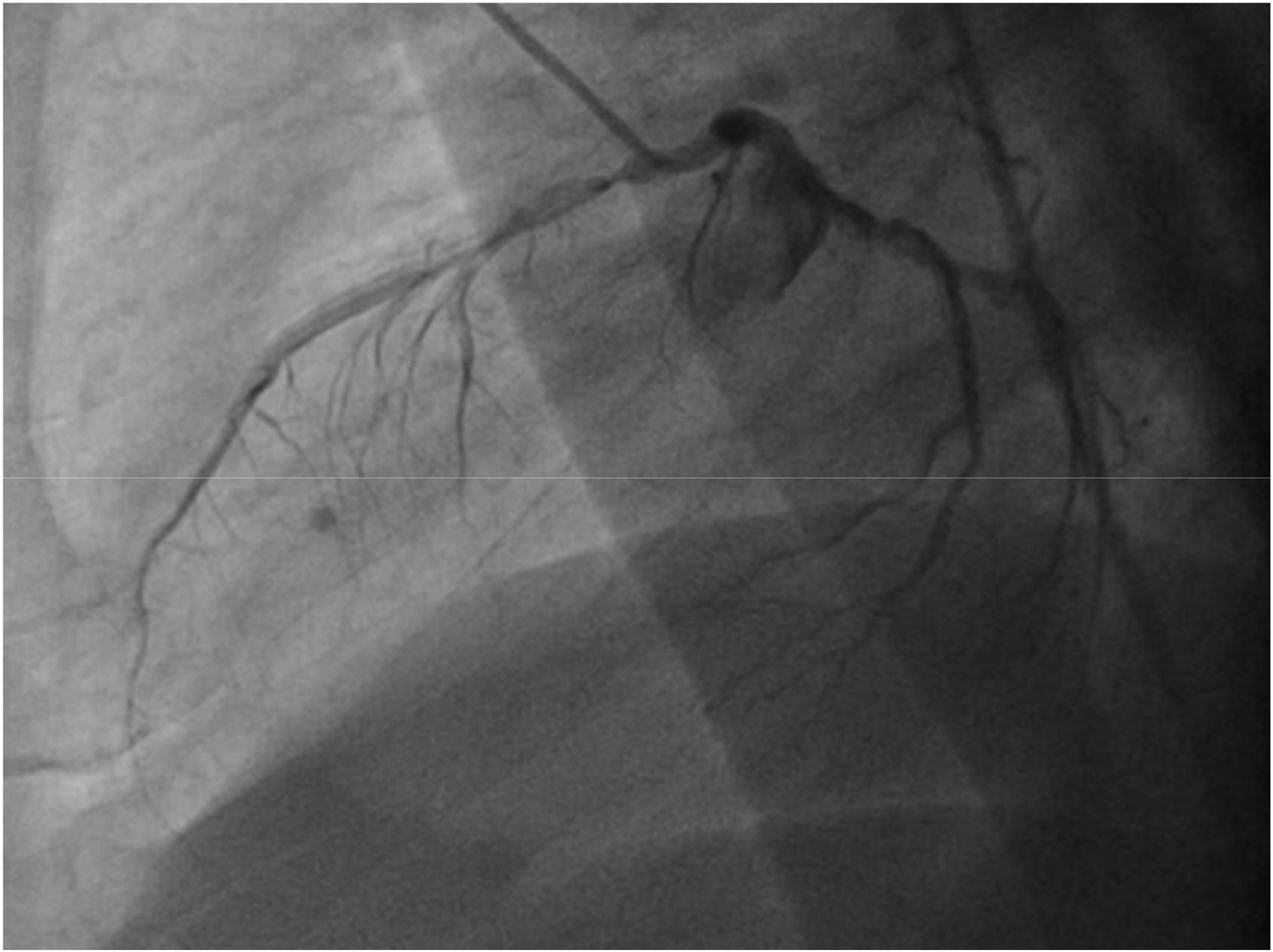
- **DRUG-ELUTING STENT (DES)**

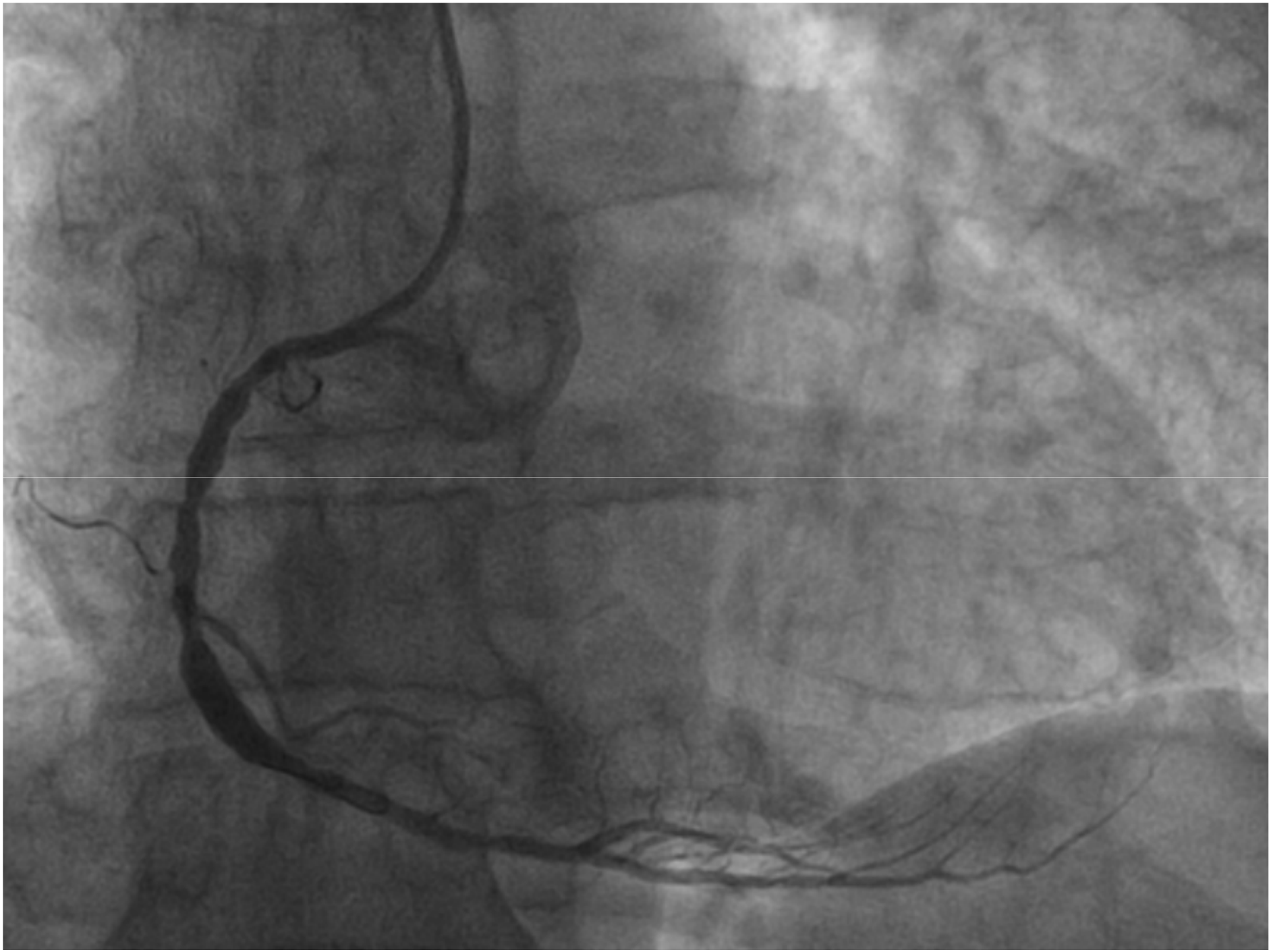


dPCI DETERMINUJE FARMAKOTERAPEUTICKÝ POSTUP (3)

- **KORONÁRNY SCAFFOLD**







- **ZALIEČENIE V AKÚTNEJ FÁZI (1)**

  - ANTIKOAGULANCIA (heparin ...)
  - ANODYNA (fentanyl, morfin)
  - β-BLOKÁTORY (metoprolol ...)

  - ANTIEMETIKA
  - ANXIOLYTIKA

- **ZALÉČENIE V AKUTNEJ FÁZI (2)**

  - **HEPARIN** V DÁVKE 70 – 100 J/KG IV BOLUS
  - SUBSTITÚCIA **ANTITROMBINU III**
  - ZÁSADNE I.V.

  - **alebo LMWH** i.v. - enoxaparin

  - **AKCELERÁCIA** PROTEOLYTICKÝCH REAKCIÍ ANTITROMBINU III

ZÁKLADNÉ SKUPINY FARMÁK POUŽÍVANÝCH K LIEČBE AKS A ICHS

- Antiagreganciá

- β-blokátory
- Inhibítory ACE (sartany)

- Hypolipidemiká

Antiagreganciá (1)

- Kyselina acetylsalicylová
  - CARDEGIC 500 mg i.v.
  - Aspirin 100 mg p.o.

- Inhibitory receptoru P_2Y_{12} pre ADP
  - Klopidogrel
  - Prasugrel
  - Ticagrelor

Kyselina acetylsalicylová (1)

- Farmakodynamická aktivita závislá na dávke
  - 25 – 375 mg - antiagregans
  - 500 mg - antipyretikum
  - 1000 mg – antiflogistikum

- V súčastnosti je ASA nezastupiteľné antiagregans, v iných FD účinkoch **obsolentná**

Kyselina acetylsalicylová (2)

- Inhibícia agregácie trombocytov
  - Ireverzibilná acylácia L-serínu v molekule
  - COX-1,COX-2 a COX-3

- Zložka duálnej antiagregačnej terapie
  - Zníženie rizika rezistencie

Kyselina acetylsalicylová (3)

- Loading dose 500 mg i.v.
- Udržovacia dávka 100 mg p.o.
  - Sekundárna prevencia po AKS

- Primárne preventívne štúdie nepreukázali benefit, len zvýšené riziko toxicity

- Nežiadúce účinky ?

Inhibitory receptoru P_2Y_{12} pre ADP

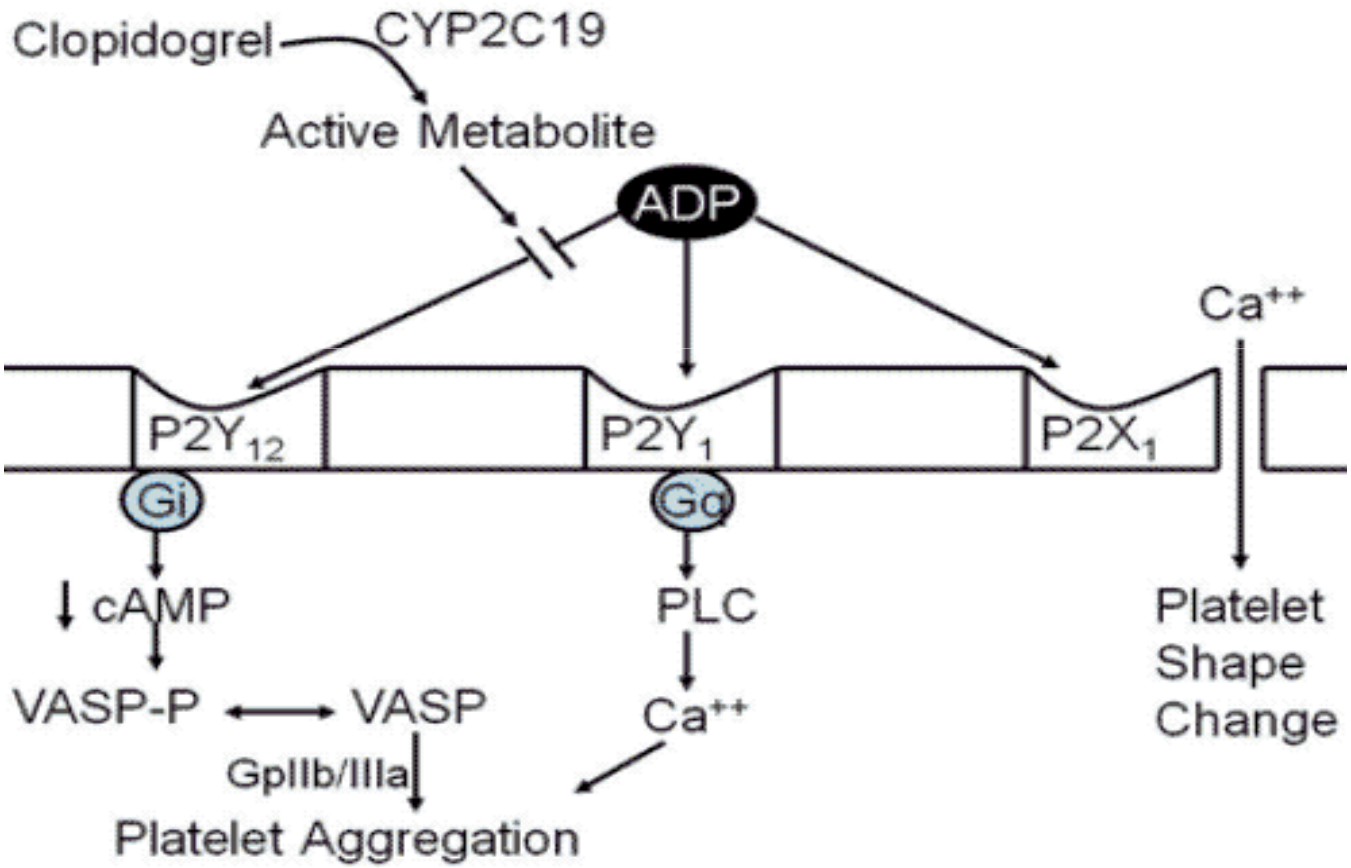
- Klopidogrel
- Prasugrel

- Ticagrelor

Inhibitory receptoru P_2Y_{12} pre ADP

- Kombinácia s ASA po indikovanú dobú duálnej antiagregačnej liečby
- Metóda testovania agregácie a vylúčenie rizika rezistencie na DAPT
  - **MULTIPLATE**
- **REZISTENCIA NA DAPT** PODMIENENÁ
  - FARMAKOLOGICKY
  - GENETICKOU PREDISPOZÍCIOU

Klopidogrel - farmakodynamika



Klopidogrel a AKS

- Loading dávka 600 mg
- Udržovacia 75 mg

THE LANCET

Articles

A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)

*CAPRIE Steering Committee**

Summary

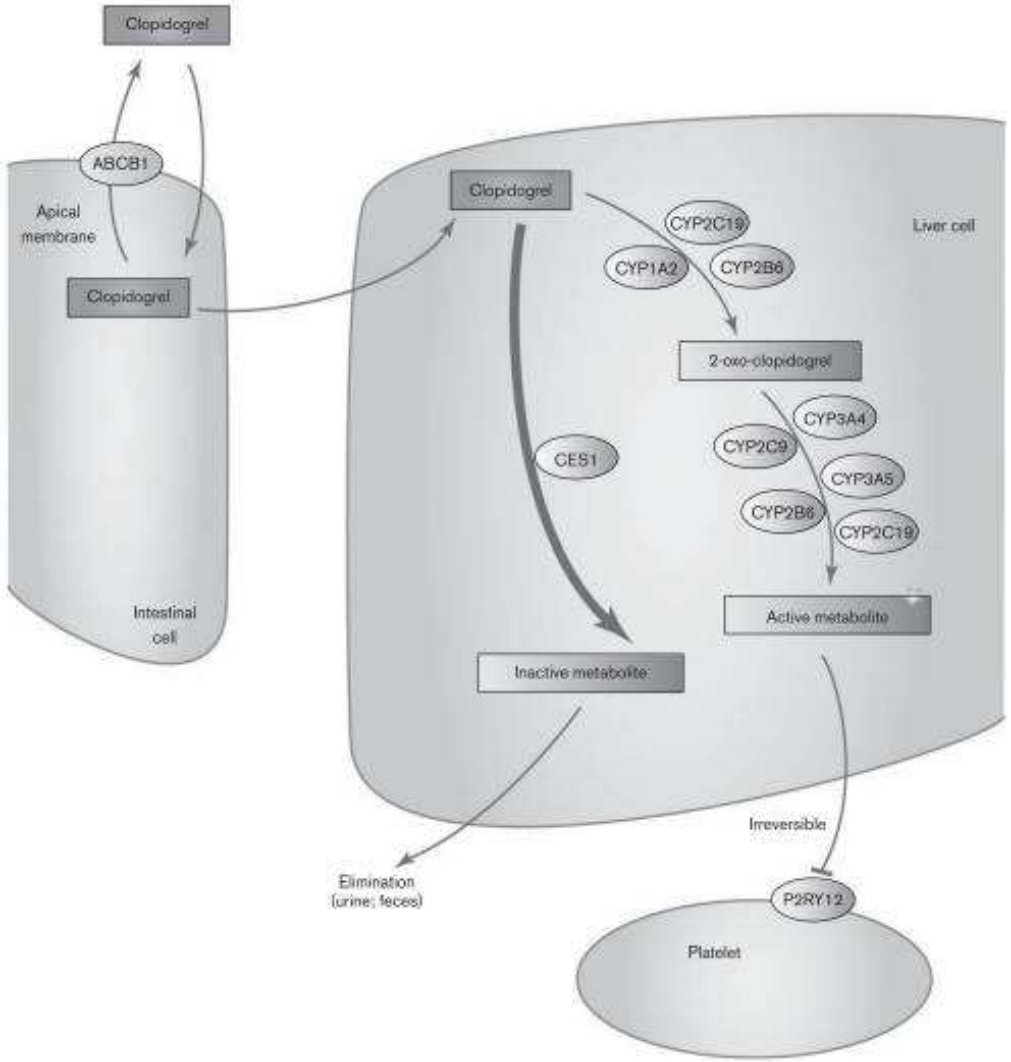
Background Many clinical trials have evaluated the benefit of long-term use of antiplatelet drugs in reducing the risk of clinical thrombotic events. Aspirin and ticlopidine have been shown to be effective, but both have potentially serious adverse effects. Clopidogrel, a new thienopyridine derivative similar to ticlopidine, is an inhibitor of platelet aggregation induced by adenosine diphosphate.

Methods CAPRIE was a randomised, blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in

Introduction

There have been several randomised trials of antiplatelet drugs in patients with disorders in which platelet activation is involved.[1] Their purpose was to determine the extent of reduction in various subsequent risks; in particular, risks of ischaemic stroke, myocardial infarction, and death from vascular disease (vascular death). Patients at increased risk of such outcomes included those with atherothrombotic disease such as transient ischaemic attacks or mild stroke, moderate or severe stroke, unstable angina, acute and remote myocardial infarction, and atherosclerotic peripheral arterial disease.[2,3]

KLOPIDOGREL - farmakokinetika



Sangkuhl K., Klein T.e., Altman E.B.: Clopidogrel pathway; *Pharmacogenet Genomics.* 2010: 20: 463 - 465

- **CLOPIDOGREL**

  - NEVYHNUTNÁ **AKTIVÁCIA** Z PROLIEČIVA POMOCOU ***CYP P450 2C19***

  - ***OVPLYVNENIE RÝCHLOSTI KONVERZIE KLOPIDOGRELU URČUJE RIZIKO ZLYHANIA DUÁLNEJ ANTIAGREGÁCIE***

LIEKOVO PODMIENENÉ ZLYHANIE DAPT LIEČBY

- cytochromoxidáza p450 *2C19*
  - Induktor
    - karbamazepín
  - Inhibitor y
    - Fluoxetin
    - Fluoxamin
    - Omeprazol
    - Paroxetin
    - topiramát

Zieglmeier M., Hein T. 2006

- **<u>CLOPIDOGREL – NEŽADÚCE ÚČINKY</u>**
  - EPISTAXIA
  - MOZGOVÉ KRVÁCANIE
  - TROMBOCYTOPENIA

Inhibitory receptoru P_2Y_{12} pre ADP

- **Prasugrel**
  - Ireverzibilný inhibitor receptoru pre ADP
  - Loading 60 mg
  - Udržovacia dávka 10 mg (redukcia ???)
  - **Prodrug** s nutnosťou aktivácie (p450 *2C19*)
  - **<u>Zatiaľ bez klinicky významných interakcií</u>**

Inhibitory receptoru P_2Y_{12} pre ADP

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

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*

Prasugrel vs clopidogrel - účinnosť

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

Prasugrel vs clopidogrel - bezpečnosť

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

Inhibitory receptoru P_2Y_{12} pre ADP

- **Ticagrelor**
  - Priamo FD účinný bez nutnosti aktivácie
  - Natívna molekula a metabolit sú ekvipotentné
  - Reverzibilná inhibícia receptoru pre ADP

  - Nevýhoda dávkovania 2x denne

  - Loading dávka 180 mg
  - Udržovacia 2x 90 mg

Inhibitory receptoru P_2Y_{12} pre ADP

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*

Ticagrelor vs clopidogrel - účinnosť

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

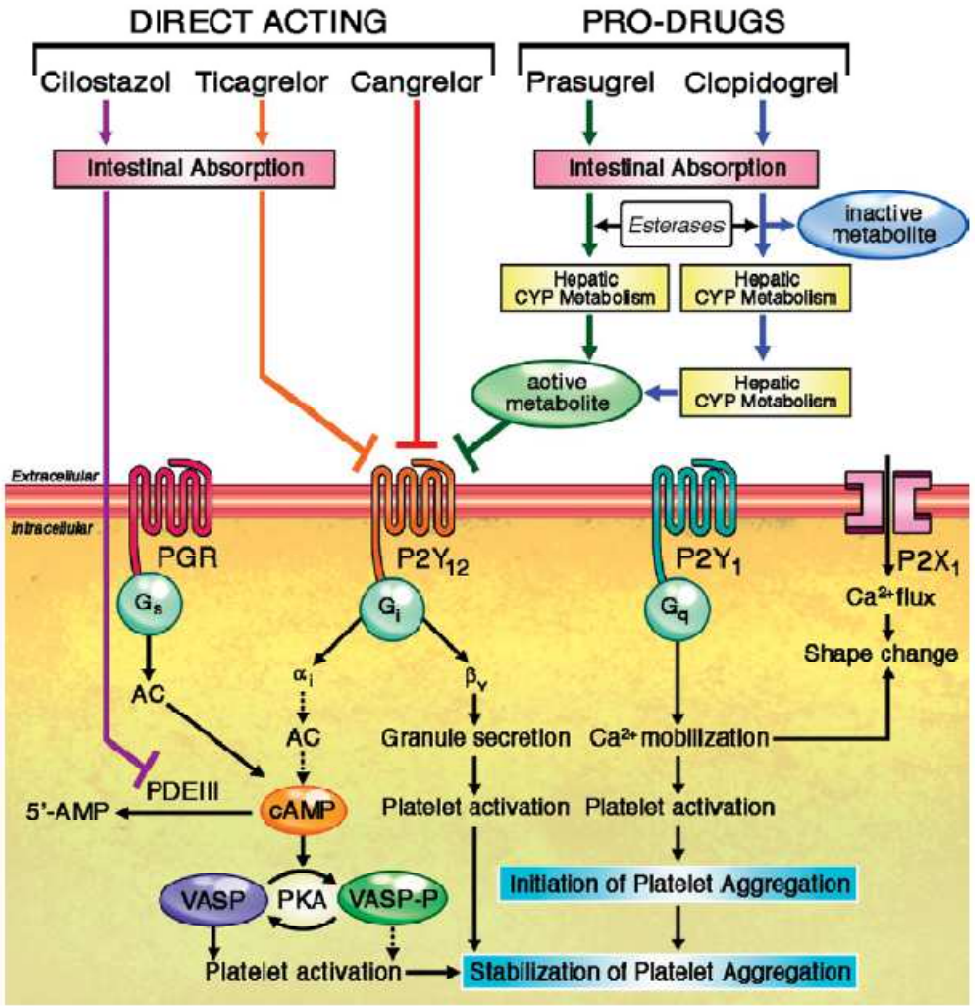
End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, 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
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
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

Ticagrelor vs clopidogrel - bezpečnosť

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

NOVÉ ANTIAGREGANCIÁ U AKS



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

Hypolipidemická terapie AKS

- **Inhibítory HMG-CoA-reduktázy (statiny)**
  - Fluvastatin
  - Simvastatin (4S; HPS)
  - Atorvastatin (MIRACL, ALLIANCE – agresivni dávka)
  - Rosuvastatin (JUPITER)
- Fibráty – **fenofibrát, klofibrát**
- Inhibítory NPC1L1-proteinu - **Ezetimib**
- Inhibítory proteinkinázy SK-9 - **Evolocumab**

STABILIZÁCIA HEMODYNAMIKY U AKS

- β-BLOKÁTORY
  - Metoprolol
  - Bisoprolol
  - Nebivolol
  - Carvedilol
- Cieľom je udržať TF 65-75 /min

STABILIZÁCIA HEMODYNAMIKY U AKS – remodelace myokardu

- INHIBÍTORY ACE
  - Perindopril
  - Ramipril
  - Trandolapril

- SARTANY
  - Telmisartan
  - Losartan
  - irbesartan

- Ďakujem za pozornosť

- milan.juhas@fnusa.cz