Антиагрегантни режими при пациентите третирани без реваскуларизация в условията на ОКС

Проф. д-р Снежана Тишева,дмн
МУ-Плевен

Клиничен случай

Клиничен случай

Петко е 68 –годишен хипертоник, диабетик и пушач.

Към датата на прегледа приема само индапамид CP 25 mg еднократно

Пристига в СПО с оплаквания от прекордиална болка, продължила 20 мин. и ЕКГ със следните промени: 2mm ST депресия във II, III, aVF, V5 и V6, АН 150/90 мм Hg

Болката намаляла и ЕКГ промените се редуцирали след прием на ASA, кислород и nitroglycerin сублингвално

Клиничен случай

Troponin T е позитивен 0.85

В кардиардиологичната клиника са му назначени ASA перорално, clopidogrel, b-блокер и iv heparin; статин и АСЕИ.

Препоръчана му е коронарна интевенция, но пациентът отказва.

Медикаментозно лечение на Петко

Каква да бъде антиагрегантната терапия при този пациент ?

A. ASA 100mg еднократно дневно
B. ASA 100 mg еднократно+ тромбоцитни P2Y12 инхибитори за 1 месец
C. ASA 100 mg еднократно + тромбоцитен инхибитор P2Y12 инхибитор за 12 месеца

Adobe Acrobat - [guidelines-AMI ESC 2008.pdf]

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Table 9 Doses of antiplatelet co-therapies

With primary PCI	
Aspirin	Oral dose of 150–325 mg or i.v. dose of 250–500 mg if oral ingestion is not possible
Clopidogrel	Oral loading dose of at least 300 mg, preferably 600 mg
GPIIb/IIIa inhibitors	Abciximab: i.v. bolus of 0.25 mg/kg bolus followed by 0.125 μg/kg per min infusion (maximum 10 μg/min for 12 h)
With fibrinolytic treatment	
Aspirin	Oral dose of 150–325 mg or i.v. dose of 250 mg if oral ingestion is not possible
Clopidogrel	Loading dose of 300 mg if age ≤75 years; 75 mg if age >75
Without reperfusion therapy	
Aspirin	Oral dose of 150–325 mg
Clopidogrel	Oral dose of 75 mg

antagonists are used). It is recommended to perform the procedure under activated clotting time (ACT) guidance: heparin should be given at a dose able to maintain an ACT of 250–350 s

at 30 days was 1% lower ($P < 0.0047$), occurred more frequently ($P < 0.001$). bolus of 0.75 mg/kg followed by an ir titrated to ACT and usually termi procedure.

Fondaparinux. Fondaparinux, a factor X pared with heparin or placebo in 12 with fibrinolytic agents or PCI, or n the PCI subset, fondaparinux was asso 1% higher incidence of death or recu These findings together with the occu bosis do not lend support to the use anticoagulant in patients undergoing p

Adjunctive devices. Adjunctive devices a distal embolization have been investig studies. Formal meta-analyses of th geneous results with no overall clinic rate of distal embolization angiographi ized study in 1071 patients, aspiration was associated with improved tissu blush grades (MBGs)] and improved su pared with conventional PCI.[59,60] Se *Table 13*.

b. Fibrinolytic treatment

11 sur 38 234,3 x 304,3 mm

Démarrer 16:23

ESC Guidelines for the Management of NSTE-ACS

- Антиисхемично лечение: β-блокери, нитрати и калциеви антагонисти
- Антиагрегантна терапия:
  - Aspirin + clopidogrel за всички пациенти , които нямат противопоказания
  - Anti-GPIIb/IIIa за всички пациенти с умерен или висок риск
- Реваскуларизация за всички пациенти с умерен или висок риск

Bassand JP, *et al.* The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *European Heart Journal* 2007; 28:1598-1660

Guidelines for the management of ACS STEMI

- Aspirin за всички
- А P2Y12 инхибитори за 12 месеца освен тези с потивопоказания и риск за кървене
- Ticagrelor също, а prasugrel само при първична PCI при липса на ефект от клопидогрел
- А блокери на протонната помпа в комбинация с DAPT се препоръчват при риск от кървене или предшестващ епизод на ГИ кървене

Антитромботично лечение без реперфузия

Антитромбоцитна комбинирано лечение:

- Аспирин орално (разтворим или за дъвчене , но не ентеросолвентен)- IA
- Или IV доза аспирин ако орално приемане не е осъществимо)
- перорална доза клопидогрел-IB

Антитромбоцитни / антикоагуланти препоръки за лечение в насоките STEMI

Дългосрочна антитромбоцитна лечение след STEMI

• Аспирин завинаги (75 до 100 мг дневно) при всички пациенти без

алергия- IA

• клопидогрел (75 мг дневно) в продължение на 12 месеца при всички пациенти независимо от остро лечение- IIa C

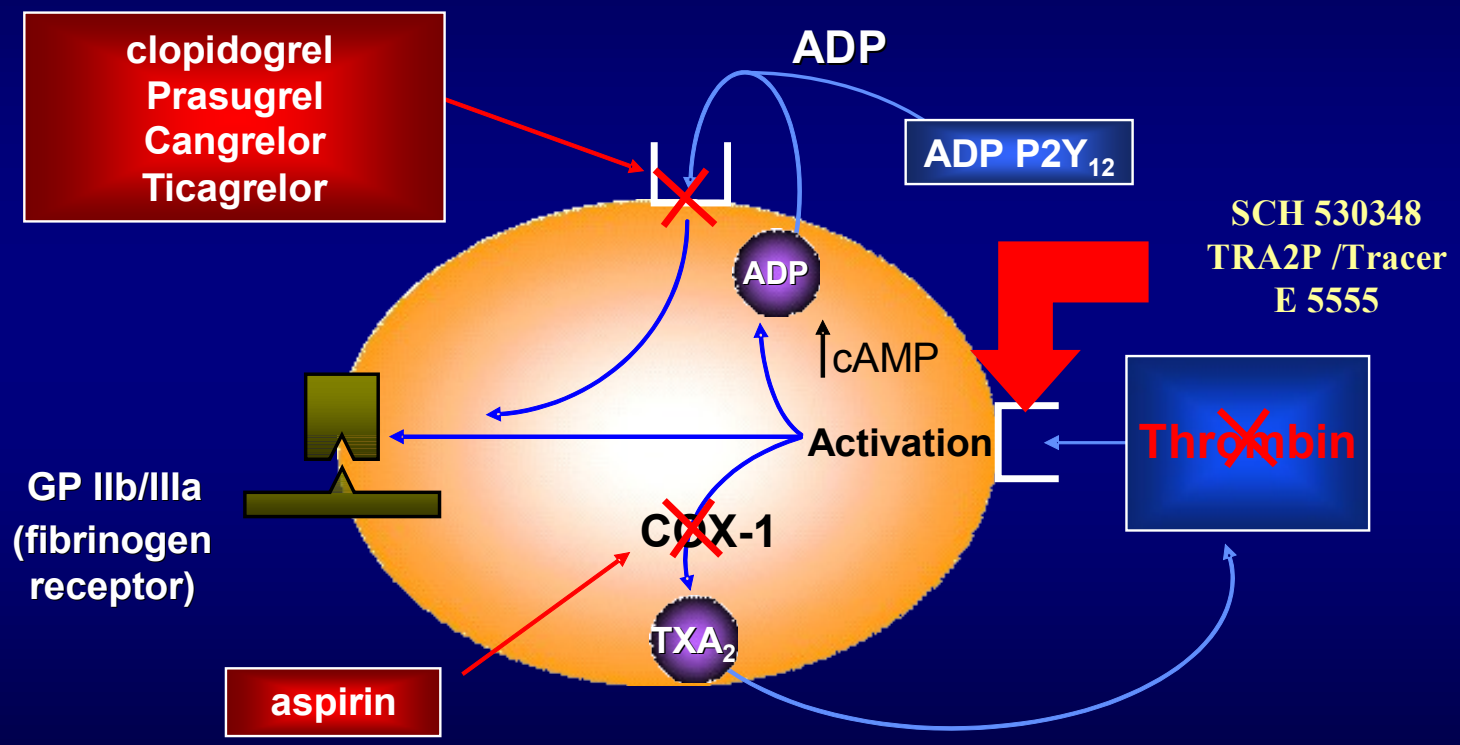
• клопидогрел (75 мг дневно) при всички пациенти с

Антитромбоцитни / антикоагуланти препоръки за лечение в насоките STEMI

- Всички пациенти със STEMI, не подложени на стентиране (медикаментозна терапия самостоятелно или PTCA без стентиране), лечението с клопидогрел трябва да продължи поне 14 дни. ***(I (B)*** **Нова препоръка)**

• Дългосрочно поддържащо лечение (напр. 1 година) с клопидогрел (75 мг на ден орално) е разумно при пациенти със STEMI независимо от дали те преминават реперфузия с фибринолитична терапия или не получават реперфузионна терапия ***(IIa (C)***

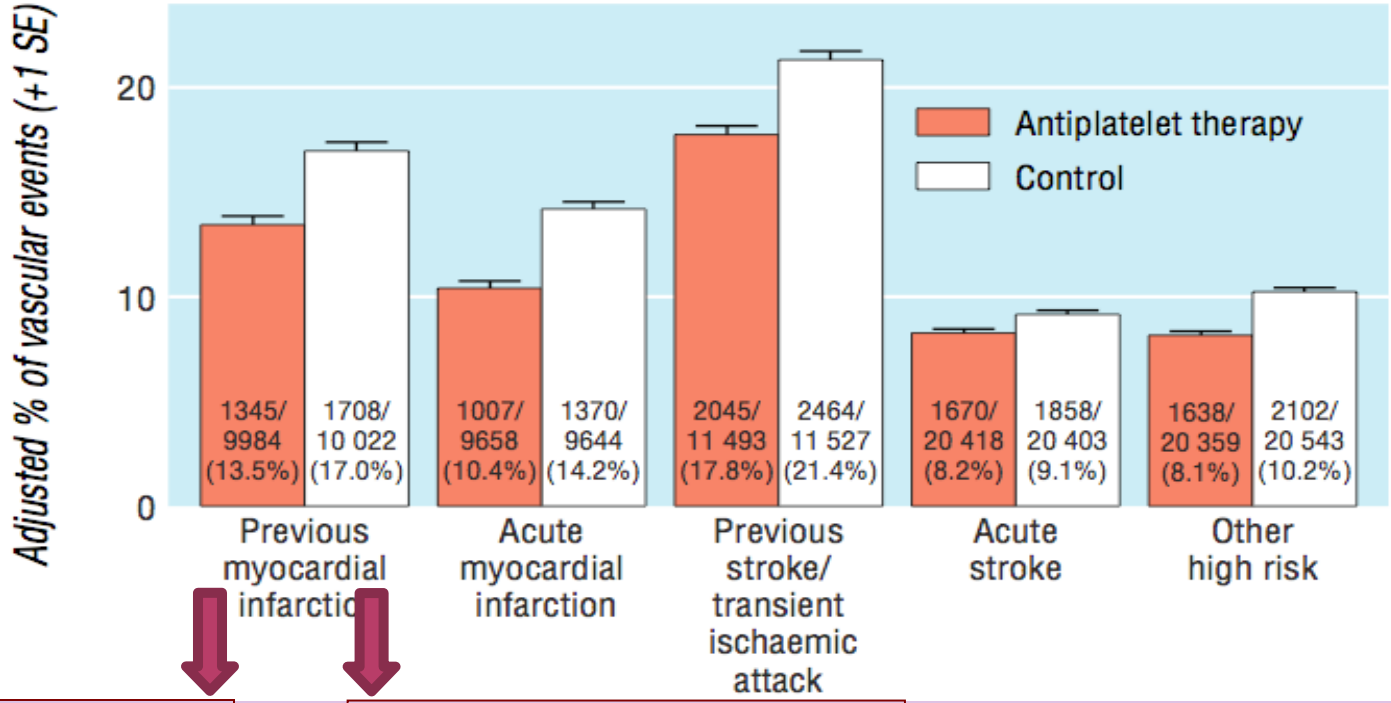
New Antiplatelets agents



adapted from Schafer AI. *Am J Med*. 1996;101:199-209.

Успех на антитромбозната терапия

Benefit per 1000 patients (SE):	36 (5)	38 (5)	36 (6)	9 (3)	22 (3)
Mean months of treatment:	27	1	29	0.7	22
P value:	<0.0001	<0.0001	<0.0001	0.0009	<0.0001



ARR 3.5 % (13.5% vs 17.0%)
NNT 29

ARR 3.8 (10.4% vs 14.2%)
NNT 26

BMJ 2002; 324: 71-86.

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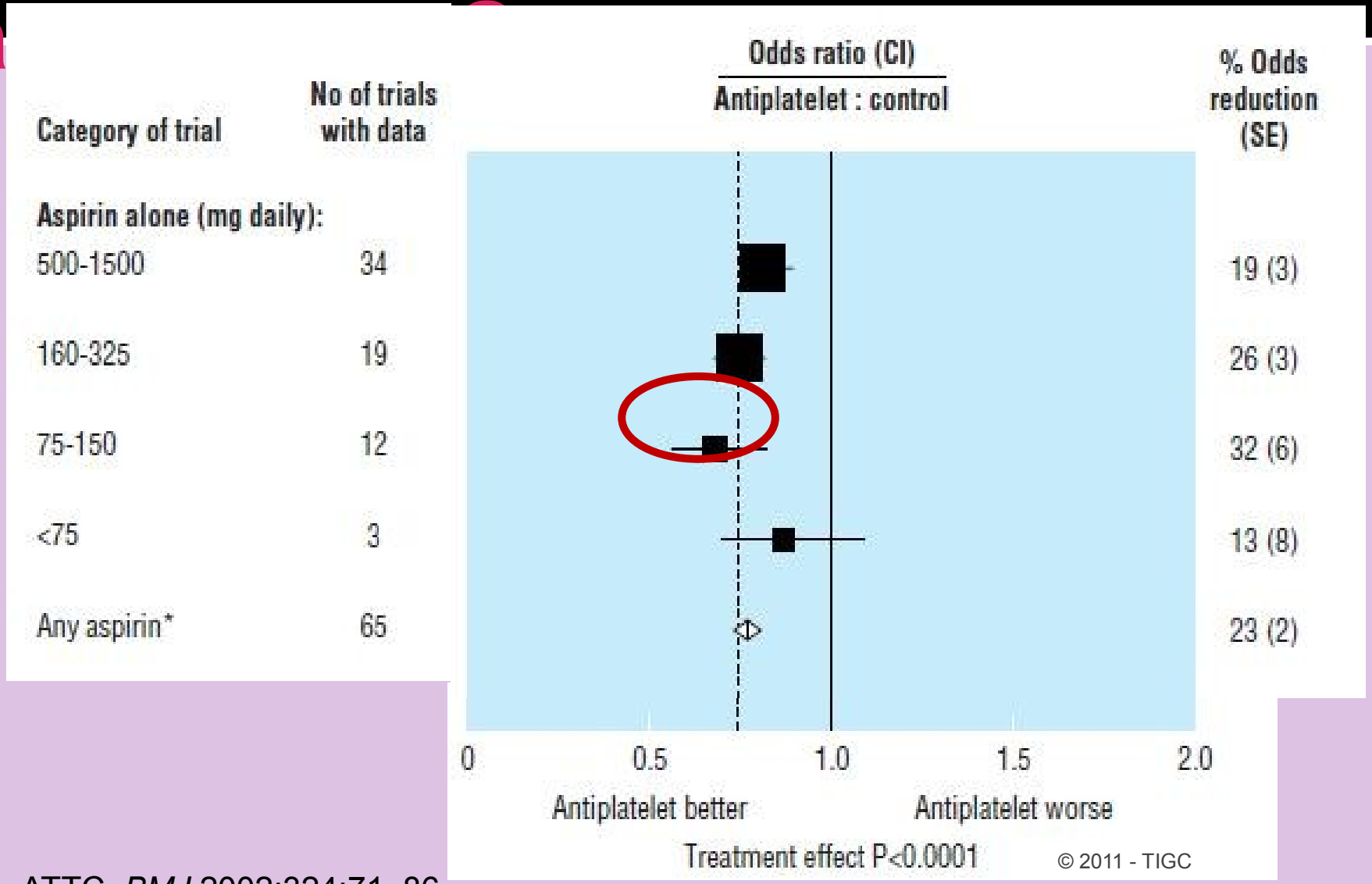
Какъв е успехът за а



ATTC, *BMJ* 2002;324:71–86

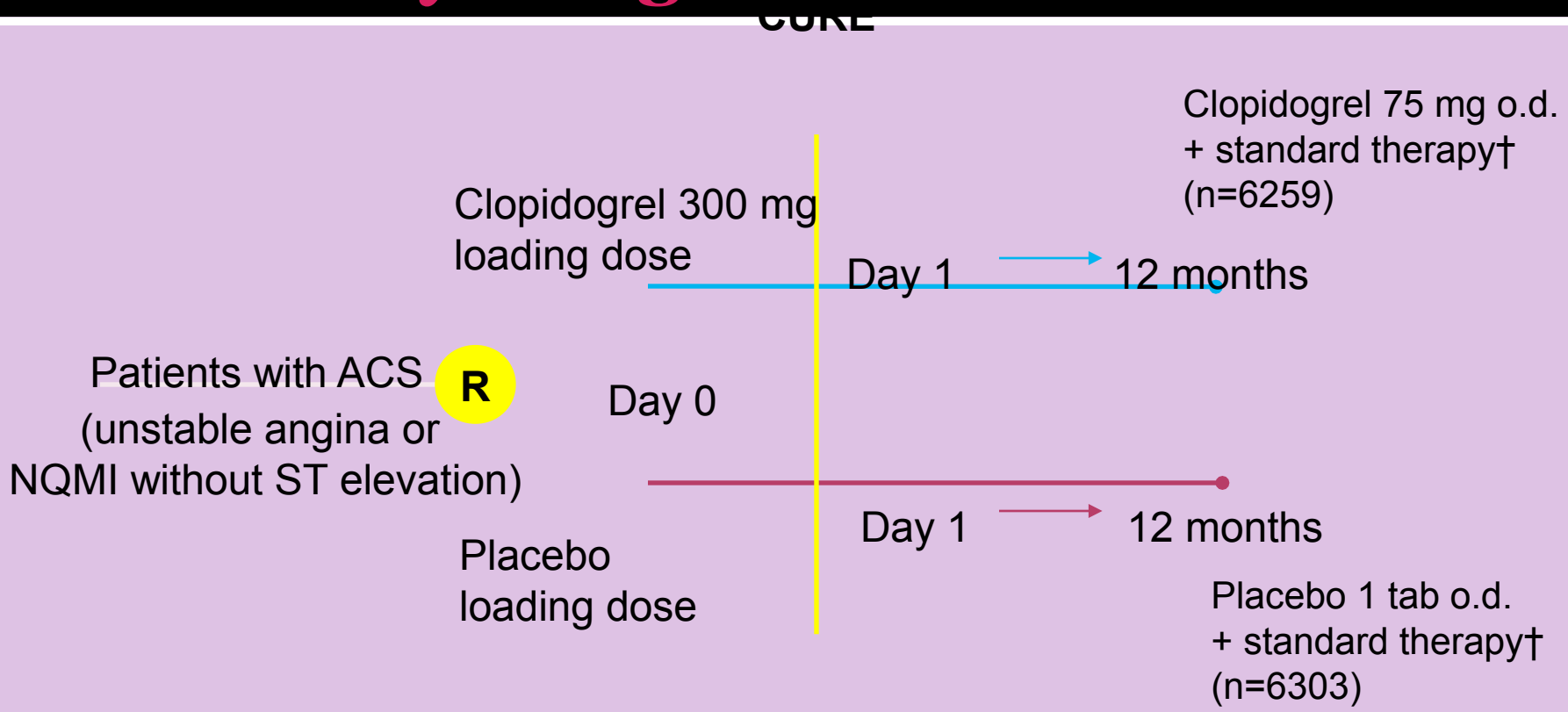
Оптималните дози Aspirin при ССЗ

вторична профилактика 75 mg – 325 mg
първична

ОКС 162.5 mg – 325 mg

Hennekens CH, Dyken M, Fuster V:Circ. 1997

ASA + Clopidogrel CURE Study design



R=Randomization, occurred within 24 hours of symptom onset

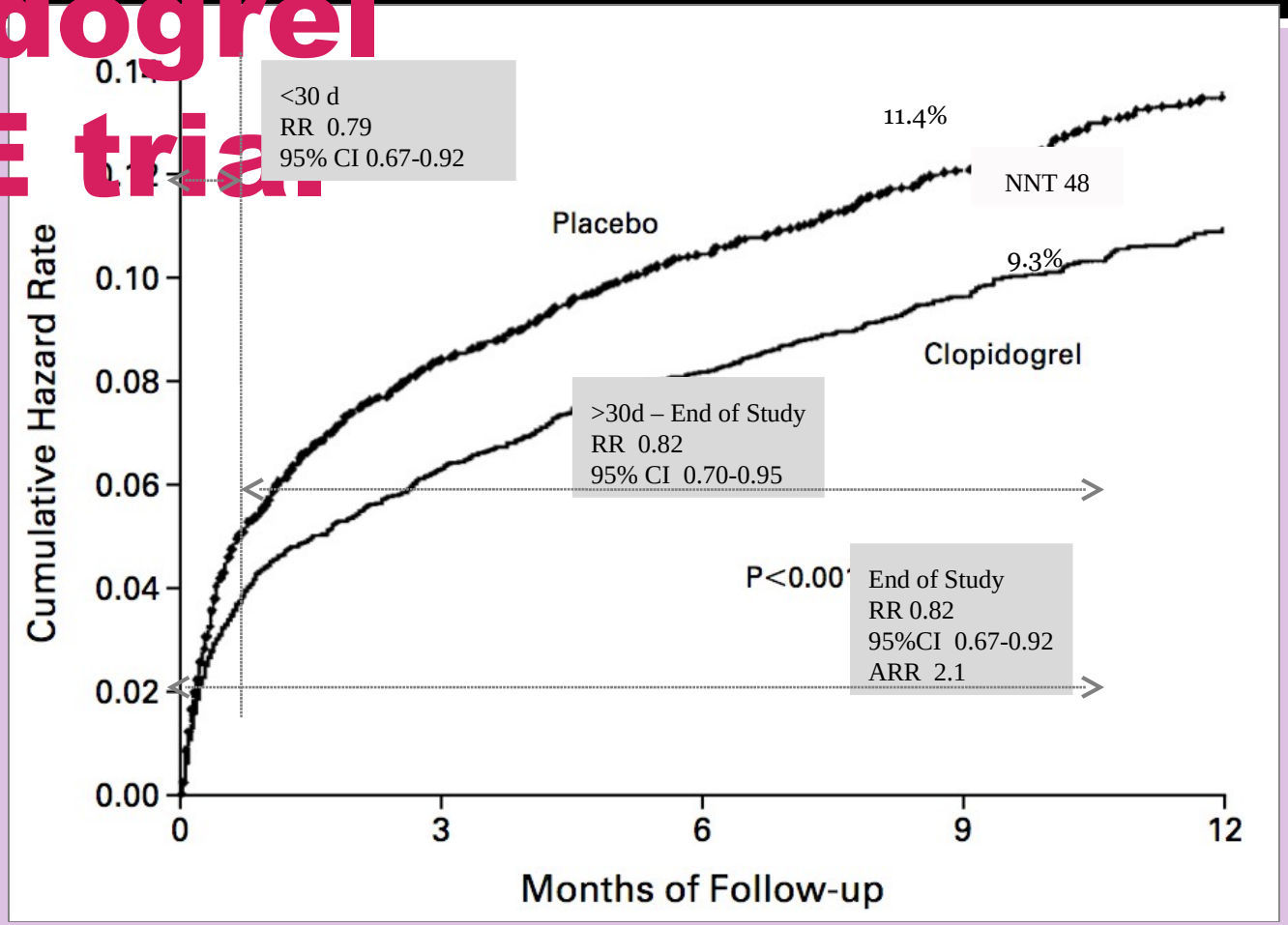
†Standard therapy always included ASA, and could also include heparin, LMWH, GP IIb/IIIa inhibitors post-randomization, beta-blockers,

ACE-inhibitors, lipid-lowering agents, and/or other therapies or interventions (e.g. PTCA, CABG) at physician's discretion.

LMWH, low-molecular-weight heparin; GP, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft

CURE Study Investigators. Eur Heart J 2000; 21:2033–2041. The CURE Investigators. N Eng J Med

Данни за ASA and clopidogrel CURE trial



NEJM 2001; 345: 494-502.

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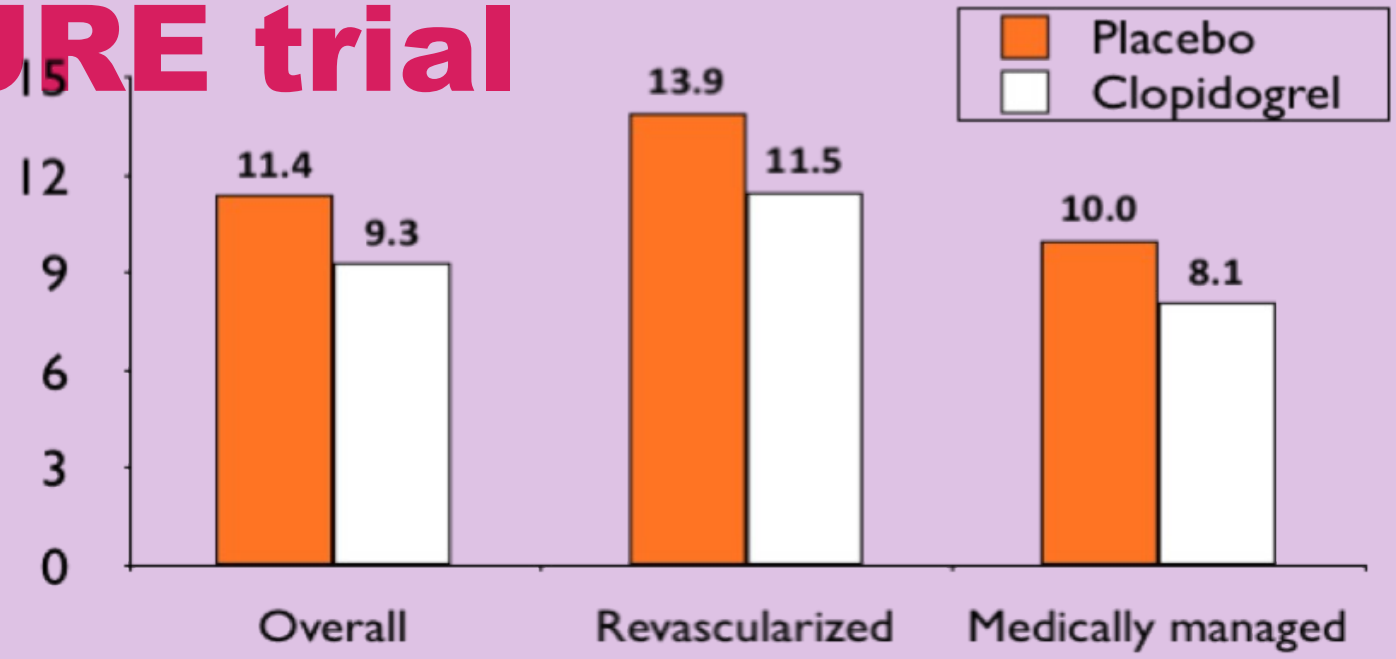
Данни за ASA and clopidogrel CURE trial

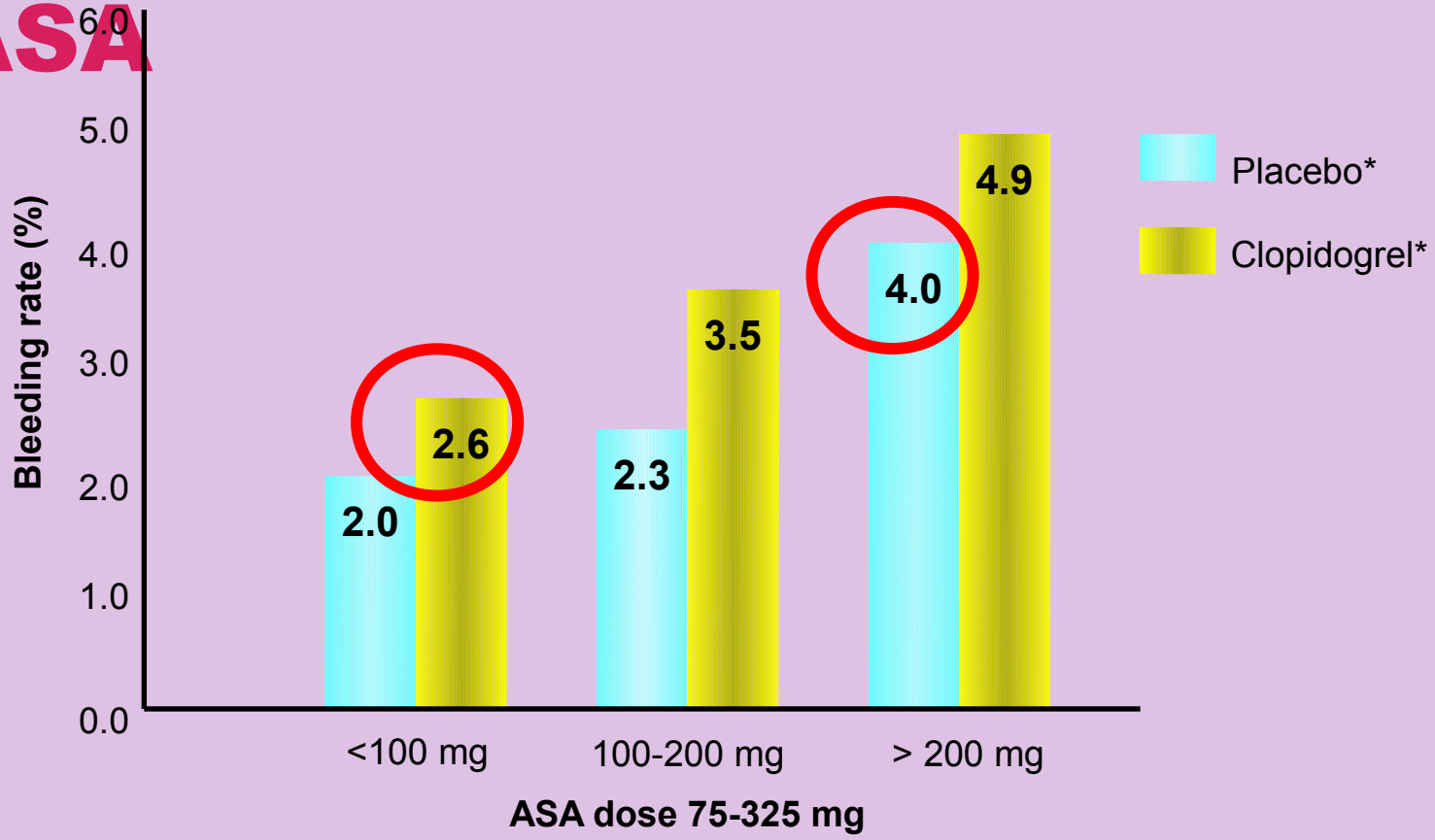


NEJM 2001; 345: 494-502.

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Société canadienne de cardiologie
Communauté. Connaissances. Leadership.

CURE
Голямо кървене при дозите на ASA



*In addition to standard therapy (including ASA).

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CURE Trial Investigators. *N Engl J Med* 2001;345(7):494-502

Clopidogrel + Aspirin

- Clopidogrel допринася за ефекта на aspirin
- CURE, проучването при остър МИ, показва, че clopidogrel увеличава приноса на aspirin за редукция на ССсъбития, но увеличава голямото кървене
- COMMIT/CCS-2, рандомизирано проучване при ОМИ в Китай доказващо, че clopidogrel към aspirin намалява ССС и общата смъртност , но не увеличава кървенето.

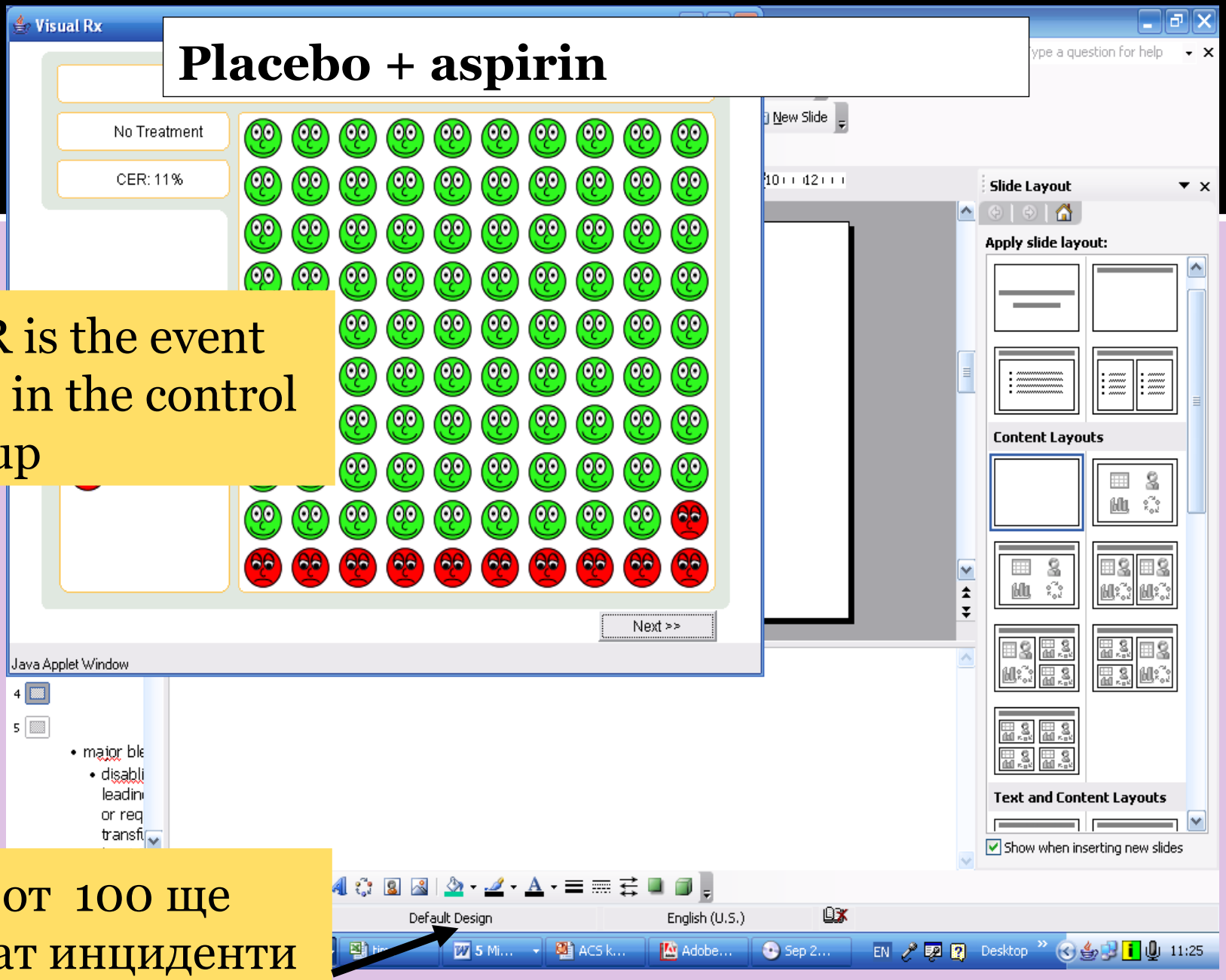
Комбинирана терапия при ОКС

NICE. MI: secondary prevention. CG48. May 2007
NICE. Unstable angina and STEMI. CG94. March 2010

Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation acute coronary syndrome. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended unless there are other indications to continue dual antiplatelet therapy.

After an ST-segment-elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy.

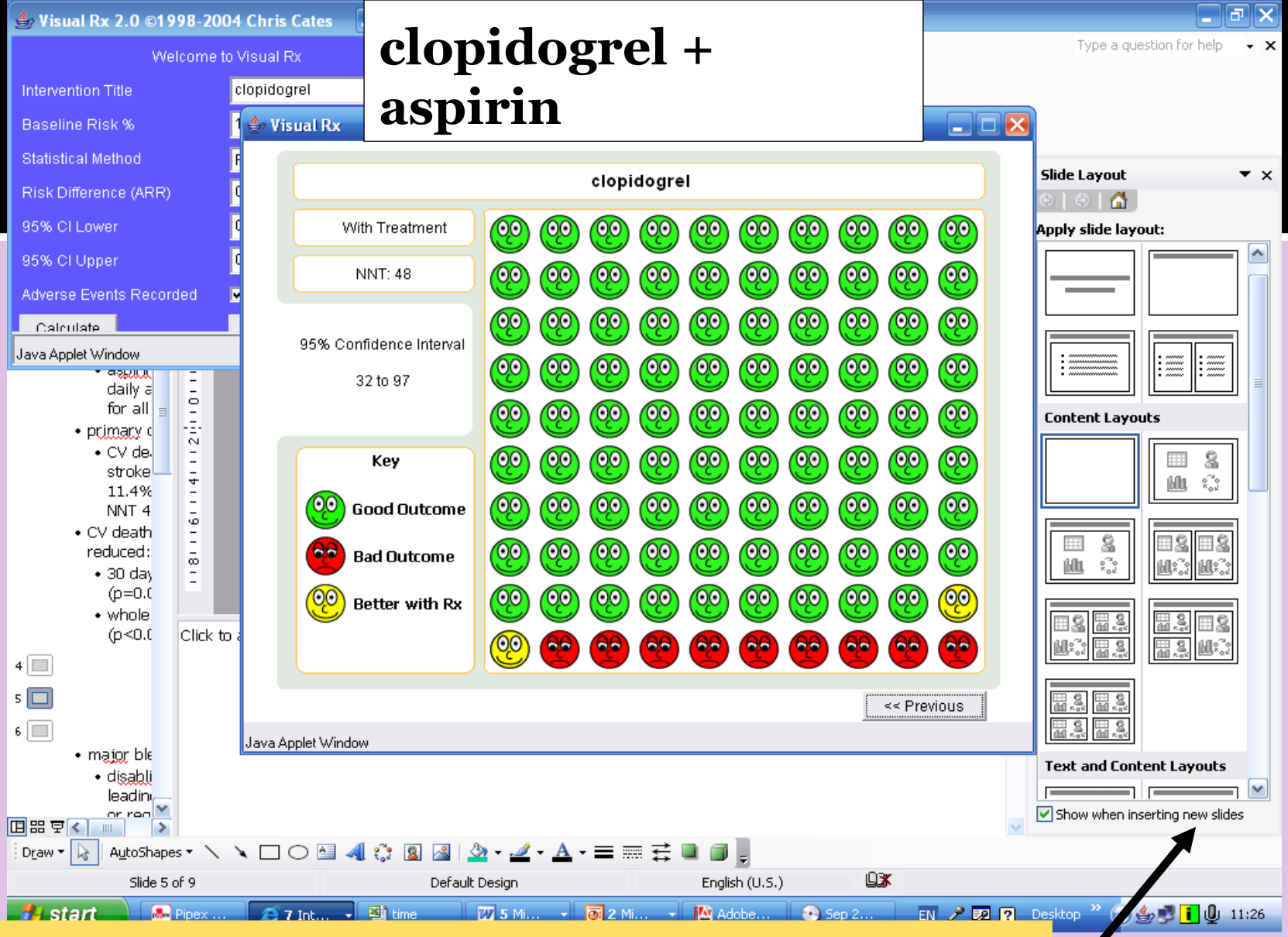
Placebo + aspirin



CER is the event rate in the control group

11 от 100 ще имат инциденти

clopidogrel + aspirin

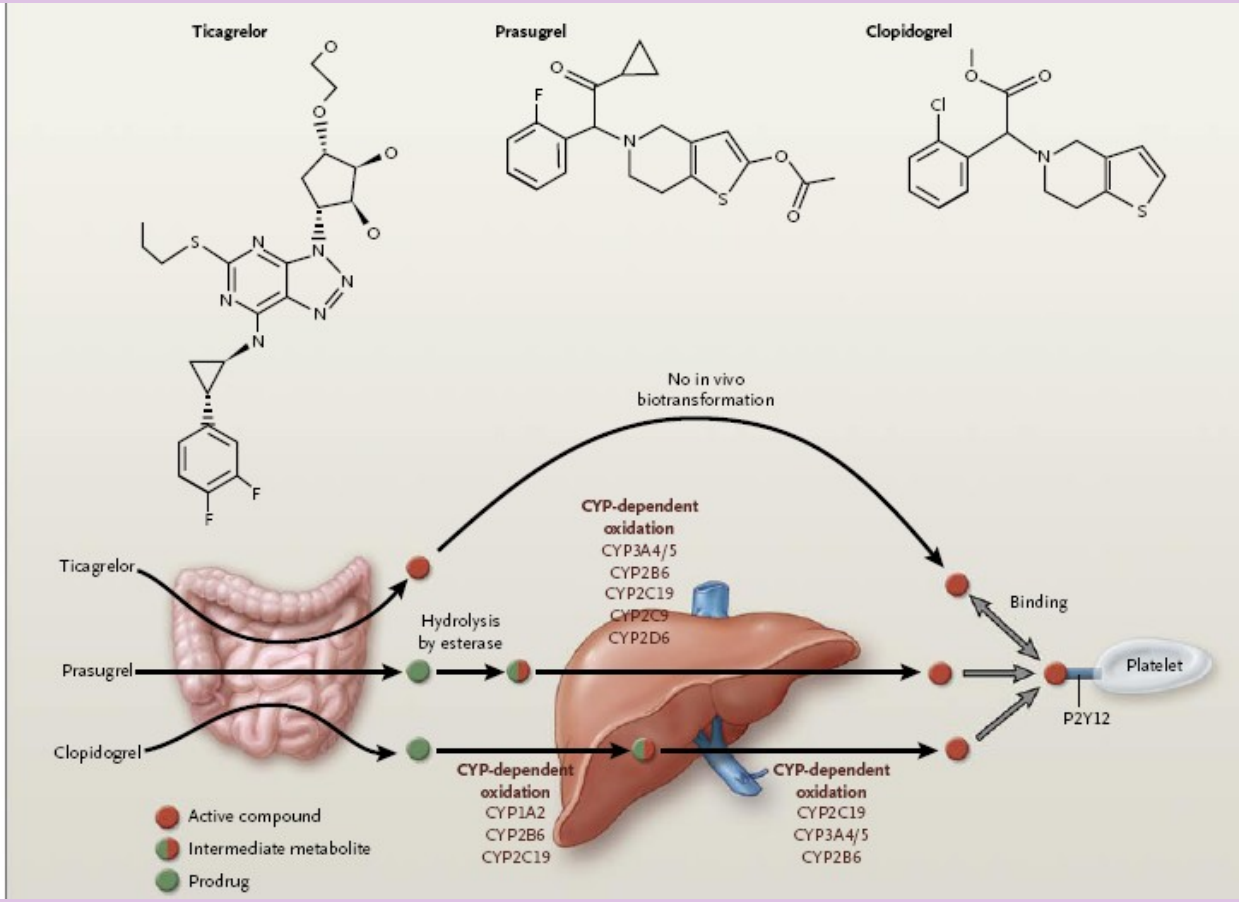


На 100 лекувани пациенти 9 имат инциденти. 2 ще предотврятат инцидент с clopidogrel

PLATO
Lars Vallentin

Новите агенти:
Clopidogrel
Prasugrel
Ticagrelor

Бързо действие
обратимост
Риск от хеморагия
Клиничен ефект



Albert Schoming Editorial NEJM 2009, 361,11, 1108

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

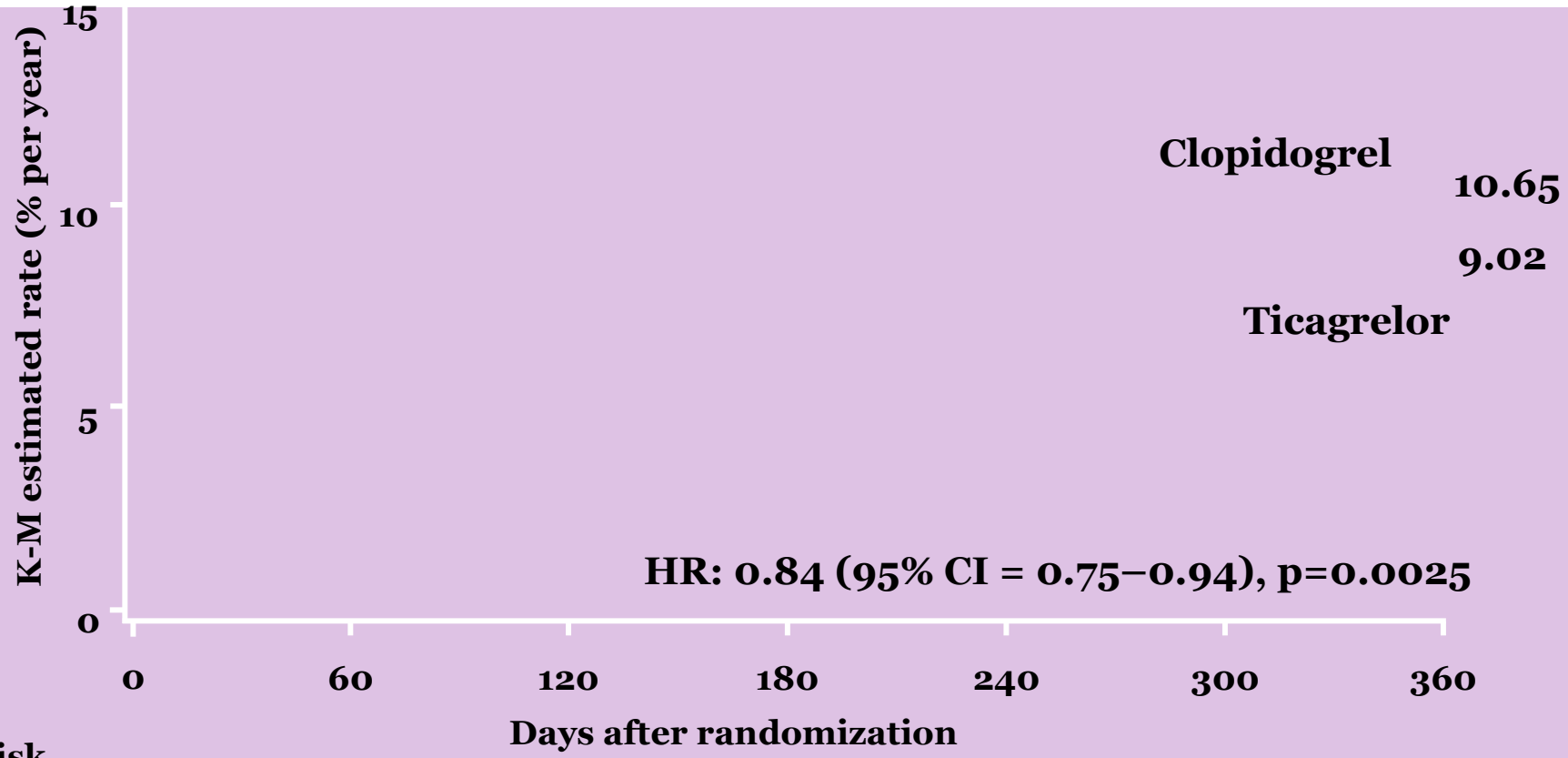
Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary end point: CV death + MI + Stroke

Primary safety end point: Total major bleeding

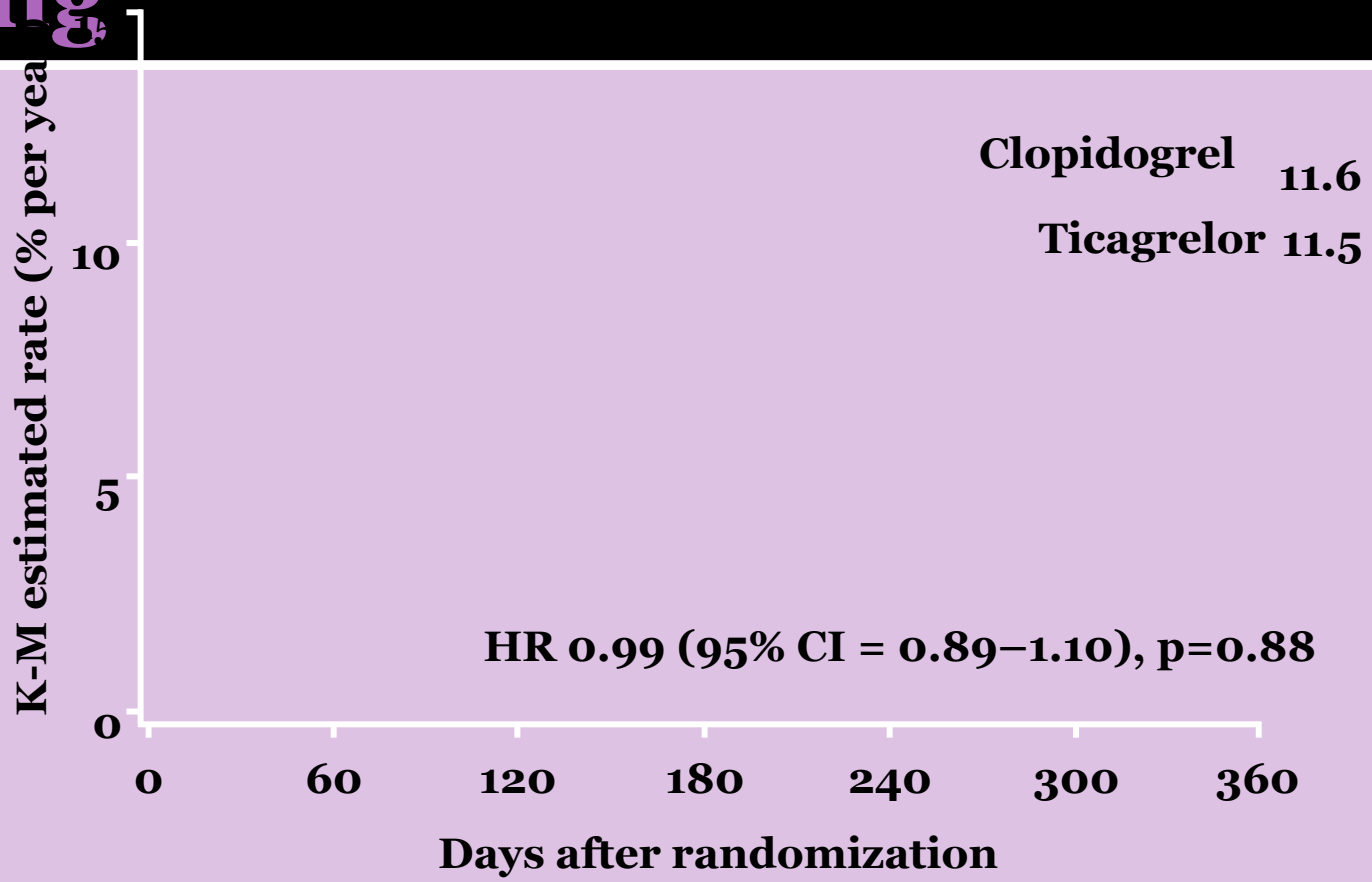
Primary endpoint: CV death, MI or stroke



No. at risk							
Ticagrelor	6,732	6,236	6,134	5,972	4,889	3,735	3,048
Clopidogrel	6,676	6,129	6,034	5,881	4,815	3,680	2,965

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

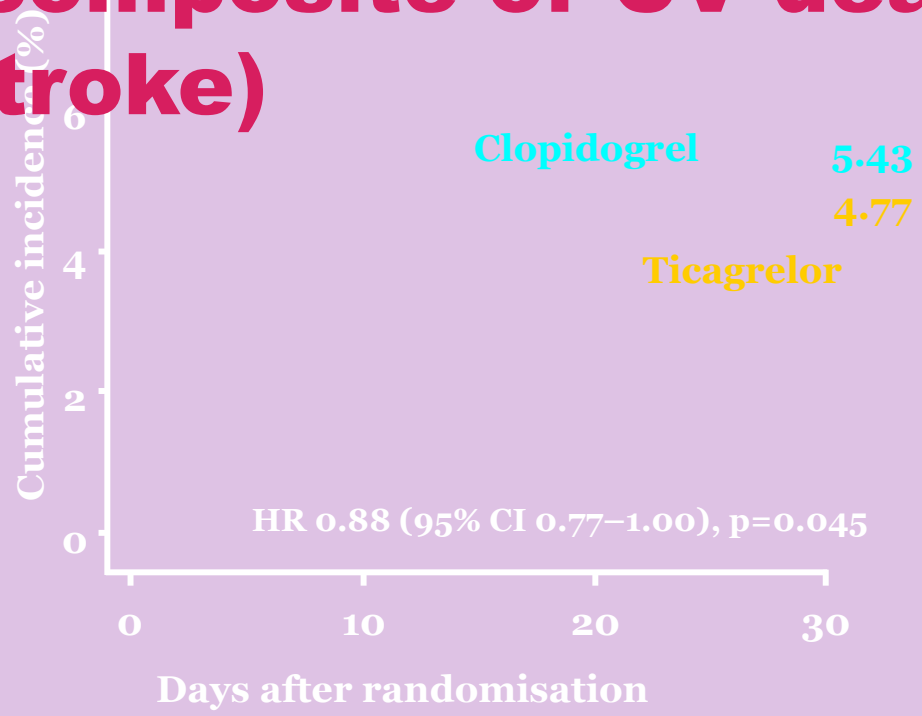
Primary safety event: Major bleeding*

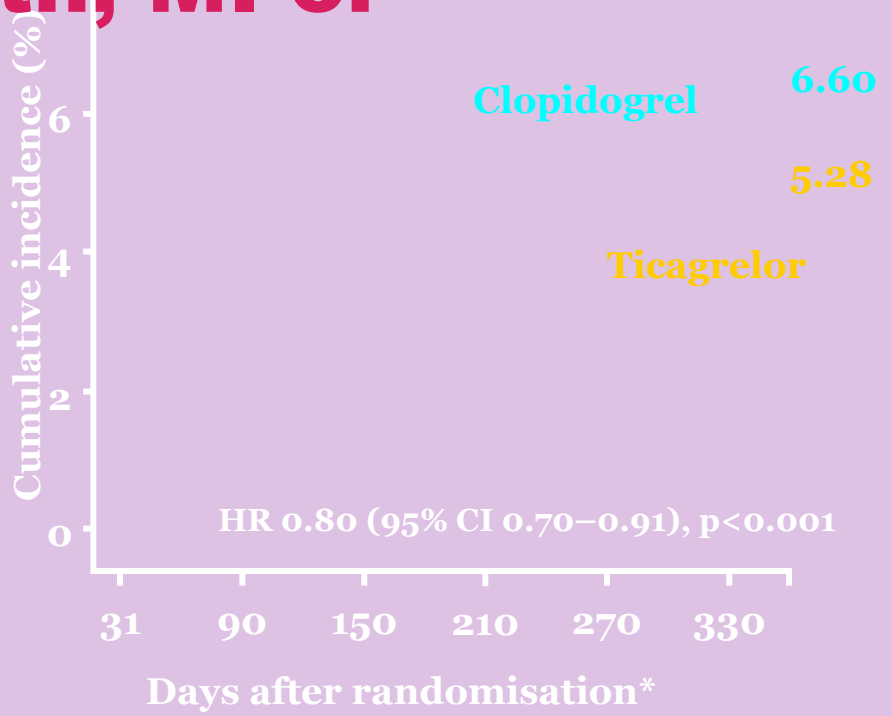


No. at risk							
Ticagrelor	6,651	5,235	4,947	4,755	3,726	2,741	2,503
Clopidogrel	6,585	5,215	4,984	4,786	3,753	2,754	2,496

* PLATO definitions

Primary efficacy end point over time (composite of CV death, MI or stroke)

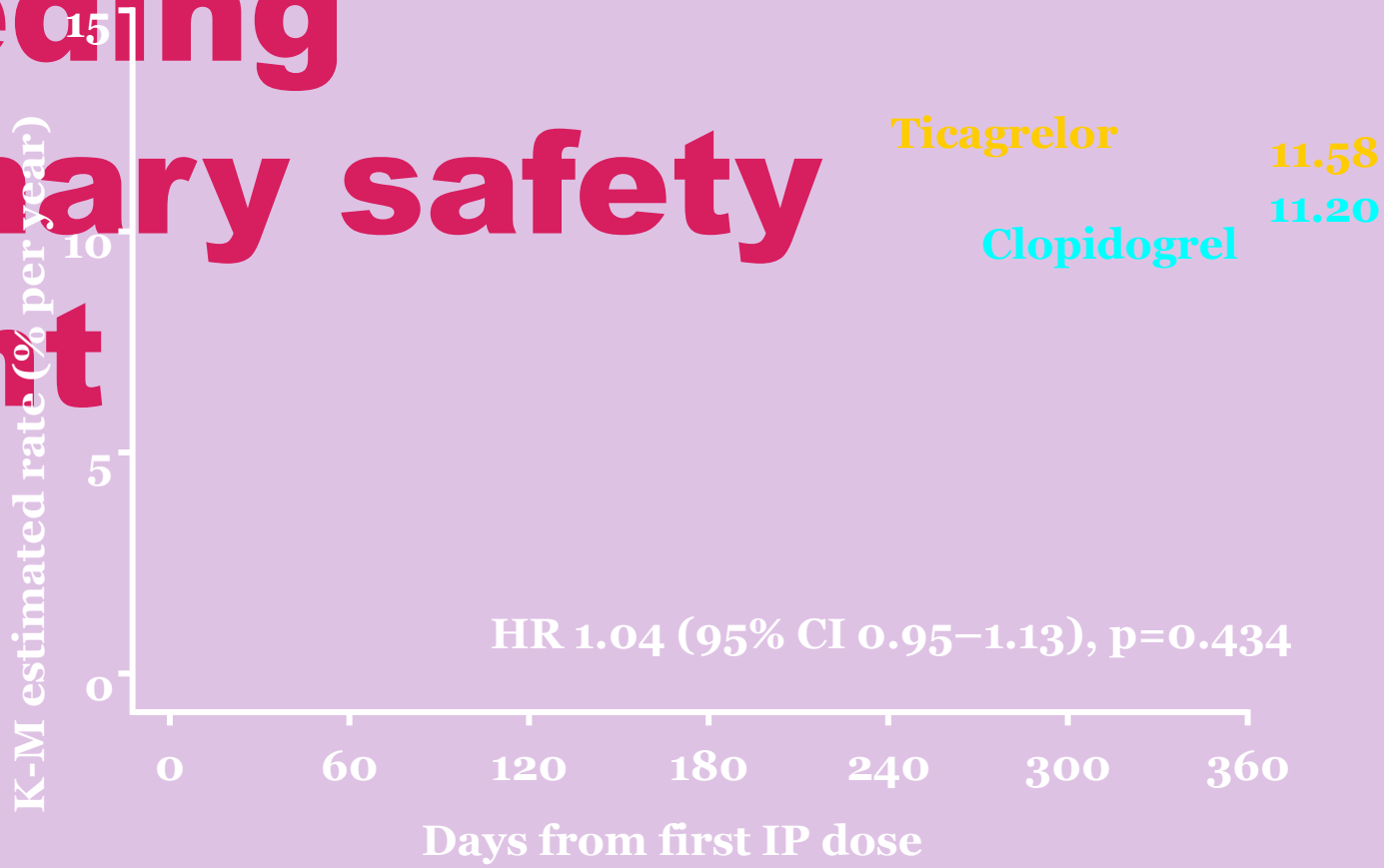




No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

*Excludes patients with any primary event during the first 30 days

Time to major bleeding Primary safety event



No. at risk							
Ticagrelor	9,235	7,246	**6,826**	6,545	**5,129**	3,783	3,433
Clopidogrel	9,186	7,305	6,930	**6,670**	5,209	3,841	3,479

Time to non-procedure-related Major bleeding

Completeness of follow-up 99.97% = five patients lost to follow-up

No. at risk							
Ticagrelor	9,235	7,641	7,247	6,979	5,496	4,067	3,698
Clopidogr	9,186	7,718	7,371	7,134	5,597	4,147	3,764

Wallentin L et al. NEJM . 2009; 361:1045-57 (Supplementary Appendix).

Prasugrel?

По- ефикасен от clopidogrel при пациенти с PCI в TRITON TIMI-38, но увеличава риска от кървене

При нинвазивна стратегия за ОКС не е проучен

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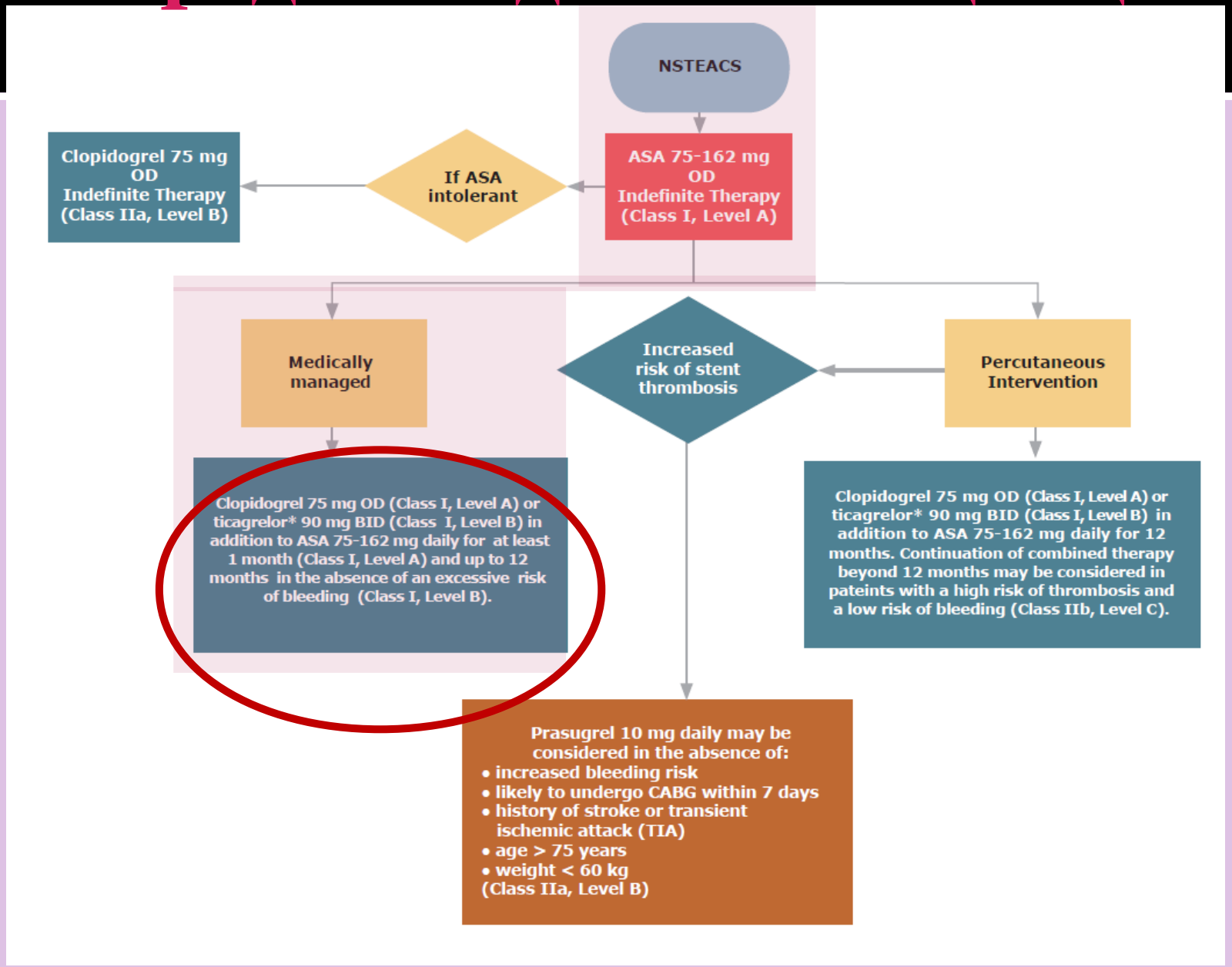
Според Канадската асоциация



Antiplatelet therapy for secondary prevention in the first year following an acute coronary syndrome

1. За пациенти с ОКС и медикаментозно лечение след изписване, терапия с ASA (75-162 mg дневно) (Class I, Level A). За пациенти нетолериращи ASA, терапия с clopidogrel 75 mg дневно (Class IIa, Level B).
2. За пациенти с NSTEMИ които са лекувани медикаментозно , clopidogrel 75 mg дневно заедно с ASA 75-162 mg дневно(Class I, Level A) един месец и до 12 месеца ако няма риск от кървене (Class I, Level B).

Antiplatelet therapy for secondary prevention in the first year following an acute coronary syndrome

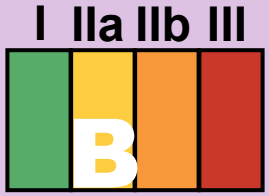
3. **Пациенти със STEMI които са медикаментозно лекувани , се препоръчва clopidogrel 75 mg дневно заедно с ASA 75-162 mg дневно заследващите 14 дни (Class I, Level B) и може до 12 месеца ако няма противопоказания и кървене (Class IIb, Level C).**
4. **За пациенти с ОКС , ticagrelor 90 mg двукратно дневно можеда се добави към ASA 75-162 mg дневно 12 месеца (Class I, Level B).**

Adjunctive Antiplatelet Therapy With Fibrinolysis

In patients with STEMI who receive fibrinolytic therapy:

- aspirin should be continued indefinitely and
- clopidogrel (75 mg daily) for at least 14 days
  - and up to 1 year

Adjunctive Antiplatelet Therapy With Fibrinolysis



It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy.

Diabetes and Cardiovascular Disease

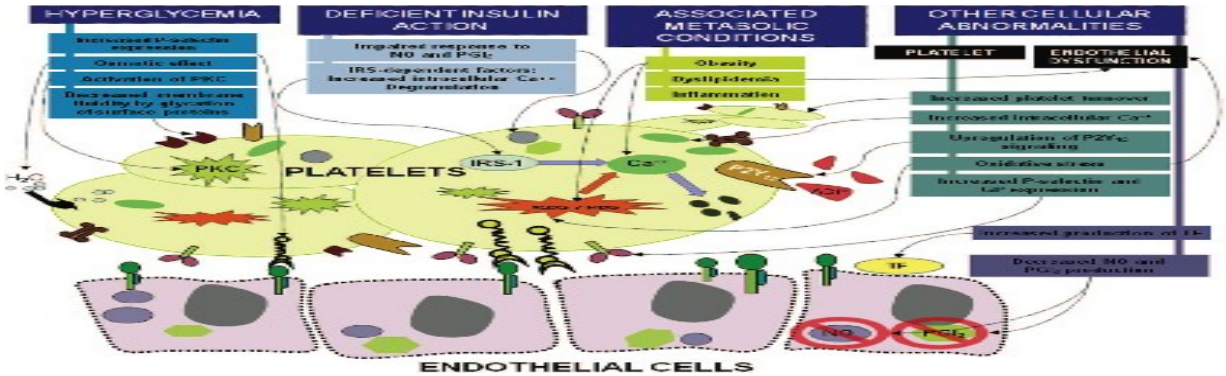


Figure 1. Mechanisms involved in platelet dysfunction in patients with DM. Several mechanisms contribute to platelet dysfunction in diabetes mellitus (DM) patients, including hyperglycemia, insulin deficiency, associated metabolic conditions, and other cellular abnormalities. Hyperglycemia may increase platelet reactivity by inducing P-selectin (a surface adhesion protein) expression, glycating platelet surface proteins (decreasing membrane fluidity and, thus, increasing platelet adhesion), and activating protein kinase C (PKC; a mediator of platelet activation) and as a result of the osmotic effect of glucose. Insulin deficiency also contributes to platelet dysfunction by different mechanisms. Some have been suggested to be IRS dependent such as the increase in intracellular calcium concentration, which leads to enhanced platelet degranulation and aggregation. Other factors associated with insulin resistance are not dependent on IRS, eg, the impaired response to NO and PGI_2, which enhances platelet reactivity. Some metabolic conditions frequently associated with DM may play a role in platelet hyperreactivity, including obesity, dyslipidemia, and enhanced systemic inflammation. In addition to being associated with insulin resistance, obesity contributes to platelet dysfunction, mainly in terms of adhesion and activation, with factors like augmented cytosolic calcium concentration and increased oxidative stress. Abnormalities of the lipid profile, especially hypertriglyceridemia, also affect platelet reactivity by different mechanisms, which include inducing endothelial dysfunction. The presence of endothelial dysfunction is another characteristic feature associated with DM, which enhances platelet reactivity by decreasing the production of NO and PGI_2, and contributes to a prothrombotic state through increased production of tissue factor (TF). Other platelet abnormalities present in DM patients can enhance platelet adhesion and activation, including increased expression of surface proteins (P-selectin and GP IIb/IIIa), augmented cytosolic calcium concentration, upregulation of certain pathways like $P2Y_{12}$ signaling, increased platelet turnover, and oxidative stress, which causes an impairment in platelet function as a result of overproduction of reactive oxygen (ROS) and nitrogen species (NOS).

Control Cardiovascular Risk in Diabetes (ACCORD) study, which randomized DM patients (n=10 251) to receive an intensive glucose-lowering regimen or a standard regimen, because the trial was interrupted after 3.5 years of follow-up as a result of an increased mortality in the intensive therapy group.[32]

Insulin Deficiency and Resistance

The majority of cases of DM fall into 2 etiopathogenetic categories. In type 1 DM, the underlying cause is an autoimmune destruction of the β cells of the pancreas, leading to an absolute deficiency of insulin secretion. In type 2 DM, which accounts for ~90% to 95% of DM, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, usually having relative (rather than absolute) insulin deficiency.[33] Deficient insulin action resulting from inadequate insulin secretion and/or diminished tissue responses is the cardinal factor for the development of DM and contributes to platelet dysfunction.[34] Platelets express both insulin receptors and insulin-like growth factor-1 (IGF-1) receptors.[35,36] Among other effects, the binding of insulin to platelets increases surface expression of adenylate cyclase–linked prostacyclin receptor.[37] However, insulin receptor expression is relatively low because the majority of its subunits heterodimerize with those of the IGF-1 receptor to form an insulin/IGF-1 hybrid receptor, which avidly binds IGF-1 but not insulin.[38] However, IGF-1 is present in the α granules of platelets, and its receptor is expressed on the platelet surface, which may contribute to the amplification of platelet responses and the pathogenesis of cardiovascular disease. The functional and signaling pathways involved in IGF-1 modulation of platelet function, however, are currently

Клиничен случай

Нашият пациент с неусложнен NSTEMI на медикаментозно лечение ще проведе лечението си с:

Статин, АСЕИ и Beta блокер.

Неговата антиагрегантна терапия ще бъде:

- ASA 100 mg дневно
- Clopidogrel 75 mg дневно, ако няма усложнения до 1 година :

  Но може да бъде прекратена употребата му на края на 1 месец, ако има риск от кървене .

  Ако има висок риск от тромбоза и нисък риск от кървене може лечението и с клопидогрел да продължи повече от година

Благодаря за вниманието!