# AKUT KORONER SENDROMDA ANTİPLATELET SEÇİMİ; NE, NE ZAMAN?

**DOÇ. DR. AYHAN SARITAŞ**

**DÜZCE ÜNİVERSİTESİ**

**ACİL TIP AD**

# Plan

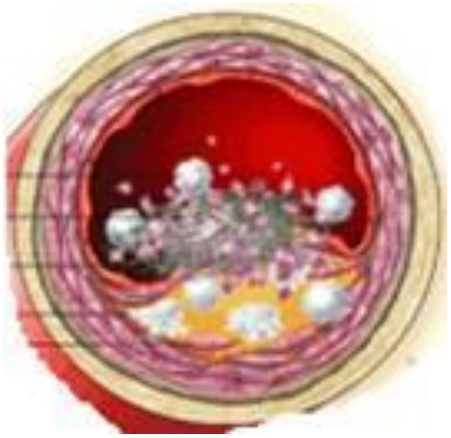
- AKS Patofizyolojisi
- Antiplatelet Mekanizma
- Antiplatelet İlaç Çalışmaları
- UA/NSTEMI’de Antiplatelet Tedavi
- STEMI’ Antiplatelet Tedavi
- Özet

# AKS Patofizyoloji

Plak

Plak hasarı/
yırtılması

Platelet aktivasyonu-agregasyonu
Trombüs formasyonu
Vazospazm



Koroner kan akımının
kısmen/tam
oklüzyonu

# Antiplatelet İlaç Etki Mekanizması

- Siklooksijenaz inhibisyonu (ASA)
- P2Y12 reseptör inhibisyonu (klopidogrel, prasugrel, tikagrelor)

- AKS tedavisinde antiplatelet tedavi önemli bir yere sahip
- Antiplatelet ajanlar ile ilgili son yıllarda yapılan çalışmalar kılavuzların güncellenmesine yol açmıştır

# Antiplatelet İlaç Özellikleri

| | Clopidogrel | Prasugrel | Ticagrelor | Cangrelor |
|---|---|---|---|---|
| Chemical class | Thienopyridine | Thienopyridine | Cyclopentyl-triazolopyrimidine | Stabilized ATP analogue |
| Administration | Oral | Oral | Oral | Intravenous |
| Dose | 300–600 mg orally then 75 mg a day | 60 mg orally then 10 mg a day | 180 mg orally then 90 mg twice a day | 30 μg/kg bolus and 4 μg/kg/min infusion |
| Binding reversibility | Irreversible | Irreversible | Reversible | Reversible |
| Activation | Prodrug, with variable liver metabolism | Prodrug, with predictable liver metabolism | Active drug, with additional active metabolite | Active drug |
| Onset of loading dose effect[a] | 2–6 hours[b] | 30 min[b] | 30 min[b] | 2 min |
| Duration of effect | 3–10 days | 7–10 days | 3–5 days | 1–2 hours |
| Withdrawal before surgery | 5 days[c] | 7 days[c] | 5 days[c] | 1 hour |
| Plasma half-life of active $P2Y_{12}$ inhibitor | 30–60 min | 30–60 min[e] | 6–12 hours | 5–10 min |
| Inhibition of adenosine reuptake | No | No | Yes | Yes ('inactive' metabolite only) |

2015 ESC, European Heart Journal, doi:10.1093/eurheartj/ehv320

# Increased Active Metabolite Formation Explains the Greater Platelet Inhibition With Prasugrel Compared to High-dose Clopidogrel

*Christopher D. Payne, MS,* Ying Grace Li, MS,† David S. Small, PhD,†*
*C. Steven Ernest II, MS,† Nagy A. Farid, PhD,† Joseph A. Jakubowski, PhD,†*
*John T. Brandt, MD,† Daniel E. Salazar, PhD,‡ and Kenneth J. Winters, MD†*

J Cardiovasc Pharmacol 2007;50:555-62.

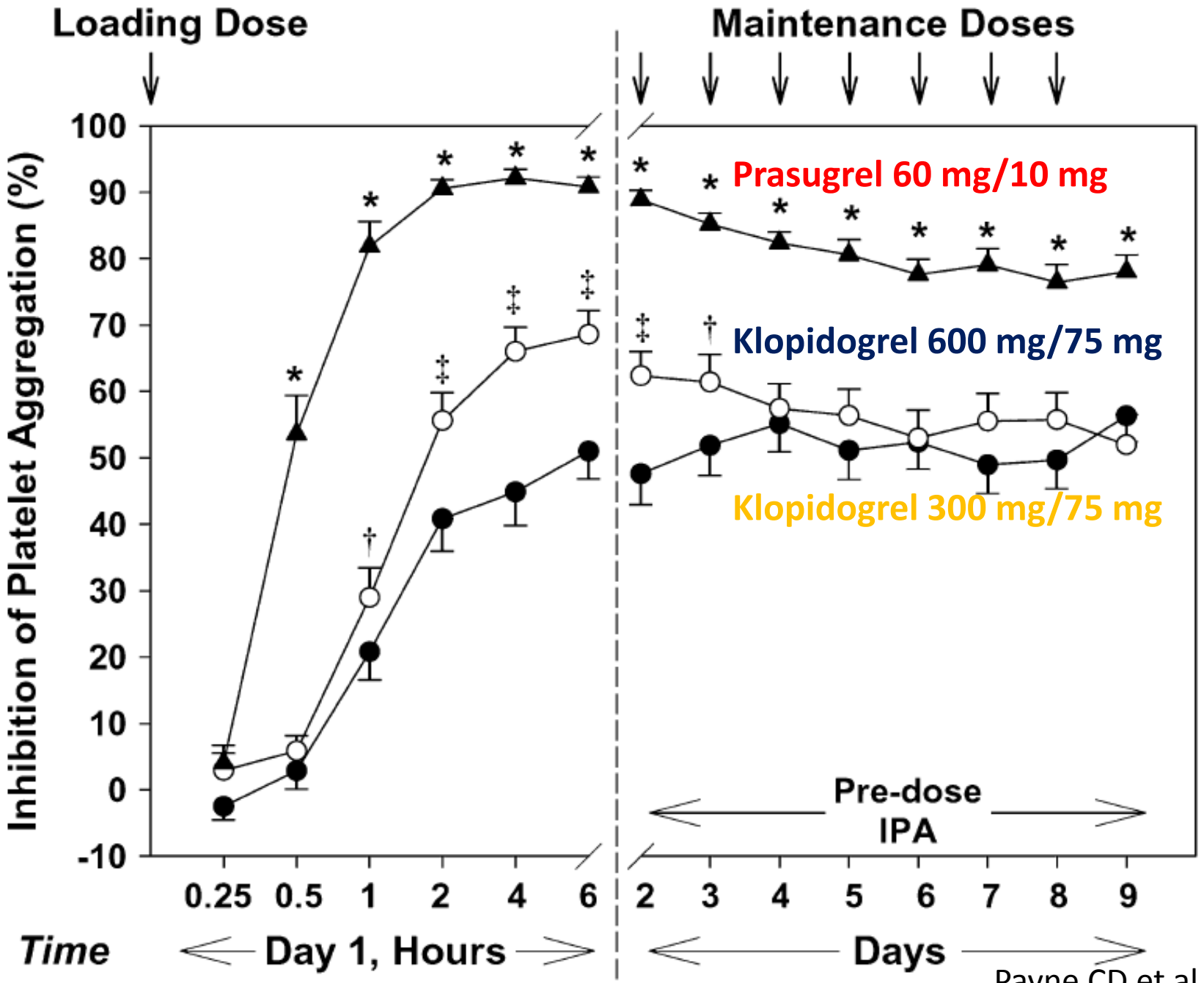



**FIGURE 1.** Inhibition of platelet aggregation (20 μM ADP). Data are expressed as mean ± SEM after clopidogrel 300-mg/75-mg (●), clopidogrel 600-mg/75-mg (○), and prasugrel 60-mg/10-mg (▲) LD and MD, respectively. *$P < 0.001$ versus clopidogrel 300-mg/75-mg and 600-mg/75-mg regimen; †$P < 0.05$ versus clopidogrel 300-mg/75-mg; ‡$P < 0.001$ versus clopidogrel 300-mg /75-mg. Arrows (↓) indicate day of dose administration.

**Prasugrel ile daha güçlü trombosit agregasyonu inhibisyonu**

Payne CD et al. J Cardiovasc Pharmacol 2007;50:555-62.

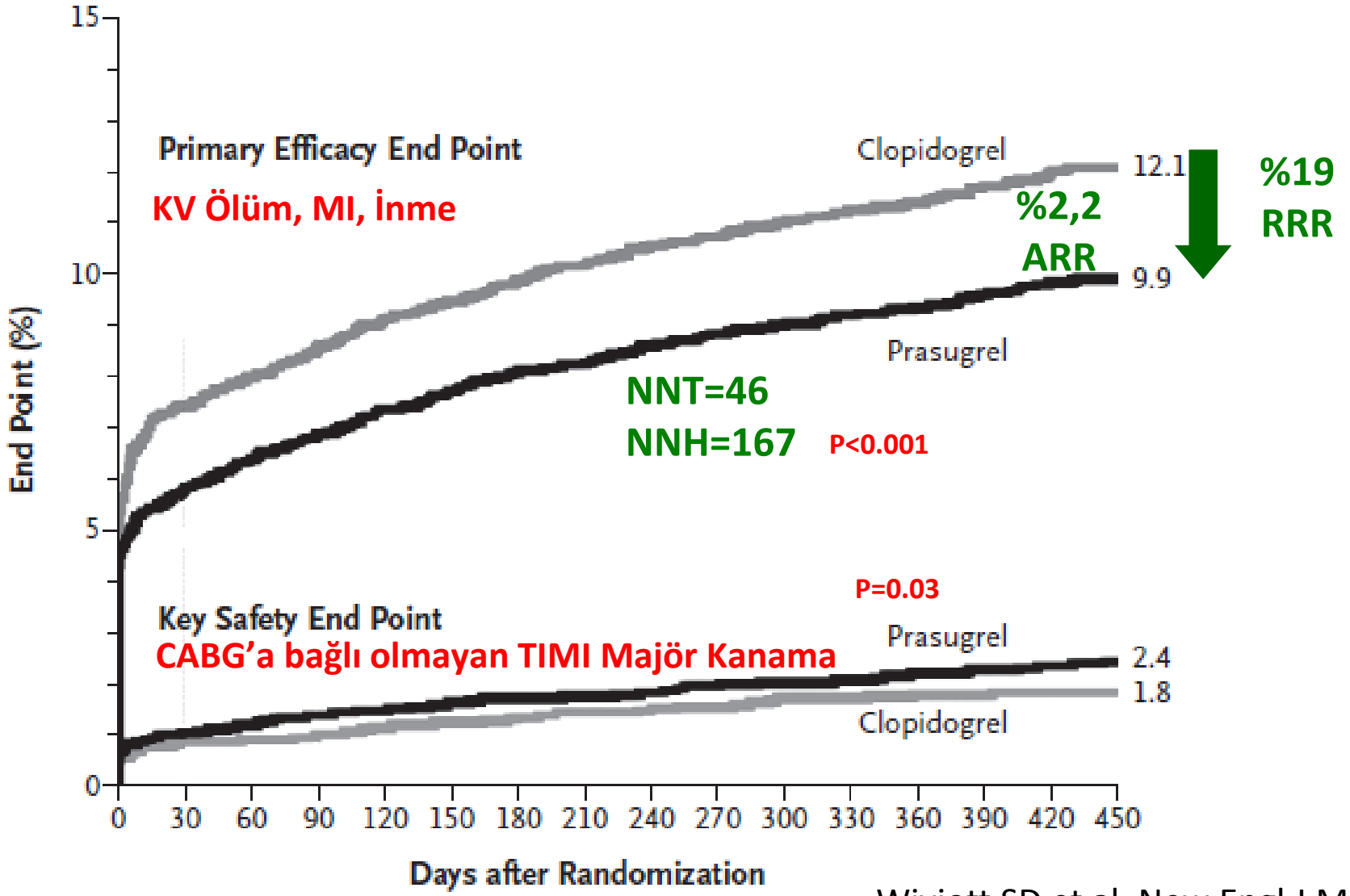
The NEW ENGLAND JOURNAL of MEDICINE

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*

# TRITON-TIMI 38



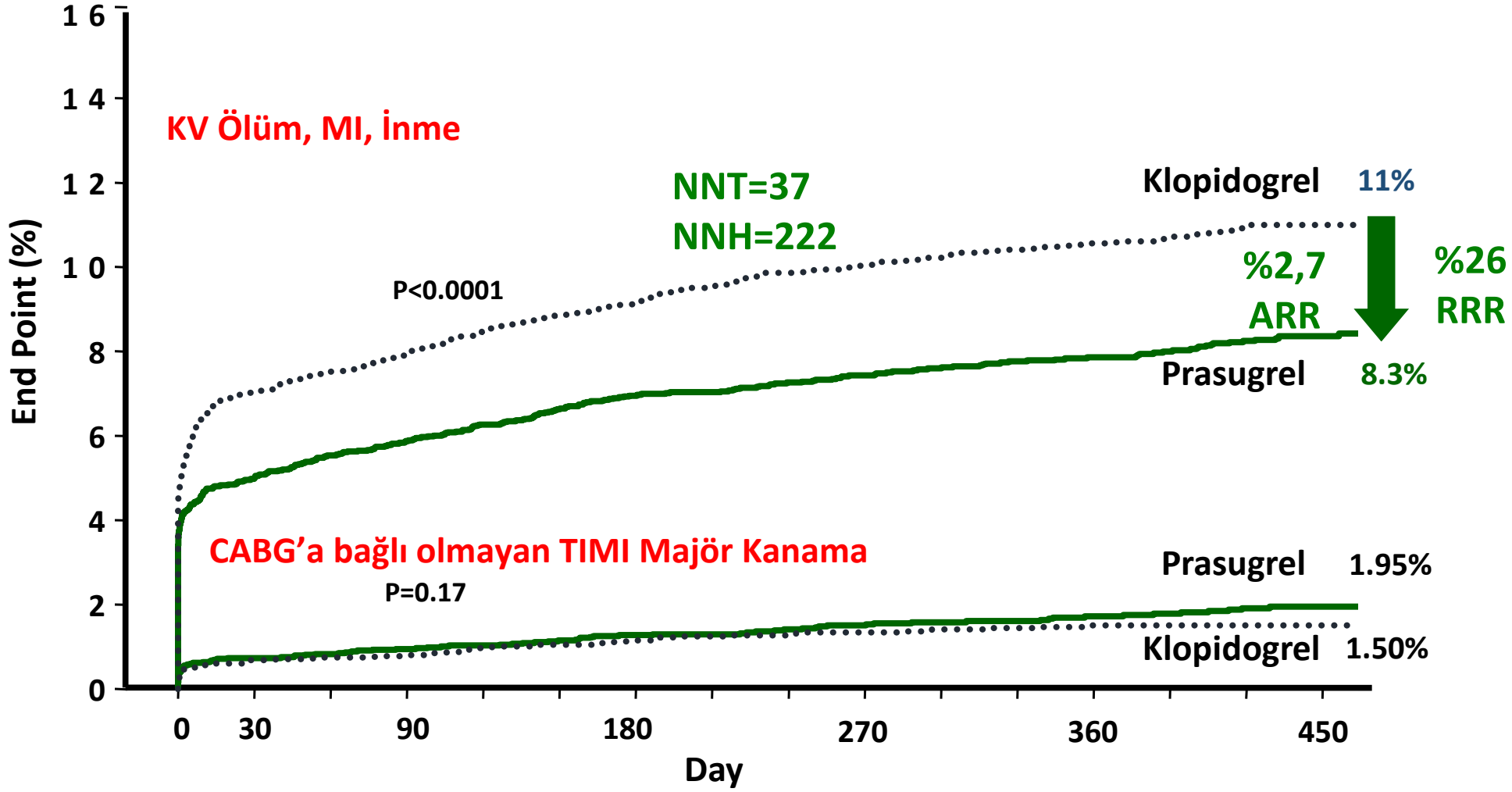

Wiviott SD et al. New Engl J Med 2007;357:2001-2015

# Efficacy and Safety of Intensive Antiplatelet Therapy With *Prasugrel* from TRITON-TIMI 38 in a Core Clinical Cohort Defined by Worldwide Regulatory Agencies

Stephen D. Wiviott, MD[a,*], Nihar Desai, MD[a], Sabina A. Murphy, MPH[a], Guiseppe Musumeci, MD[b], Michael Ragosta, MD[c], Elliott M. Antman, MD[a], and Eugene Braunwald, MD[a]

TRITON-TIMI 38 showed that in patients with acute coronary syndrome undergoing percutaneous coronary intervention prasugrel decreased ischemic events compared to standard clopidogrel, but with more bleeding. The United States Food and Drug Administration and the European Medicines Agency approved prasugrel but provided contraindications in patients with previous stroke or transient ischemic attack and recommended limited use or reduced dose in patients ≥75 years old and weighing <60 kg. This defined 3 clinically relevant groups of patients for use of prasugrel at the studied dose regimen: group I (core clinical cohort), group II (noncore cohort), and group III (contraindicated). We assessed clinical outcomes of patients within these cohorts in the TRITON-TIMI 38 trial. Survival analysis methods were used to compare outcomes by treatment assignment (prasugrel vs clopidogrel) and by cohort (groups I and II or III). Patients in group I (n = 10,804, 79%) treated with prasugrel had a clinically significant and robust decrease in the primary end point of cardiovascular death, myocardial infarction, or stroke (8.3 vs 11.0%, hazard ratio [HR] 0.74, 95% confidence interval 0.66 to 0.84, p <0.0001), whereas patients in group II (n = 2149, 16%) had limited efficacy (15.3% vs 16.3%, HR 0.94, 0.76 to 1.18, p = 0.61, p for interaction = 0.07). For Thrombolysis In Myocardial Infarction major bleeding not related to coronary artery bypass grafting, there were tendencies to higher rates with prasugrel in group I (1.9% vs 1.5%, HR 1.24, 0.91 to 1.69, p = 0.17) and group II (4.1% vs 3.4%, HR 1.23, 0.77 to 1.97, p = 0.40); however, the absolute difference was greater for group II. The net clinical outcome (all-cause death/myocardial infarction/stroke/Thrombolysis In Myocardial Infarction major bleeding) in group I patients was highly favorable (10.2% vs 12.5%, HR 0.80, 0.71 to 0.89, p <0.0001) and neutral in group II (19.5% vs 19.7%, HR 0.98, 0.81 to 1.20, p for interaction = 0.07). Patients in group III (n = 518, 4%) did poorly with regard to efficacy and safety. In TRITON-TIMI 38 patients without previous stroke, <75 years old, and weighing ≥60 kg had substantial decreases in ischemic events with prasugrel compared to clopidogrel. Although relative bleeding excess exists in this population, absolute rates and differences in bleeding were attenuated. In conclusion, these data indicate that use of prasugrel in a core clinical cohort that has been defined by regulatory action will maximize the benefit of prasugrel and limit the risk of adverse outcomes.  (Am J Cardiol 2011;108:905–911)

# TRITON-TIMI 38
## <75 Yaş, ≥60 kg ve inme/GİA öyküsü olmayan hastalarda




Wiviott SD et al. Am J Cardiol 2011;108(7):905-11

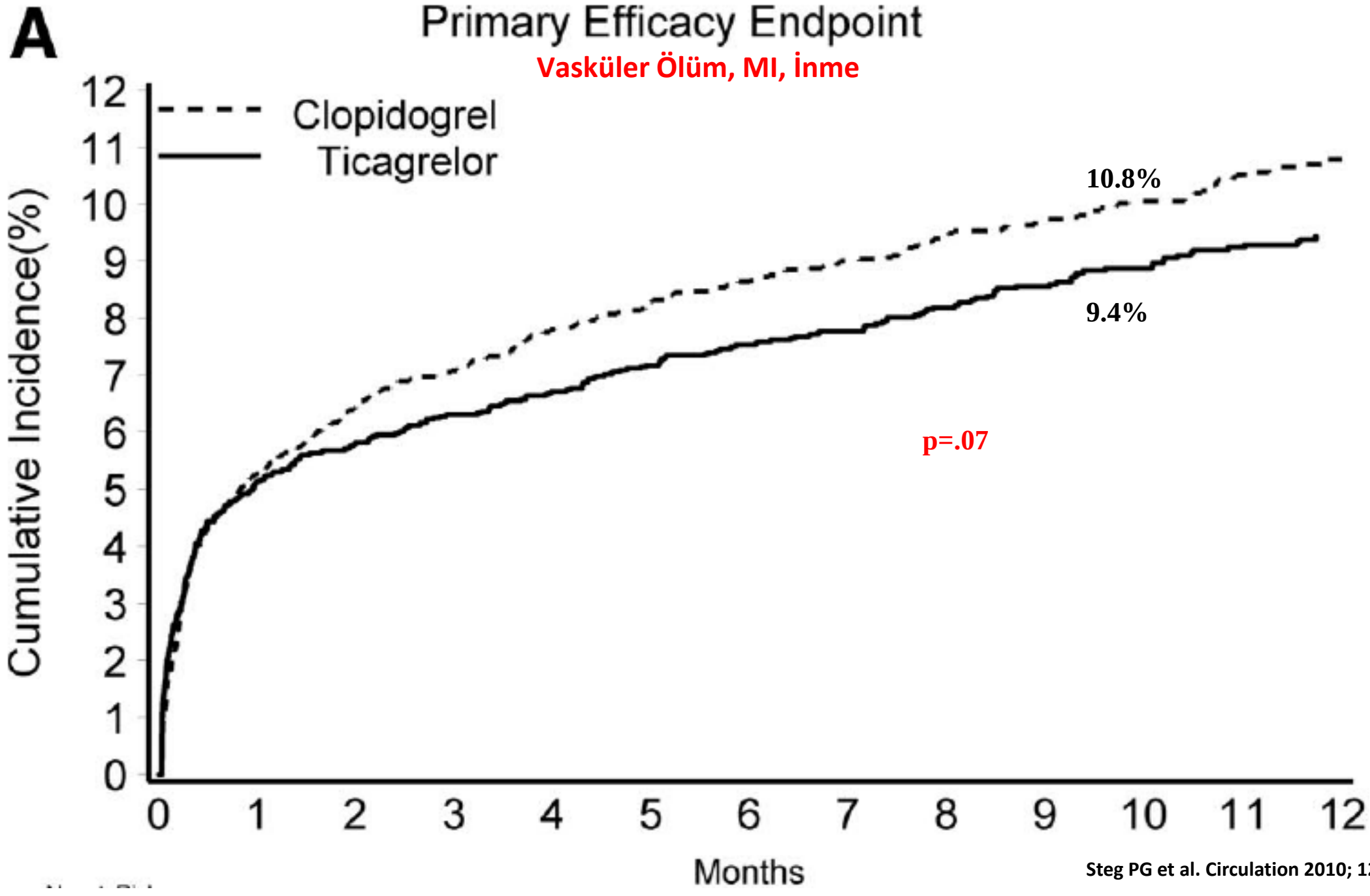
**PRASUGREL**
**İnme/GİA geçirenlerde**
**≥75 yaş ve <60 kg**
**kullanılmamalı**

# Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention

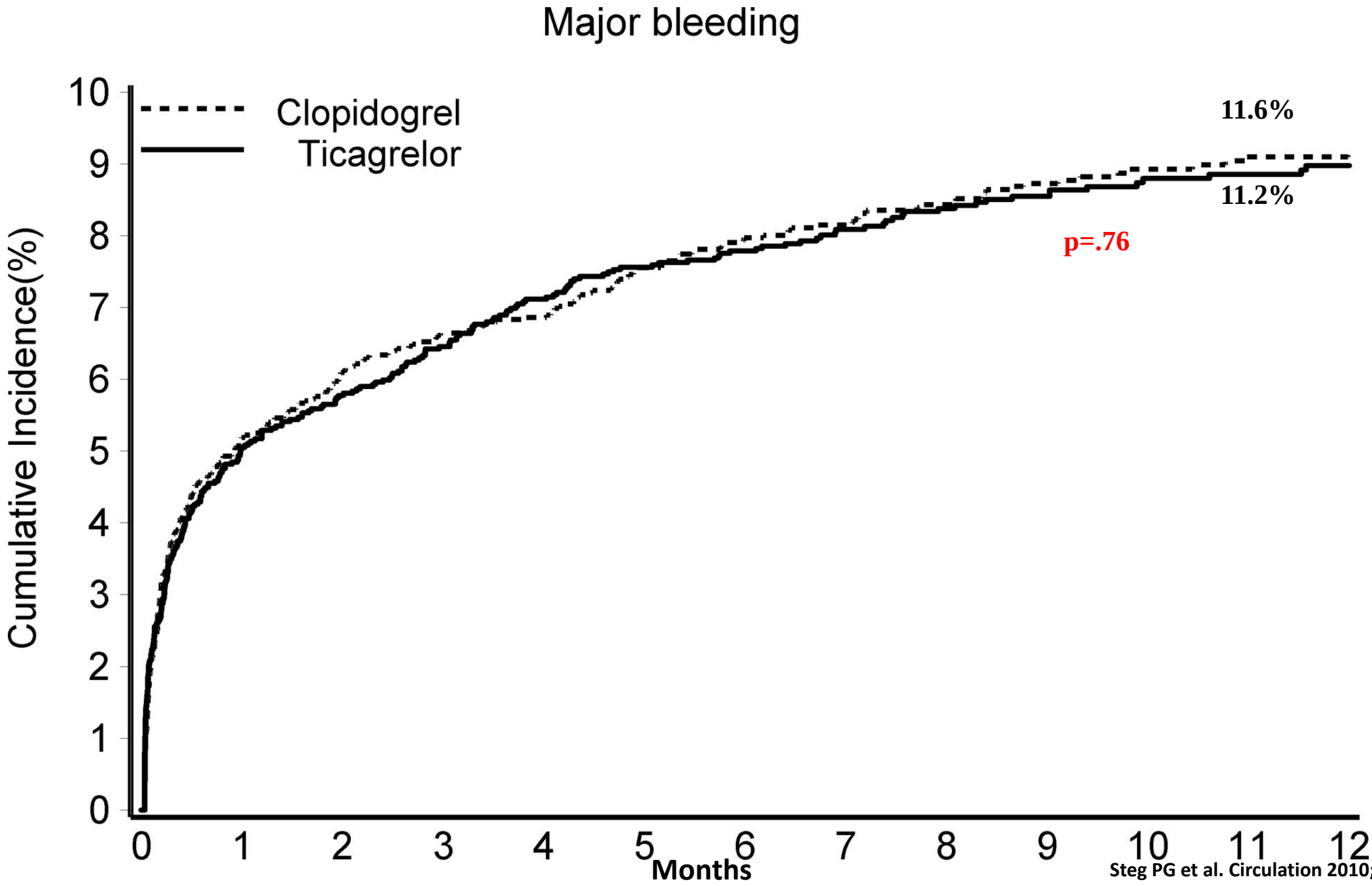
## A Platelet Inhibition and Patient Outcomes (PLATO) Trial Subgroup Analysis

Philippe Gabriel Steg, MD; Stefan James, MD, PhD; Robert A. Harrington, MD; Diego Ardissino, MD; Richard C. Becker, MD; Christopher P. Cannon, MD; Håkan Emanuelsson, MD, PhD; Ariel Finkelstein, MD; Steen Husted, MD, DSc; Hugo Katus, MD; Jan Kilhamn, MD, PhD; Sylvia Olofsson, BSc; Robert F. Storey, MD, DM; W. Douglas Weaver, MD; Lars Wallentin, MD, PhD; for the PLATO Study Group

Circulation 2010; 122: 2131-41.




Steg PG et al. Circulation 2010; 122: 2131-41.




Steg PG et al. Circulation 2010; 122: 2131-41.

# Meta-Analysis of Comparison of the Newer Oral $P2Y_{12}$ Inhibitors (Prasugrel or Ticagrelor) to Clopidogrel in Patients With Non–ST-Elevation Acute Coronary Syndrome

Chirag Bavishi, MD, MPH[a], Sadik Panwar, MD[b], Franz H. Messerli, MD[b,c], and Sripal Bangalore, MD, MHA[d,*]

Tikagrelor ve prasugrel klopidogrele kıyasla

- MI ve majör istenmeyen kardiyak olay oranını ↓
- Majör kanamaları ↑

Am J Cardiol 2015;116:809–17

# STEMI’de Antiplatelet Tedavi

- Tedavi stratejisi ne olursa olsun ilk basamakta hemen ASA verilmesi tüm kılavuzlarda Sınıf 1
- **ESC**
  - 150-300 mg yükleme
  - 75-100 mg idame
- **ACCF/AHA**
  - 162-325 mg yükleme
  - 81-325 mg idame

# STEMI’de Antiplatelet Tedavi

- Hem ESC hem de ACCF/AHA kılavuzu ikili antiplatelet tedavinin ivedilikle başlanması Sınıf 1 öneri

# STEMI’de Antiplatelet Tedavi

Fibrinolitik tedavi planlanıyorsa

**ESC**

Litik tedaviye tamamlayıcı olarak ASA ile birlikte rutin klopidogrel kullanımı iyi bir görüş

Sınıf 1 Öneri

- Klopidogrel 300 mg yükleme, 75 mg/gün idame
- Hasta >75 yaşında ise yükleme dozu verilmeden 75 mg/gün dozda devam edilmesi önerilmekte

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# Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

| | |
|---|---|
| ***$P2Y_{12}$ receptor inhibitors*** | |
| • Clopidogrel: | I |
| • Age ≤75 y: 300-mg loading dose | |
| • Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding | I |
| • Age >75 y: no loading dose, give 75 mg | I |
| • Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding | I |

Fibrinolitik tedavi planlanıyorsa

Prasugrel ve tikagrelor
fibrinolize tamamlayıcı olarak
çalışılmamıştır ve
**kullanılmamalı**

European Heart Journal Advance Access published August 29, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu278

ESC/EACTS GUIDELINES

# 2014 ESC/EACTS Guidelines on myocardial revascularization

## Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Antiplatelet therapy** | | |
| ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy. | I | A |
| A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are: | I | A |
| • Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication | I | B |
| • Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication | I | B |
| • Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated. | I | B |
| It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact. | I | B |

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American Heart Association®

# Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

## *$P2Y_{12}$ inhibitors*

### Loading doses

| | | |
|---|---|---|
| • Clopidogrel: 600 mg as early as possible or at time of PCI | I | B |
| • Prasugrel: 60 mg as early as possible or at time of PCI | I | B |
| • Ticagrelor: 180 mg as early as possible or at time of PCI | I | B |

# Fibrinolitik tedavi almış STEMI hastalarında PCI planlanıyorsa

**ESC kılavuzu**

- P2Y12 reseptör inhibitörü dozunu primer PCI dozunda önermekte

# Fibrinolitik tedavi almış STEMI hastalarında PCI planlanıyorsa

**ACCF/AHA kılavuzu**

Daha önce klopidogrel yükleme dozu almamış

- Fibrinolitik tedavi sonrası ilk 24 saat içinde — Klopidogrel 300 mg yükleme
- >24 saat zaman geçmiş ise — Klopidogrel 600 mg yükleme

Daha önce klopidogrel yükleme dozu verilmişse yeniden yükleme dozu gerekli değil

# UA / NSTEMI’de Antiplatelet Tedavi

- ASA tedavisi hem mortalite hem de reenfarktüsü anlamlı olarak azaltmış
- ASA hem ESC hem de ACCF/AHA kılavuzunda Sınıf 1 öneri
- **ESC**
  - 150-300 mg yükleme
  - 75-100 mg idame
- **ACCF/AHA**
  - 162-325 mg yükleme (kanama riski yüksek ise 75-162 mg)
  - 81-162 mg idame

# UA / NSTEMI’de Antiplatelet Tedavi

- P2Y12 reseptör inhibitörlerinin ASA ile beraber verilmesi additif etki sağlamakta
- İkili antiplatelet tedavi

2014 ACCF/AHA

2015 ESC kılavuzu

2014 ESC Miyokardiyal Revaskülarizasyon Kılavuzu

**Sınıf 1 öneri**

European Heart Journal (2016) 37, 267–315
doi:10.1093/eurheartj/ehw320



# 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

## Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

**Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)**

| | | |
|---|---|---|
| A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds. | I | A |
| • Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). | I | B |
| • Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e] | I | B |
| • Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. | I | B |

| | | |
|---|---|---|
| It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known. | III | B |

| Intravenous antiplatelet therapy | | |
|---|---|---|
| Cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI. | IIb | A |

European Heart Journal Advance Access published August 29, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu278

ESC/EACTS GUIDELINES

# 2014 ESC/EACTS Guidelines on myocardial revascularization

| Antiplatelet therapy | | |
|---|---|---|
| ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy. | I | A |
| A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are: | I | A |
| • Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication. | I | B |
| • Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication. | I | B |
| • Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated. | I | B |

Cangrelor has not yet been approved by the European Medical Agency or the Federal Drug Administration and therefore no specific recommendation about its use can be given.

# UA / NSTEMI’de Antiplatelet Tedavi

**ACCF/AHA**

- Tikagrelor / Klopidegrol **Sınıf 1** öneri
- Prasugrel: Hasta laboratuvara alınıp koroner anatomi görüldükten sonra ve hasta laboratuvara alınıncaya kadar P2Y12 reseptör inhibitörü verilmemişse **Sınıf 1**

# Amsterdam EA, et al.
# 2014 AHA/ACC NSTE-ACS Guideline

| | | | |
|---|---|---|---|
| **Aspirin** | | | |
| • Non–enteric-coated aspirin to *all* patients promptly after presentation | 162 mg–325 mg | I | A |
| • Aspirin maintenance dose continued indefinitely | 81 mg/d–162 mg/d | I | A |
| **$P2Y_{12}$ inhibitors** | | | |
| • Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin | 75 mg | I | B |
| • $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: | | I | B |
| – Clopidogrel | 300-mg or 600-mg loading dose, then 75 mg/d | | |
| – Ticagrelor* | 180-mg loading dose, then 90 mg BID | | |
| • $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post–PCI patients treated with coronary stents | N/A | I | B |
| • Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy | N/A | IIa | B |

# İkili antiplatelet tedaviye ne zaman başlayalım?

## STEMI

- İvedilikle ikili antiplatelet tedavi başlanması konusunda kılavuzlar hemfikir

# İkili antiplatelet tedaviye ne zaman başlayalım?

## UA / NSTEMI

- Kılavuzlar ikili antiplatelet tedaviye hemen başlanmasını önermekte
- Ancak..
  - Tanı?
  - Koroner anjio sonrası cerrahi tedavi gerekebileceği

Aydoğdu S, *Turk Kardiyol Dern Ars 2015;43 Suppl 2:13-19*

# ÖZET

- STEMI’de ikili antiplatelet tedavi zaman kaybetmeden başlanmalı
- NSTEMI’de ise invaziv tedavi planlanan hastalarda eğer merkezin kateter laboratuvarı mevcut ve hızla KAG yapılma imkanı varsa ikili antiplatelet tedavinin kateter laboratuvarında başlanması uygun bir yaklaşım

# ÖZET

- ASA tedavideki önemini korumakta
- Klopidogrel yavaş yavaş yerini tikagrelor ve prasugrele bırakmakta
- Prasugrel;
  - <75 yaş, ≥60 kg, inme/GİA öyküsü olmayan
  - AKS-PKG hastaları
  - STEMI: İlk tıbbi temasta
  - NSTEMI: Koroner anatomi görüldükten sonra