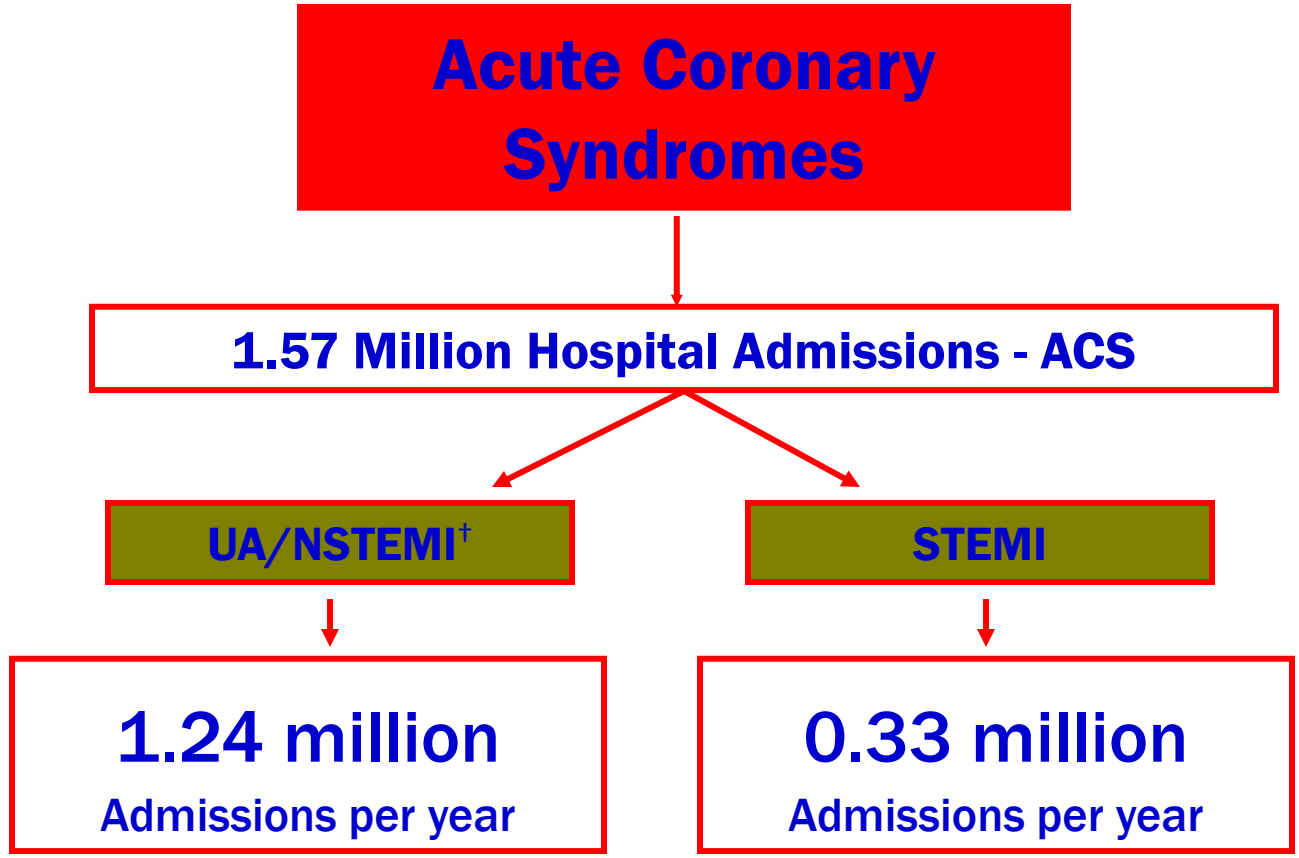
# Prasugrel vs. Ticagrelor in ACS/PCI
# Which one to choose ?

V. Voudris MD FESC FACC

2nd Cardiology Division

Onassis Cardiac Surgery Center

# Hospitalizations in the U.S. Due to ACS




†About 0.57 million NSTEMI and 0.67 million UA. Heart Disease and Stroke Statistics – Circulation 2007; 115:69–171.

# Incidence of MI in Europe

According to a recent overview of 30 countries in Europe, the annual incidence for hospital admission for

- any acute myocardial infarction varied between 90 and 312/100.000 inhabitants
- STEMI between 44 and 142/100.000

Widimsky P, Wijns W, Fajadet J, et al. Eur Heart J 2010;31:943-57.

# Clinically important attributes of an oral antiplatelet agent

- Desired attributes of these therapies are:
  - Rapid onset of effect
    - Direct acting
      - Does not require metabolic activation
  - Rapid offset of effect
    - Reversible binding
      - Does not require production of new platelets
  - Consistent and sustained inhibition of platelet aggregation
    - No nonresponders / Few drug-drug interactions

Mehta SR, et al. *J Am Coll Cardiol.* 2003;41:79S-88S;Angiolillo DJ, et al. *Am Heart J.* 2008a;156:S3-S9.

# ACS: the therapeutic gap

- Despite the benefits of dual antiplatelet therapy with clopidogrel and aspirin, morbidity and mortality remain high
  - One-third of ACS patients may die, have another ACS episode, or require rehospitalization within 6 months
  - About 11% of ACS patients sustain a subsequent CV event at one year of initial presentation

Collinson J. *Eur Heart J.* 2000;21:1450-1457; Yusuf S, et al. *NEJM.* 2001;345:494-50; Wiviott SD, et al. *NEJM.* 2007;357:2001-2015.

# $P2Y_{12}$ Inhibitors

| | Clopidogrel | Prasugrel | Ticagrelor |
|---|---|---|---|
| Class | Thienopyridine | Thienopyridine | Triazolopyrimidine |
| Reversibility | Irreversible | Irreversible | Reversible |
| Activation | Prodrug, limited by metabolization | Prodrug, not limited by metabolization | Active drug |
| Onset of effect | 2-4 h | 30 min | 30 min |
| Duration of effect | 3-10 days | 5-10 days | 3-4 days |
| Withdrawal before major surgery | 5 days | 7 days | 5 days |

# TRITON-TIMI 38: Study Design

**ACS (STEMI or UA/NSTEMI) & Planned PCI**

**ASA** **N= 13,600**

**Double-blind**

| CLOPIDOGREL | PRASUGREL |
|---|---|
| 300 mg LD/ 75 mg MD | 60 mg LD/ 10 mg MD |

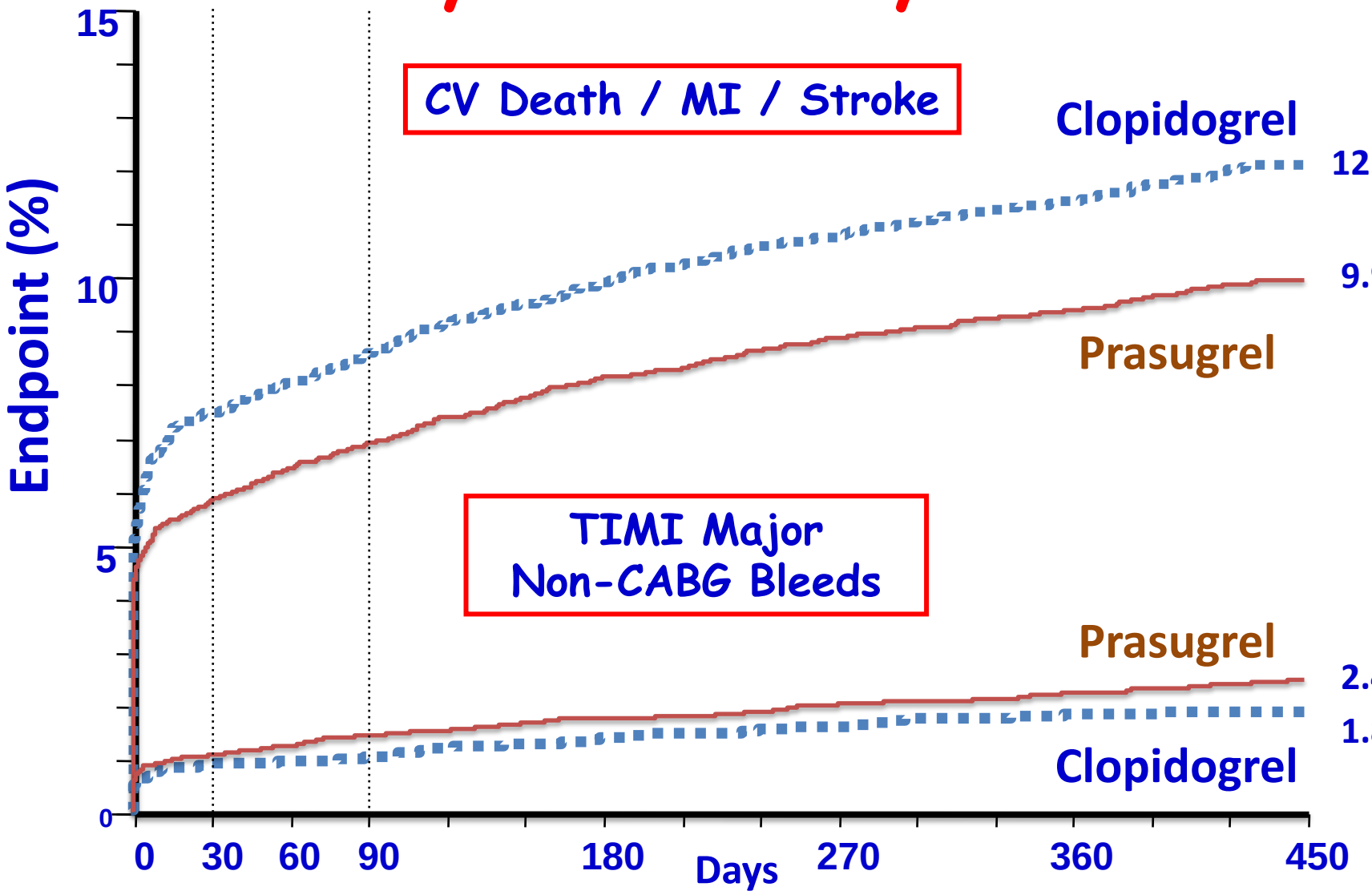
**Median duration of therapy - 12 months**

**1º endpoint: CV death, MI, Stroke**

**Safety endpoints: TIMI major bleeds, Life-threatening bleeds**

*Wiviott SD et al AHJ 152: 627,2006*

# *TRITON* TIMI 38 : Balance of Efficacy and Safety



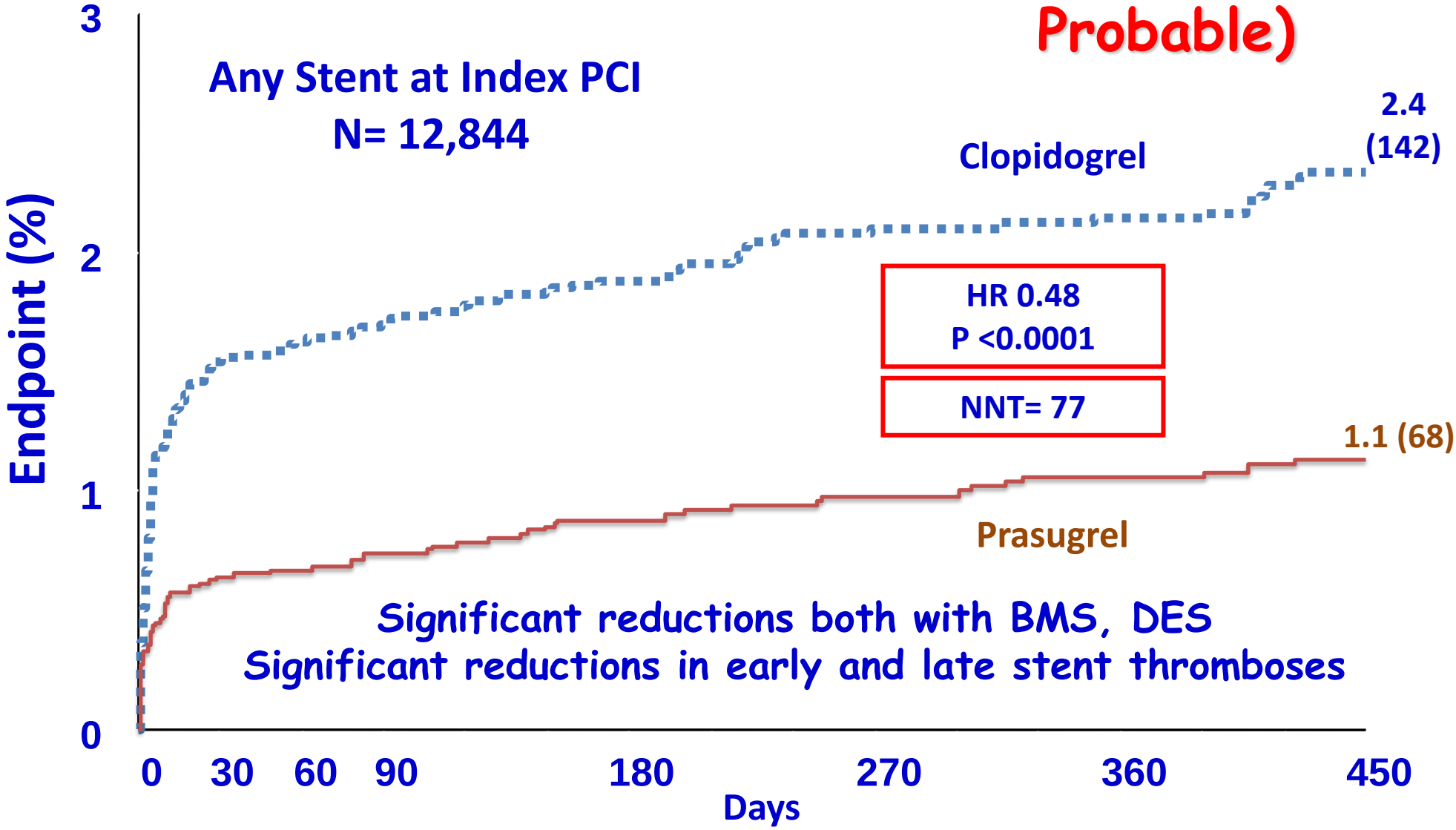

↓ 138 events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

↑ 35 events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167

Adapted with permission from Wiviott SD et al NEJM 357:2007

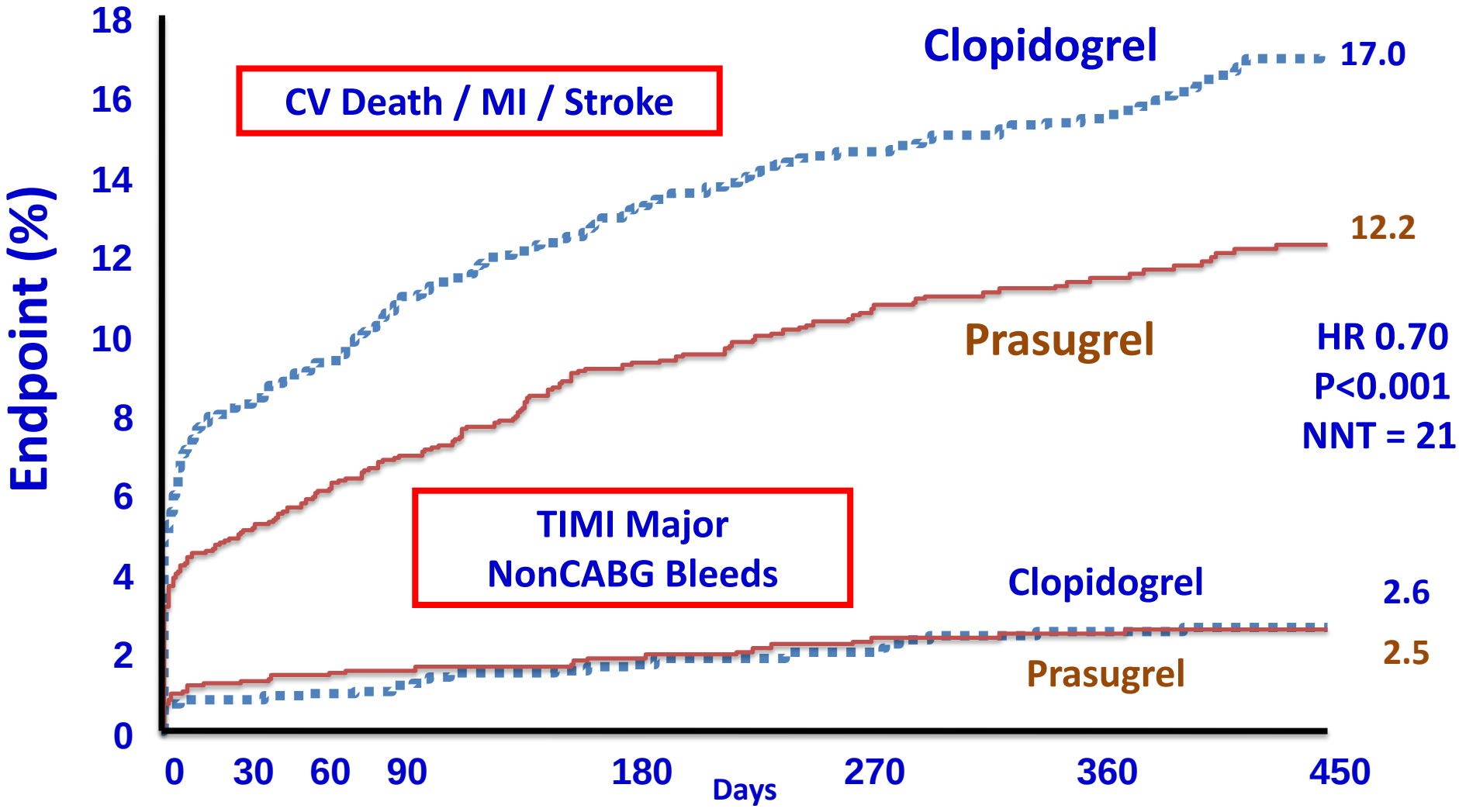
# TRITON TIMI-38

## Stent Thrombosis (ARC Definite + Probable)



# TRITON TIMI-38 Diabetic Subgroup

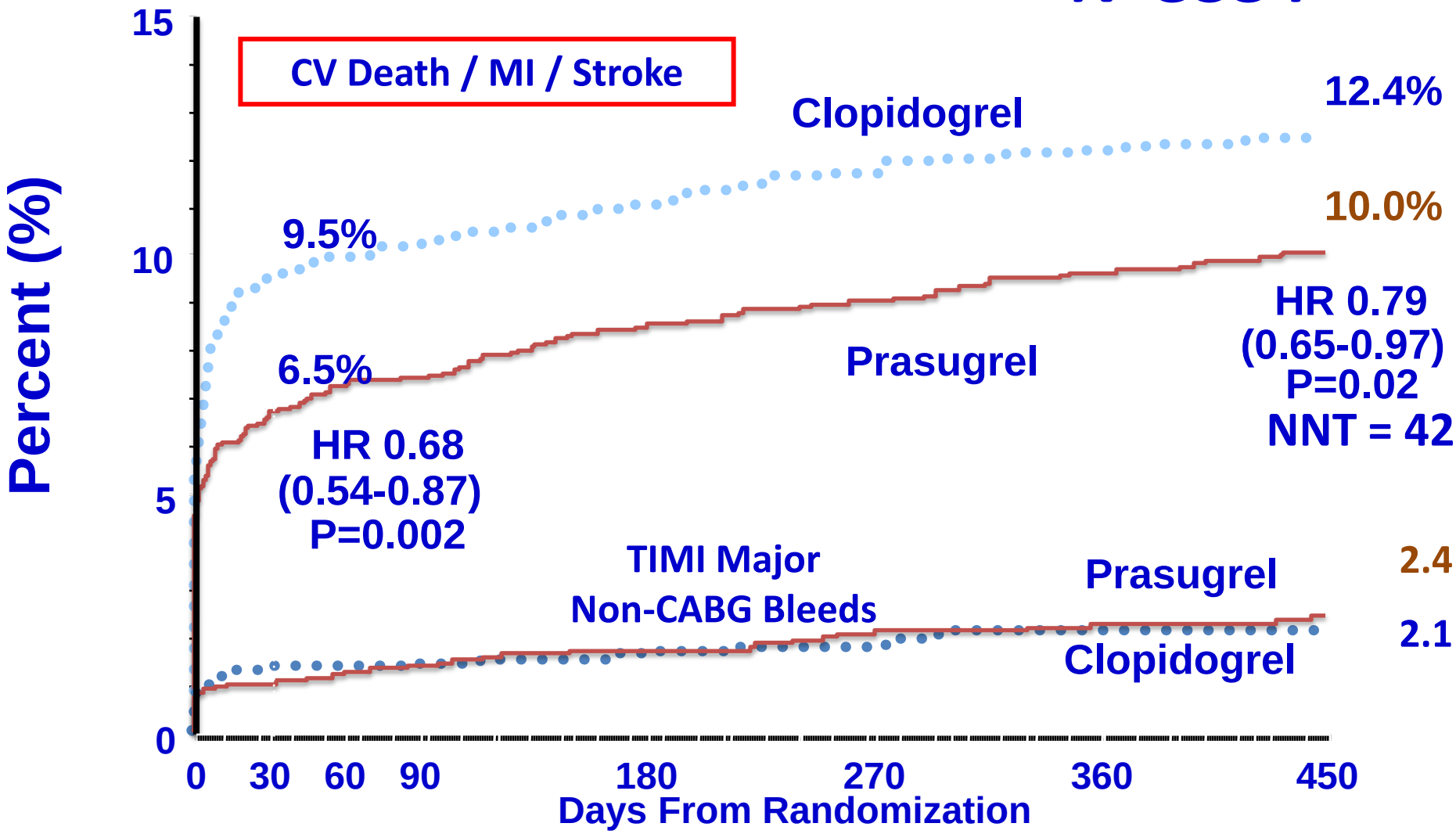
## N=3146




Adapted with permission from Wiviott SD et al NEJM 357:2007

# TRITON TIMI-38 STEMI Cohort

## N=3534




Adapted with permission from Wiviott SD et al NEJM 357:2007

# PLATO – study design

**ACS patients with UA/NSTEMI (moderate-to-high risk) STEMI (if primary PCI)**
**All receiving aspirin (75-100 mg daily); clopidogrel-treated or -naive;**
**randomized within 24 hours of index event**
**(N=18,624)**

| Clopidogrel | Ticagrelor |
|---|---|
| 300 mg loading dose (unless pretreated), then 75 mg od maintenance | 180 mg loading dose, then 90 mg bid maintenance |

**6-12 month exposure**
***Mean duration 277 days***

**Primary endpoint :** • **Composite of CV death, MI or stroke**

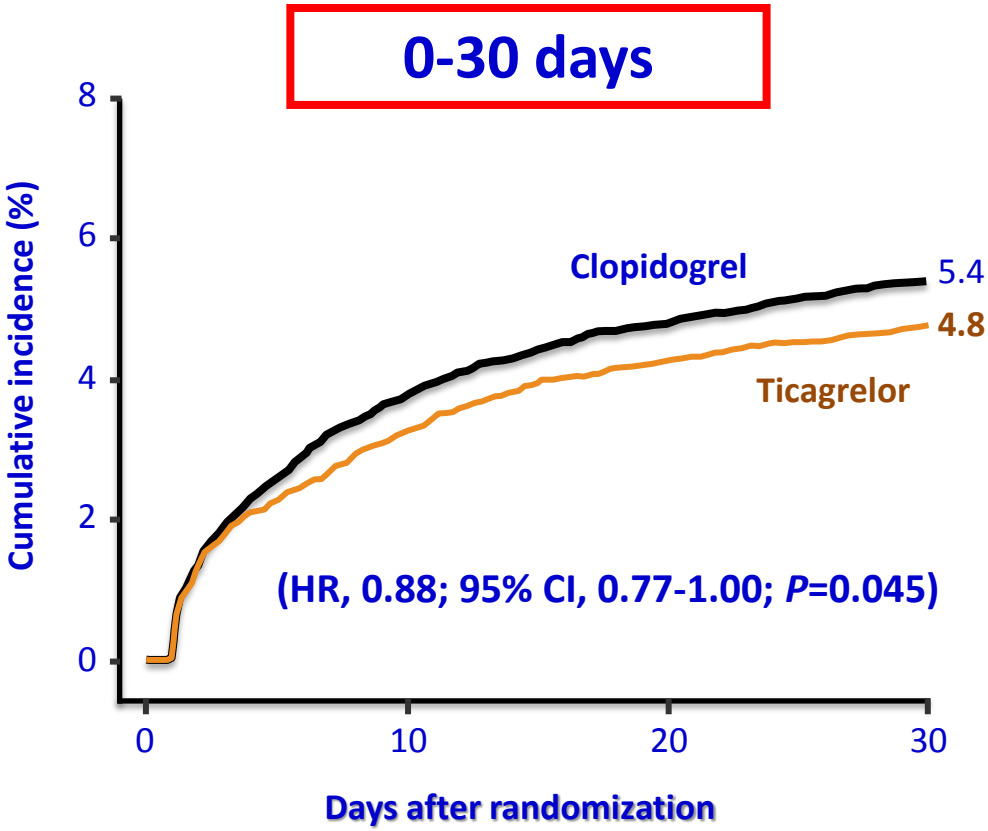
**Key secondary endpoints:**
- CV death, MI, stroke in patients intended for invasive management
- Total mortality, MI or stroke
- CV death, MI, stroke, recurrent ischemia , TIA or arterial thrombotic events
- Components of primary endpoint (CV death, MI and stroke)
- Death from any cause

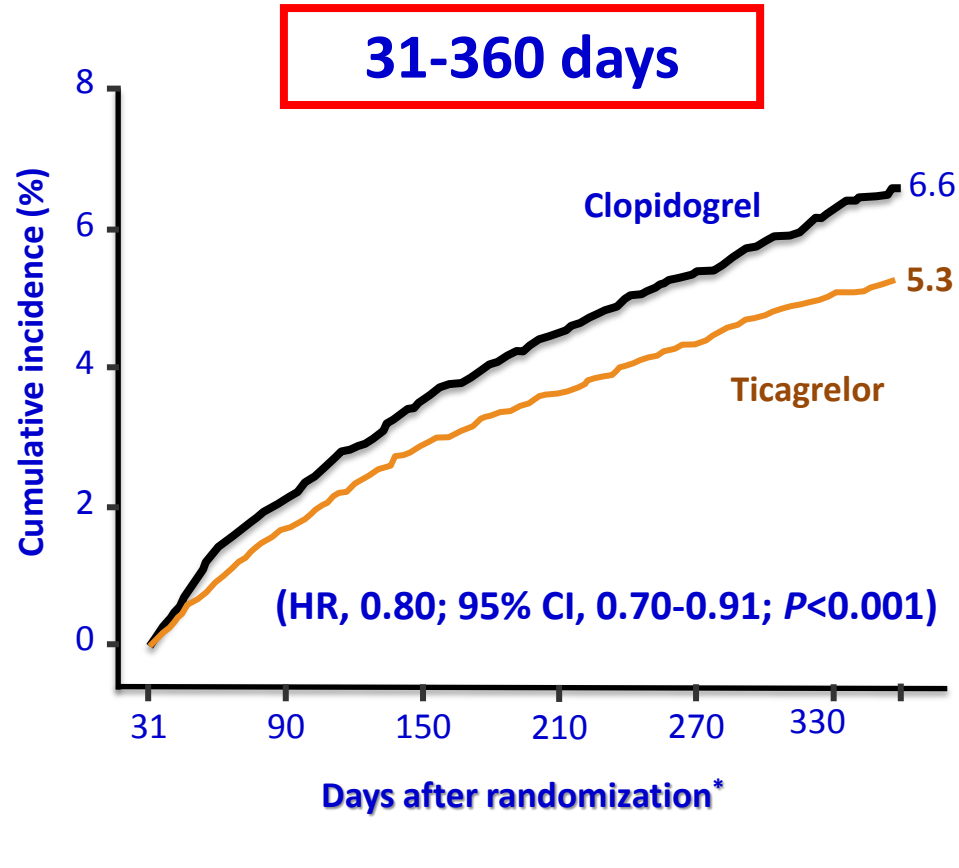
**Primary safety:** • **Total major bleeding**

Wallentin L, et al. N Engl J Med. 2009;361:1045-1057.

# PLATO: primary efficacy endpoint

## (composite of CV death, MI or stroke)

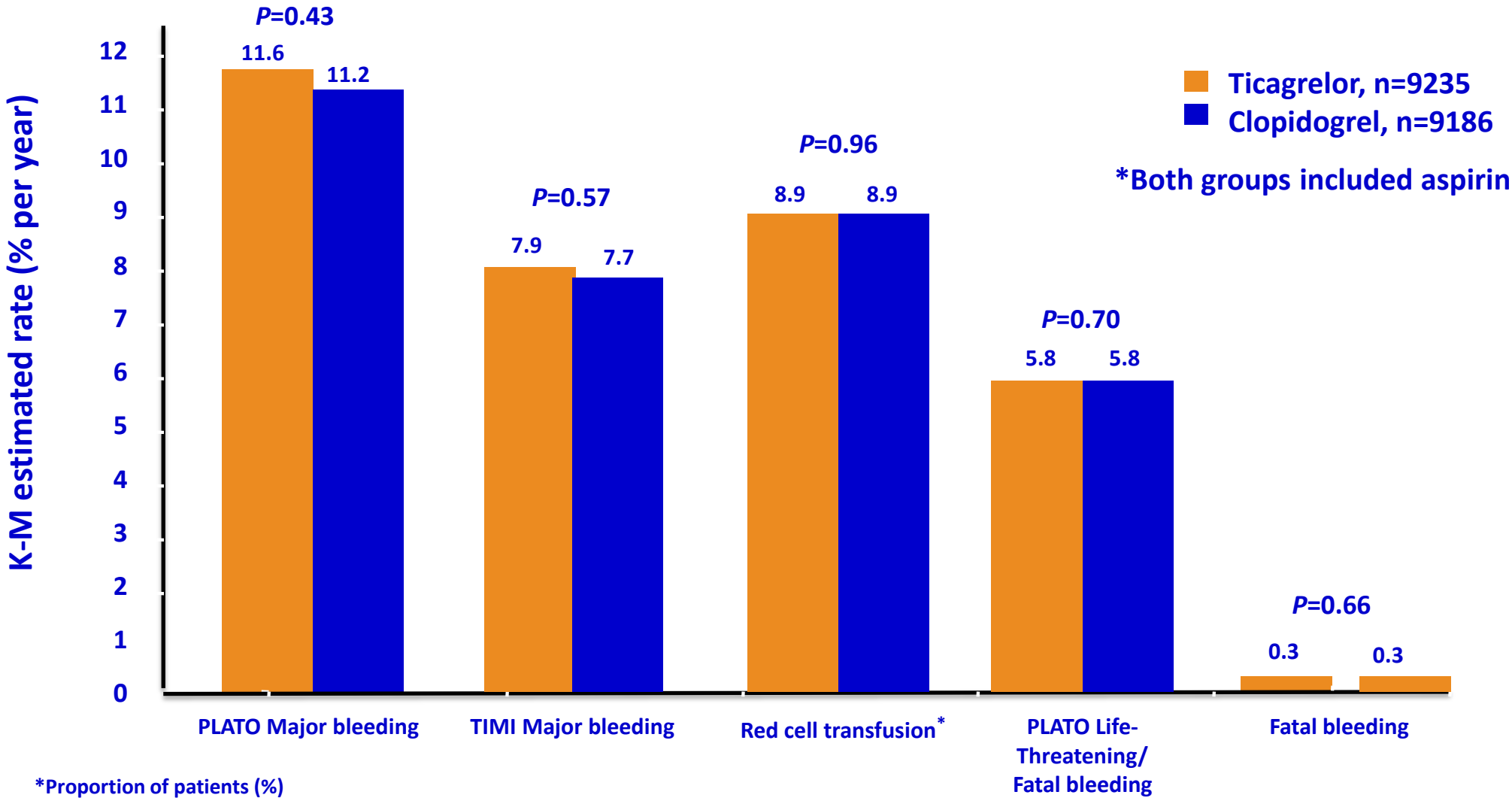



*Excludes patients with any primary event during the first 30 days

Wallentin L. Presented at the European Society of Cardiology Congress 2009, Barcelona, Spain. August 29-September 2

# PLATO: Major bleeding




*Proportion of patients (%)

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

# PLATO: minor bleedings

- As expected with a more potent antiplatelet therapy, there was an increase in bleeding with ticagrelor compared to clopidogrel

- PLATO-defined minor and non-CABG major bleeding was greater with ticagrelor than clopidogrel in this study

# Recommendations for oral antiplatelet agents (1)

| Recommendations | Class | Level |
|---|---|---|
| **Ticagrelor - Prasugrel<br>Both substances were clearly superior compared to clopidogrel and should be therefore preferred in patients with ACS** | | |
| Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced). | I | B |
| Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. | I | B |

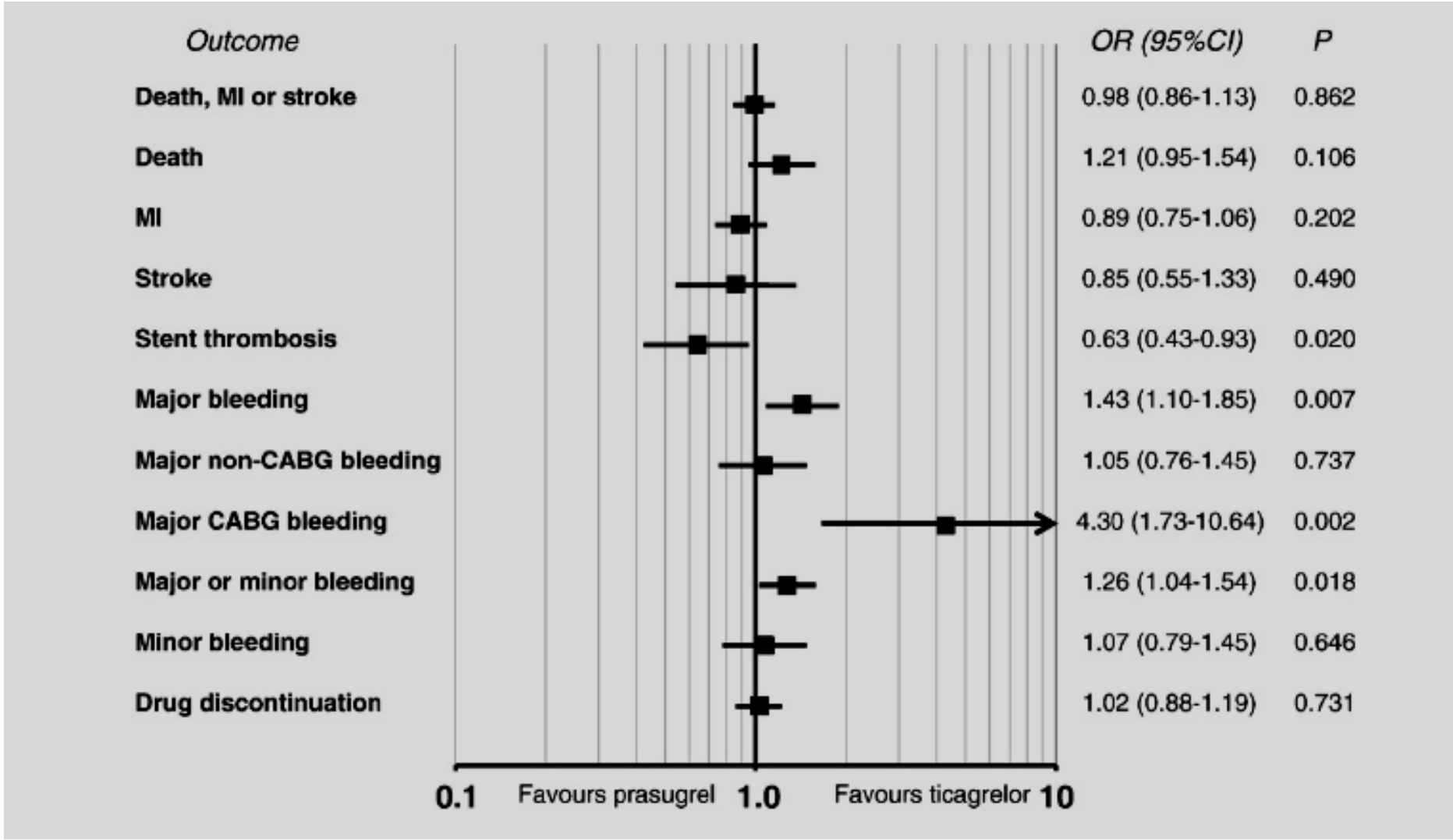
# Prasugrel vs. Ticagrelor in ACS

No prospective randomized study has directly compared efficacy as well as safety of prasugrel and ticagrelor so far

# Comparison of TRITON TIMI 38 and PLATO

| Clinical variable | TRITON | PLATO |
|---|---|---|
| Sample size (n) | 6,795 | 9,291 |
| ST-elevated MI (%) | 26 | 38 |
| Inclusion: defined coronary anatomy | Yes | No |
| CABG (%) | 1 | 4.7 |
| Pretreatment with clopidogrel (%) | 0 | 46.1 |
| Clopidogrel loading dose 600 mg+ (%) | 0 | >19.6 |
| Loading regimen for experimental agent | Yes, 6 : 1 | No, 1 : 1 |
| Glycoprotein IIb/IIIa inhibitor use (%) | 55 | 26.8 |
| Follow –up (months) | 6–15 | 12 |
| Switching to clopidogrel at the end of follow-up | Mandatory | Discretion of physician |

# Adjusted indirect comparison of prasugrel vs. ticagrelor



# Prasugrel vs. Ticagrelor
# Timing of Benefit

- Interestingly, ticagrelor showed a delayed treatment effect with significant reduction of the primary endpoint beyond 30 days
  - it has been suggested that the clopidogrel pretreatment is responsible for the delayed treatment effect
- Prasugrel had a favorable effect on outcome in the first 3 days as well as beyond

# Prasugrel vs. Ticagrelor - Mortality

- ✓The primary endpoint in the TRITON-TIMI-38 and PLATO trial was reduced to a similar extent
- ✓Ticagrelor reduced cardiovascular mortality (with an NNT of 91), whereas prasugrel had no favorable effect on death in the total patient cohort
- ✓The reason of lowering total and cardiovascular mortality with ticagrelor remains unclear; modulation of adenosine receptors may play an important role

# Prasugrel vs. Ticagrelor

While the entire prasugrel benefit in TRITON is exclusively attributed to the reduction of non fatal MIs, in PLATO, the mortality reduction (107 deaths) numerically exceeds the MI prevention benefit (89 events), and representing the major clinical outcome difference between the two trials

# Prasugrel vs. Ticagrelor – ST Thrombosis

- ✓Stent thrombosis was significantly reduced with prasugrel and ticagrelor compared to clopidogrel
  - ✓the NNT for prasugrel was 77, whereas the NNT for ticagrelor was 143; these data favoring prasugrel in lowering stent thrombosis
- ✓Consequently, one could favor prasugrel over ticagrelor in patients with a higher risk for stent thrombosis (e.g. small stent diameter, DM, "full metal jacket", etc.)
- ✓In this regard, one can be advocated to use prasugrel to prevent stent thrombosis and not only change after patients suffered a stent thrombosis

# Prasugrel vs. Ticagrelor – DM patients

- ✓Both substances were able to reduce the primary endpoint as well as important secondary endpoints compared to clopidogrel
  - ✓the NNT for prasugrel in patients with DM was 21,compared to 48 for ticagrelor
- ✓Therefore one may favor prasugrel over ticagrelor in patients with DM and an ACS as well as planned PCI
- ✓In this subset of patients, non-CABG related TIMI major bleedings were not increased with both substances

# Prasugrel vs. Ticagrelor – ACS Subsets

- In STEMI patients,there is a significant benefit for prasugrel vs. clopidogrel, which was not the case for ticagrelor
  - the NNT for prasugrel is 42 and for ticagrelor is 71
- Ticagrelor reduced the primary endpoint in NSTEMI, but had no effect in UA; prasugrel has effect on both
- The reduction in cardiovascular mortality could favor ticagrelor in NSTEMI patients

# Prasugrel vs. Ticagrelor - Bleeding

- ✓CABG-related TIMI major bleedings were significantly higher with prasugrel compared to clopidogrel (TRITON-TIMI-38); no significantly different in the PLATO study
- ✓Both substances increases nonCABG-related TIMI major bleedings to a similar degree
- ✓In patients with history of TIA/Stroke, age > 75 years, body weight < 60 Kg ticagrelor could be favored over prasugrel

# Prasugrel vs. Ticagrelor – Cancer

- ✓Cancer risks after prasugrel in TRITON are growing over time, especially in women, and results in 27% increase in colorectal, lung, and breast solid malignancies
- ✓Based on the CAPRIE, and CHARISMA trials, the FDA found no evidence that clopidogrel promotes cancer
- ✓Lack of a cancer signal in PLATO is reassuring, and will be an additional argument for future chronic use
- ✓If confirmed by regulatory agencies, differences in cancer risks will represent an extremely important finding favoring ticagrelor over prasugrel

# Ticagrelor – Side Effects

- ✓Ticagrelor has to be taken twice daily, therefore compliance may be an issue in daily clinical practice
- ✓The role of the side effects such as dyspnea and ventricular pauses as possible consequences of modulating adenosine receptors with ticagrelor is still unclear
- ✓In the PLATO study both side effects were significantly more often seen with ticagrelor especially in the early phase of treatment, but they seem to have no negative effect on the overall study results except a higher number of drug discontinuation

# Indications for Prasugrel

- Main indications for prasugrel are patients
  - at high-risk (diabetics, recurrent cardiovascular events) undergoing PCI
  - with acute STEMI referred for primary PCI
  - who exhibited stent thrombosis and re-infarction under chronic clopidogrel treatment
- Furthermore it seems to be safer in patients with chronic obstructive pulmonary disease and atrio-ventricular or intraventricular blockade

# Indications for Ticagrelor

- Based on the current knowledge typical indications for ticagrelor are patients
  - with UA/NSTEMI treated with conservative strategy, but also patients referred for invasive treatment
  - in patients with previous TIA/stroke, advanced age,small body surface which is a contraindication for prasugrel

# Final Thoughts (I)

- From indirect comparison of TRITON and PLATO trial data, ticagrelor is clearly superior to prasugrel for chronic preventive use because
  - of absolute mortality reduction
  - realistic second MI prevention
  - fewer hemorrhagic fatalities
  - potentially less CABG- related bleeding
  - lack of cancer risks

# Final Thoughts (II)

It will be wrong to assume that ticagrelor will completely substitute clopidogrel, especially considering higher discontinuation rates after ticagrelor, generic competition, and other health economics issues

Obviously, favourable safety profile and acceptable bleeding risks after clopidogrel represent a major driving force for broad use of this agent in a wide spectrum of patients with underlying vascular disease

# Thank you!