Randomised comparison of clopidogrel versus ticagrelor or prasugrel in patients of 70 years or older with non-ST-elevation acute coronary syndrome

POPular AGE trial

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Declaration of interest

- I have nothing to declare

Background

European Heart Journal
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ESC GUIDELINES

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

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

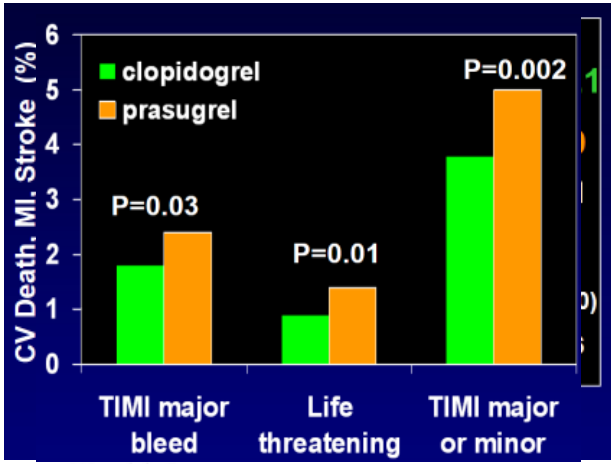
Roffi M. 2015 ESC EHJ. 2015.

TRITON-TIMI 38

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*



PLATO

The NEW ENGLAND JOURNAL of MEDICINE
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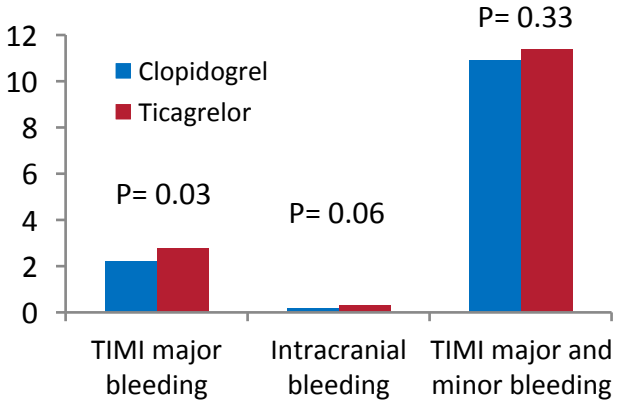
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

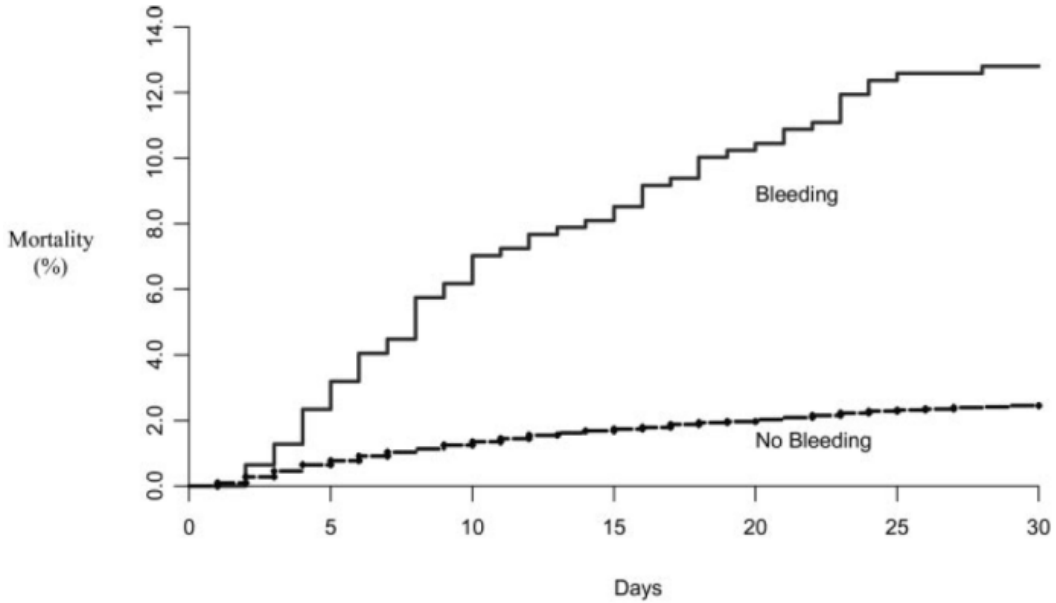
Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, 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*



Wiviott et al. NEJM. 2007;357:2001-15; Wallentin et al. NEJM. 2009;361:1045-57

Bleeding risk

- Major bleeding 5-fold increase in risk of death
- “Nuisance” bleeding → frequent discontinuation $P2Y_{12}$ inhibitor → thrombotic risk



Eikelboom et al. Circulation. 2006;114:774-782 2. Roy et al. AJC 2008;102:1614-1617

Underrepresentation of elderly in RCTs

- Elderly underrepresented
  - TRITON TIMI 38: 13% ≥ 75 years[1]
  - PLATO: 15% ≥ 75 years[2]

- Registry data: ~35% of NSTEMI population is ≥ 75 years[3,4]

- Selective inclusion of elderly in RCT's

1. Wiviott et al. NEJM. 2007;357:2001-15
2. Wallentin et al. NEJM. 2009;361:1045-57
3. De Luca et al. EHJ ACC 2015; 4:441-452
4. Hanssen et al. Heart 2012;98:699-705

Hypothesis

Clopidogrel is superior in reducing bleeding risk and non-inferior in net clinical benefit compared to ticagrelor/prasugrel in patients of 70 years or older with non-ST-elevation acute coronary syndrome

Design

- Randomized
- Open-label
- Independent, blinded clinical event committee
- Funding: ZonMw (*projectnumber: 836011016)*

  (*Dutch government institution*)

Participating centers

1. St. Antonius hospital, Nieuwegein - J.M. ten Berg
2. Isala, Zwolle - R.S. Hermanides
3. Meander Medical Center, Amersfoort - E.A. de Vrey
4. Noordwest hospital group, Alkmaar - A.A.C.M. Heestermans
5. Rijnstate, Arnhem - R.M. Tjon Joe Gin
6. Gelre, Apeldoorn - R.A. Waalewijn
7. Medical Center Leeuwarden - S.H. Hofma
8. Gelderse Vallei hospital, Ede - F.R. den Hartog
9. University Medical Center Leiden - J.W. Jukema
10. Medical Spectrum Twente, Enschede - C. von Birgelen
11. University Medical Center Utrecht - M. Voskuil

Design

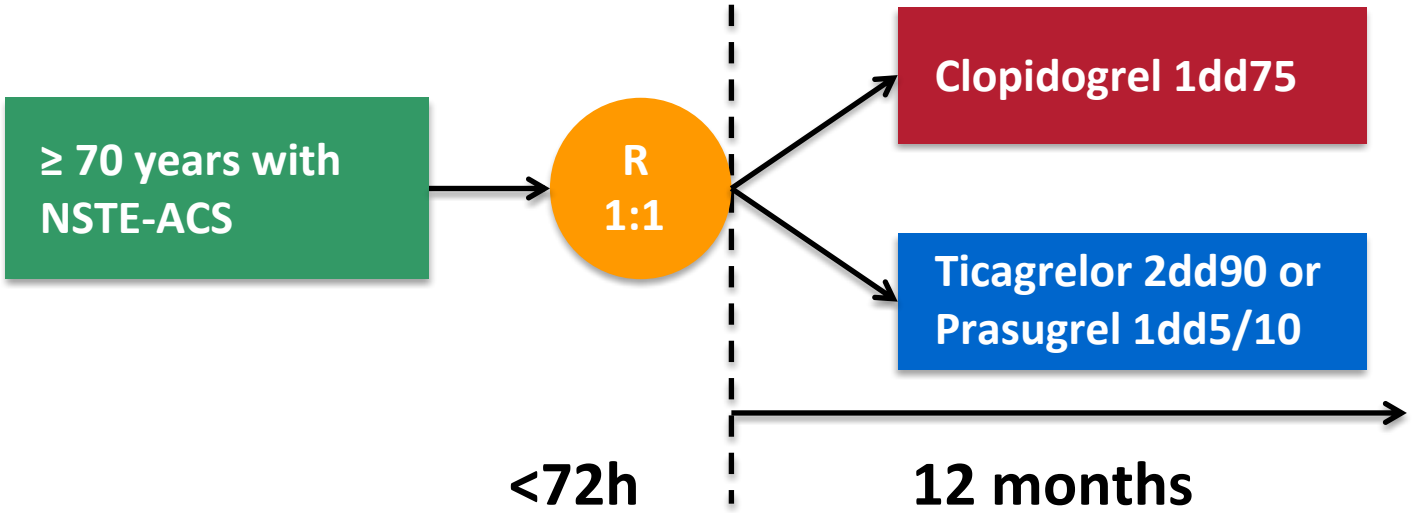
Inclusion criteria

- Age ≥ 70 years
- Admitted with NSTE-ACS

Key exclusion criteria

- Contraindication $P2Y_{12}$ inhibitors
- DAPT use prior to admission
- Indication for major surgery
- Life expectancy < 1 year

Design



- Reloading
- Choice ticagrelor or prasugrel

} according to local protocol

Primary endpoint

- PLATO major and minor bleeding

- Net clinical benefit:

  All-cause death, MI, stroke, PLATO major and minor bleeding

Sample size calculation

- Clopidogrel superior in reducing PLATO major and minor bleeding

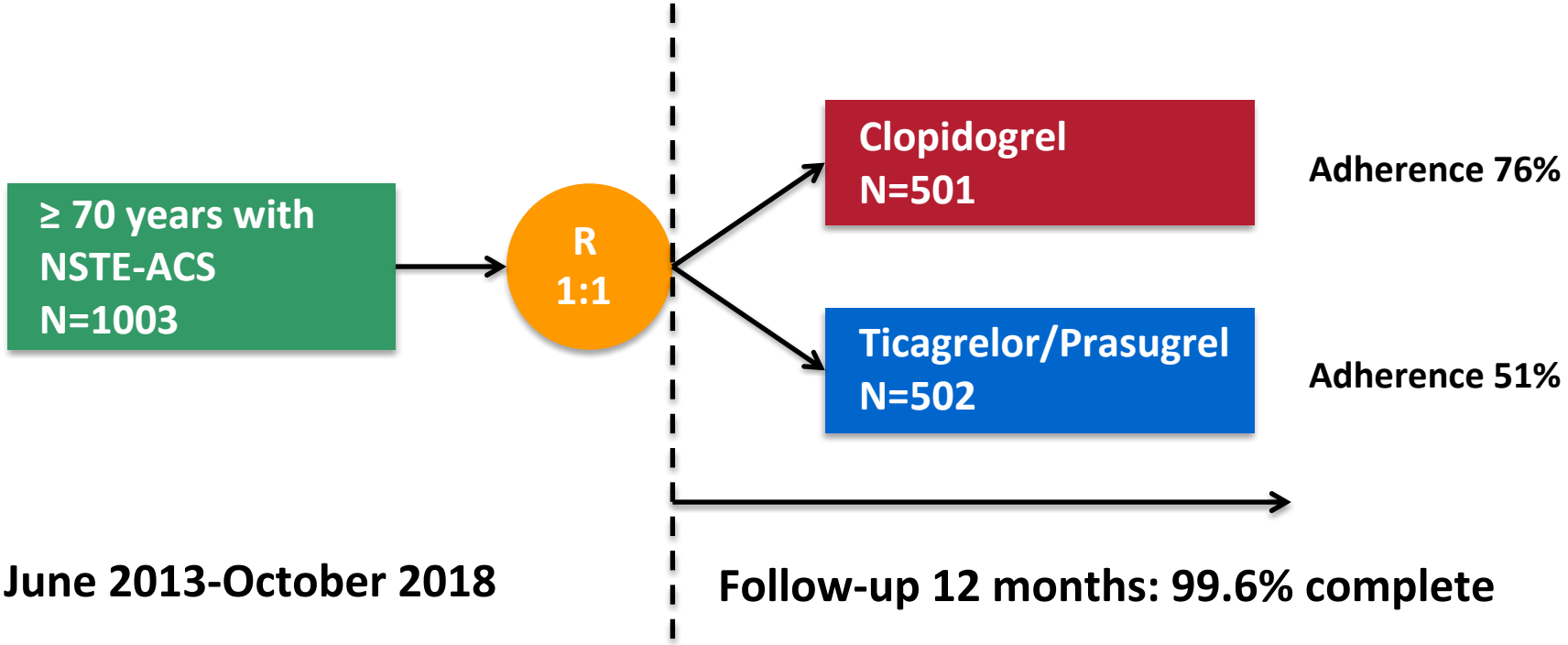
✓ *Event rate 10% vs. 17%, 80% power, α 0.05 → n=821*

- Clopidogrel non-inferior in net clinical benefit

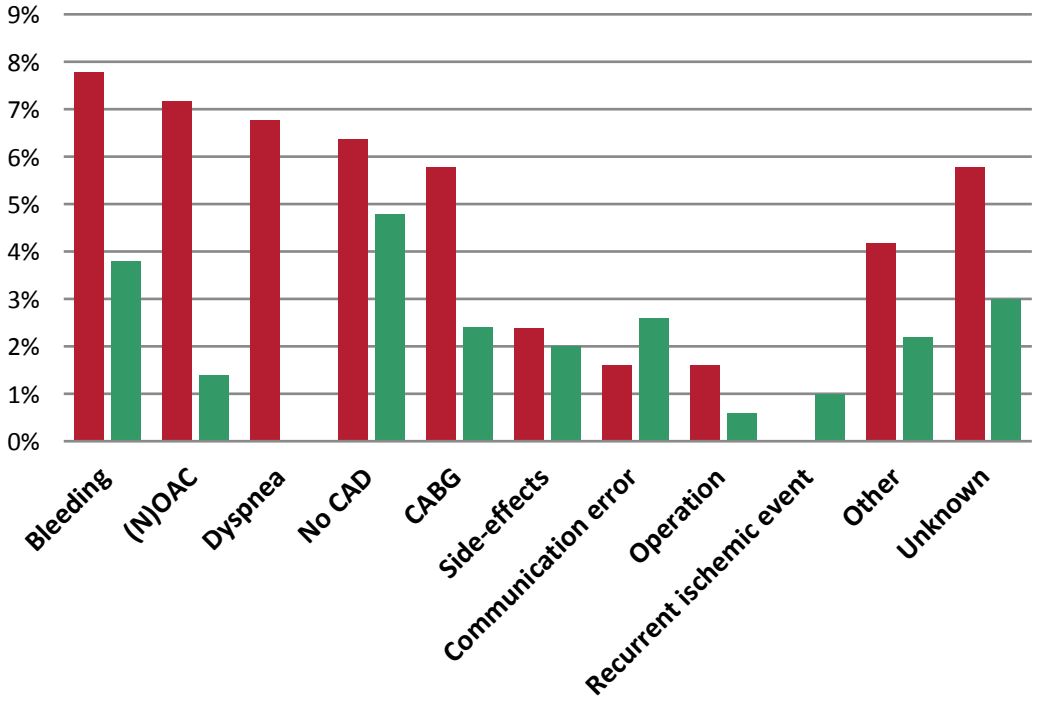
✓ *Event rate 30.8% vs. 36.0%, 80% power, α 0.05, non-inferiority threshold **2%** → n=1000*

1. Wiviott et al. NEJM. 2007;357:2001-15
2. Wallentin et al. NEJM. 2009;361:1045-57
3. Dewilde et al. Lancet 2013;381:1107-15

Participants and adherence



Reasons for switching and discontinuing study medication



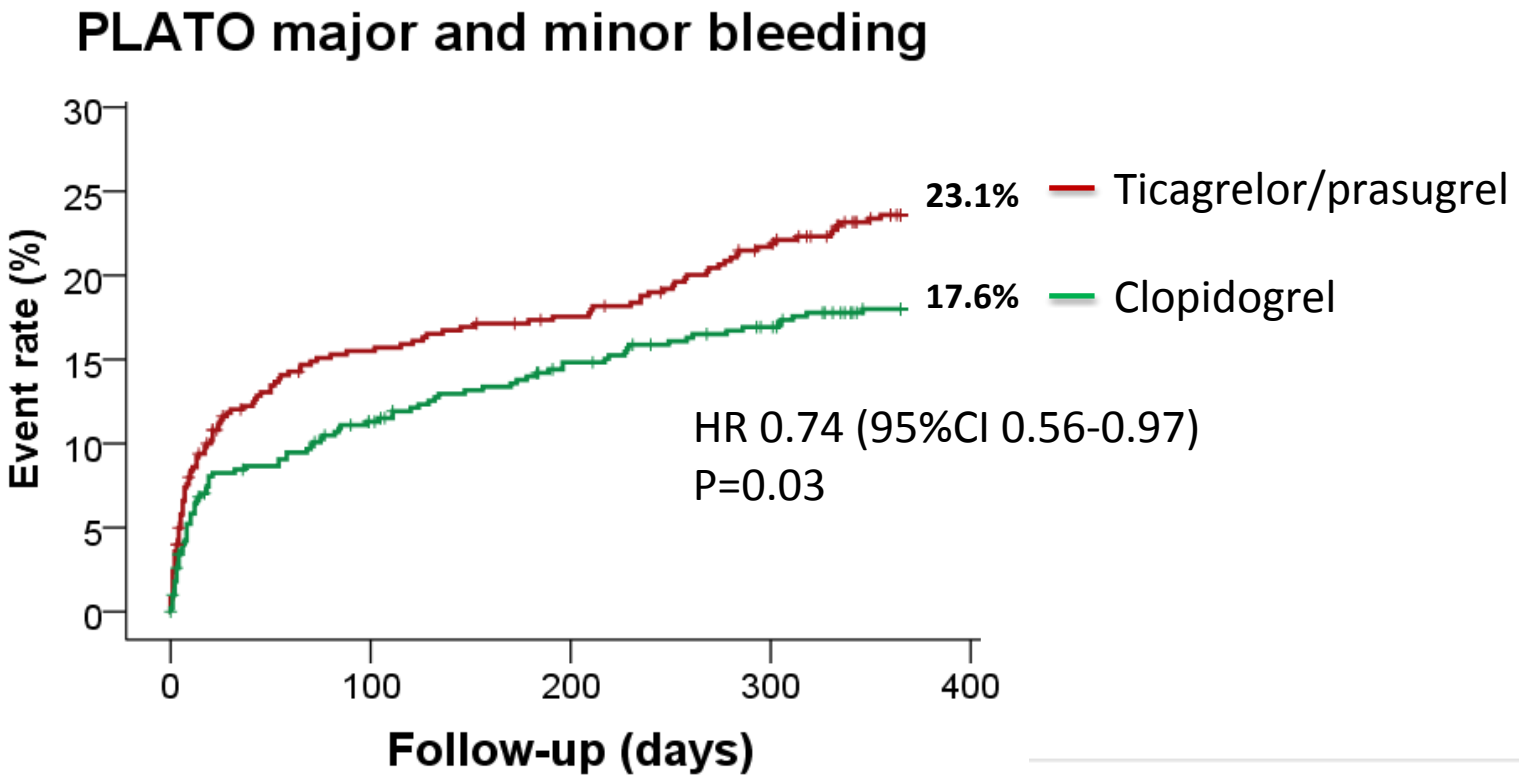
Baseline characteristics

	Clopidogrel (n=501)	Ticagrelor/prasugrel (n=502)
Age (years), median (IQR)	77 (73-81)	77 (73-82)
Male	62.7	64.7
BMI (kg/m^2), mean (SD)	26.5 ± 4.4	26.7 ± 4.8
Myocardial infarction	24.4	27.1
PCI	19.6	24.3
CABG	17.0	17.1
Ischemic stroke	4.4	5.0
Diabetes mellitus	29.1	29.9
eGFR <60 (ml/min/1.73m^2)	36.1	37.3
CAG	87.8	90.0
Radial access	73.7	77.1
PCI	47.5	48.9
CABG	15.8	17.4

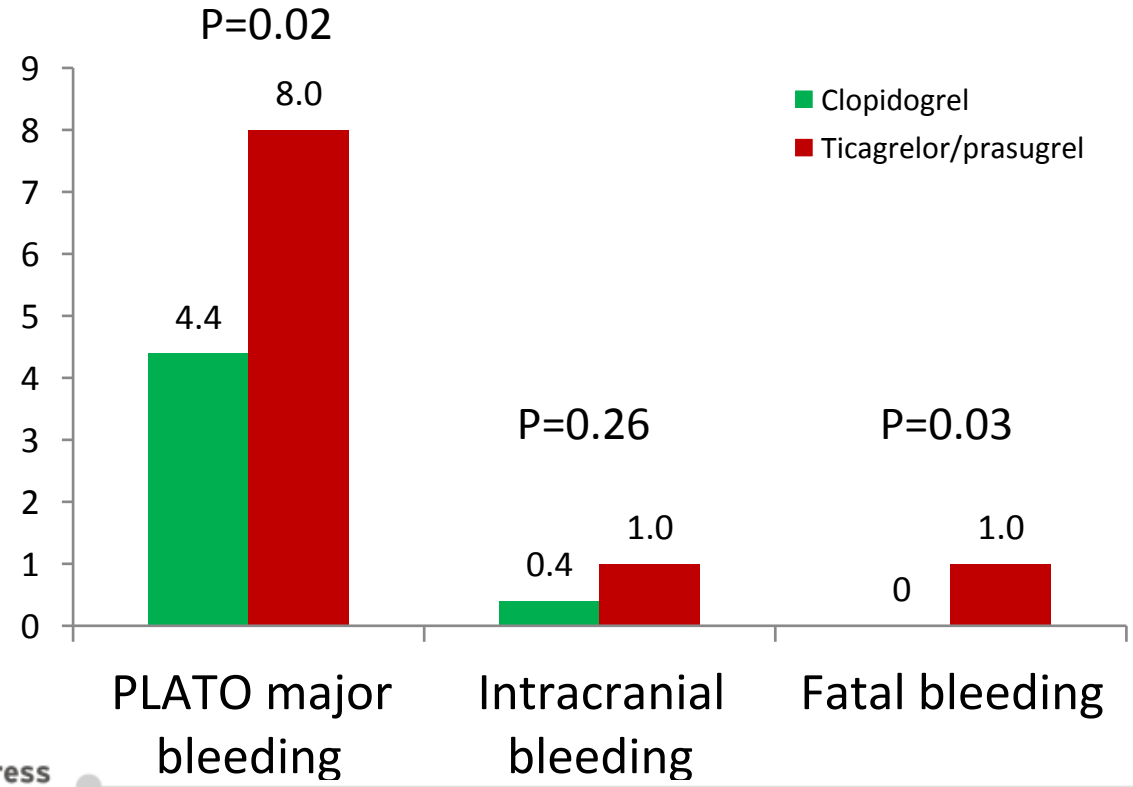
Baseline characteristics

	Clopidogrel (n=501)	Ticagrelor/prasugrel (n=502)
Aspirin	85.8	85.6
(N)OAC	16.6	20.3
Ticagrelor		93.8
Prasugrel		2.0
PPI	90.3	90.3
Diagnosis at discharge		
NSTEMI	84.6	83.9
UA	10.8	10.4
Other	4.4	5.7

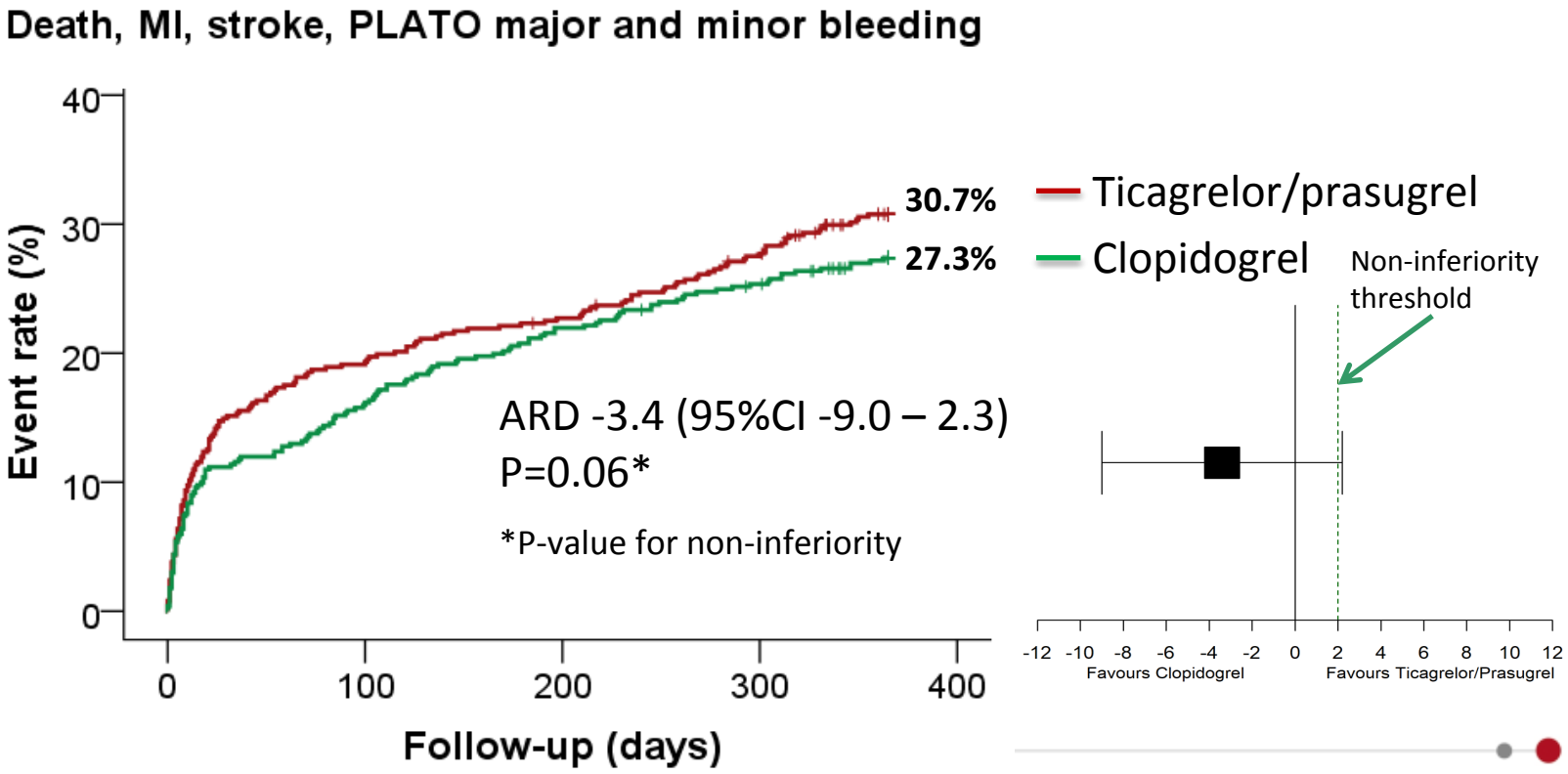
Primary safety outcome



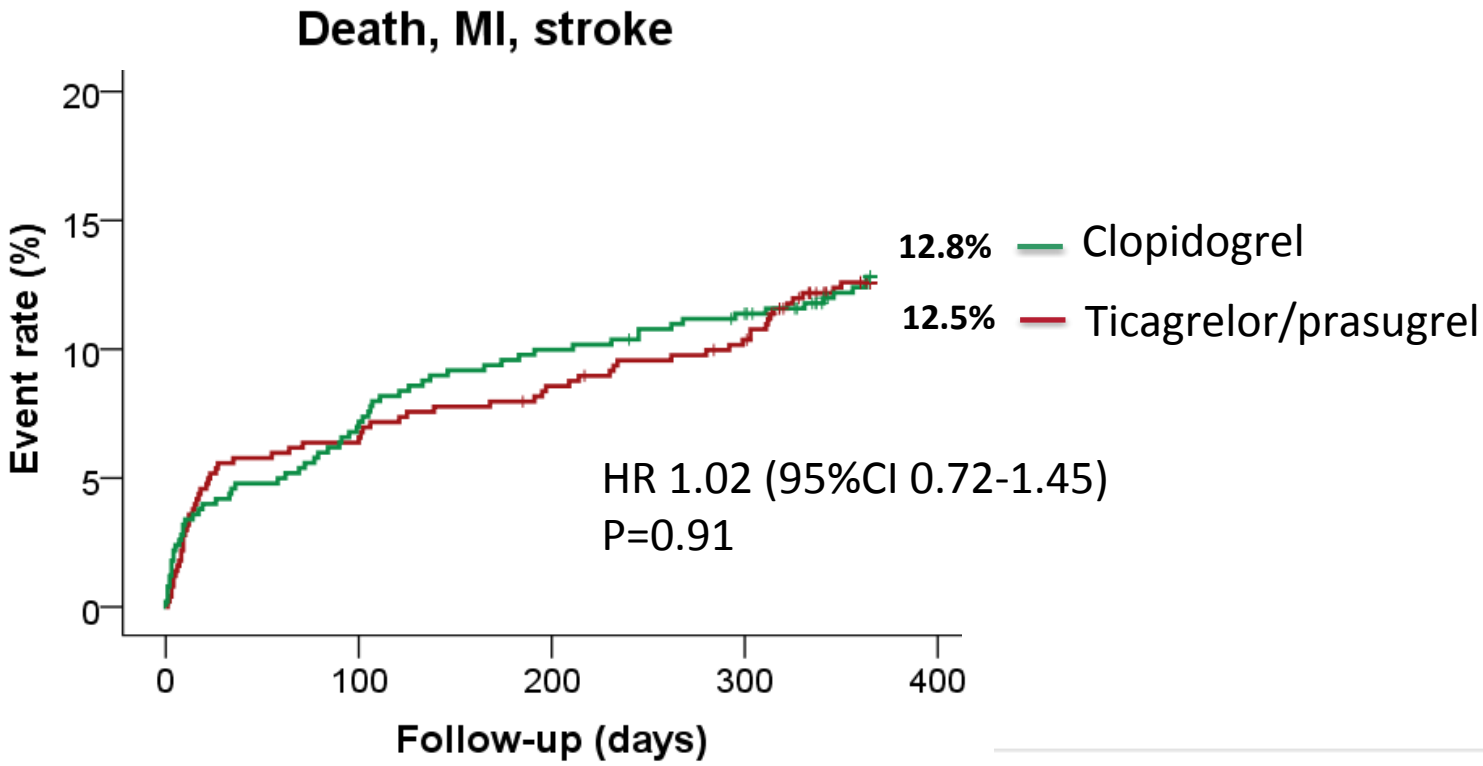
Secondary safety outcomes



Co-primary net clinical benefit outcome

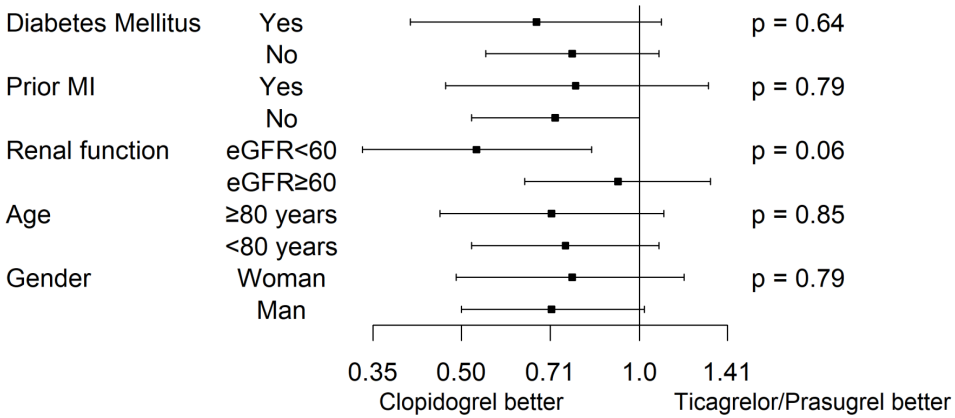


Secondary efficacy outcome

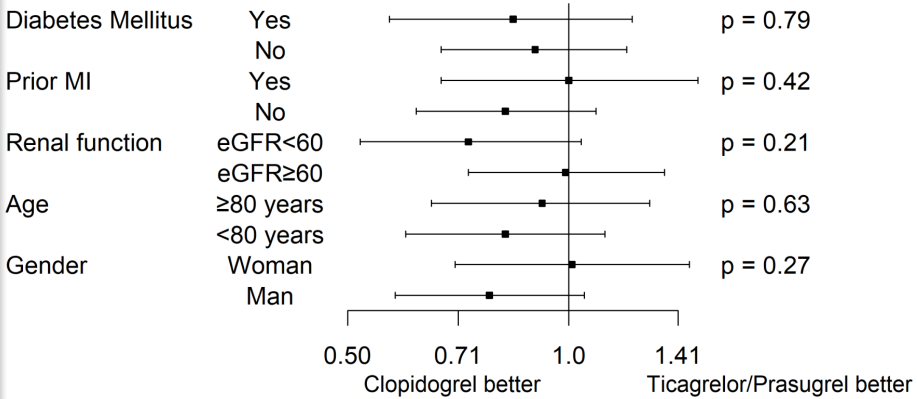


Subgroup analysis

PLATO major and minor bleeding



Net clinical benefit



P-value for interaction

Conclusion

- Compared to ticagrelor/prasugrel in the POPular AGE trial we conclude:
  - Clopidogrel significantly less bleeding
  - Clopidogrel similar in preventing thrombotic events
- Therefore, we consider clopidogrel the preferred treatment in patients ≥ 70 years with NSTE-ACS

Thank you for your attention

We would like to thank:

- All study patients
- Data Safety Monitoring Board
  - Dr. T. Plokker (chair)
  - Prof. dr. J. G.P. Tijssen
  - Prof. dr. F. Verheugt
- Clinical Event Committee
  - Dr. B.M. Swinkels
  - Dr. E. Bal
  - Dr. C. Zivelonghi
  - Dr. W. Jaarsma
- The POPular AGE study group
  - L.M. Willemsen, R.S. Hermanides, E.A. de Vrey, A.A.C.M. Heestermans, R.M. Tjon Joe Gin, R.A. Waalewijn, S.H. Hofma, F.R. den Hartog, J.W. Jukema, C. von Birgelen, M. Voskuil, J.C. Kelder, V.H.M. Deneer, J.M. ten Berg

Secondary endpoints

	Clopidogrel	Ticagrelor/Prasugrel	HR (95% CI)	p-value
All-cause death	7.4	6.8	1.09 (0.68-1.74)	0.72
CV death	4.0	3.4	1.18 (0.62-2.25)	0.62
MI	6.2	6.2	1.01 (0.61-1.66)	0.97
iCVA	1.0	2.0	0.50 (0.17-1.46)	0.20
Stenttrombose	1.0	0	65.77 (0.05-87308.30)	0.03
PLATO minor	11.6	14.9	0.75 (0.53-1.06)	0.10
PLATO other major	4.8	5.6	0.86 (0.50-1.48)	0.59
PLATO major life threatening	3.2	5.2	0.62 (0.33-1.15)	0.12
PLATO non-CABG related major	4.4	8.0	0.55 (0.33-0.92)	0.02
TIMI non-CABG related major	1.4	3.4	0.41 (0.17-0.99)	0.04
TIMI major or minor bleeding	5.2	9.2	0.56 (0.35-0.91)	0.02
ICH	0.4	1.0	0.40 (0.08-2.07)	0.26
Fatal	0	1.0	0.02 (0-20.41)	0.03

Additional information (1)

Duration from admittance until receiving the fist dosis of study medication:

- Clopidogrel median 40 (IQR 7-56)
- Ticagrelor/prasugrel median 3 (IQR 1-29)

Duration from admittance until randomization:

- Clopidogrel median 26 (IQR 18-49)
- Ticagrelor/prasugrel median 27 (IQR 18-48)

Mean duration of exposure to study drug was 253±155 days.

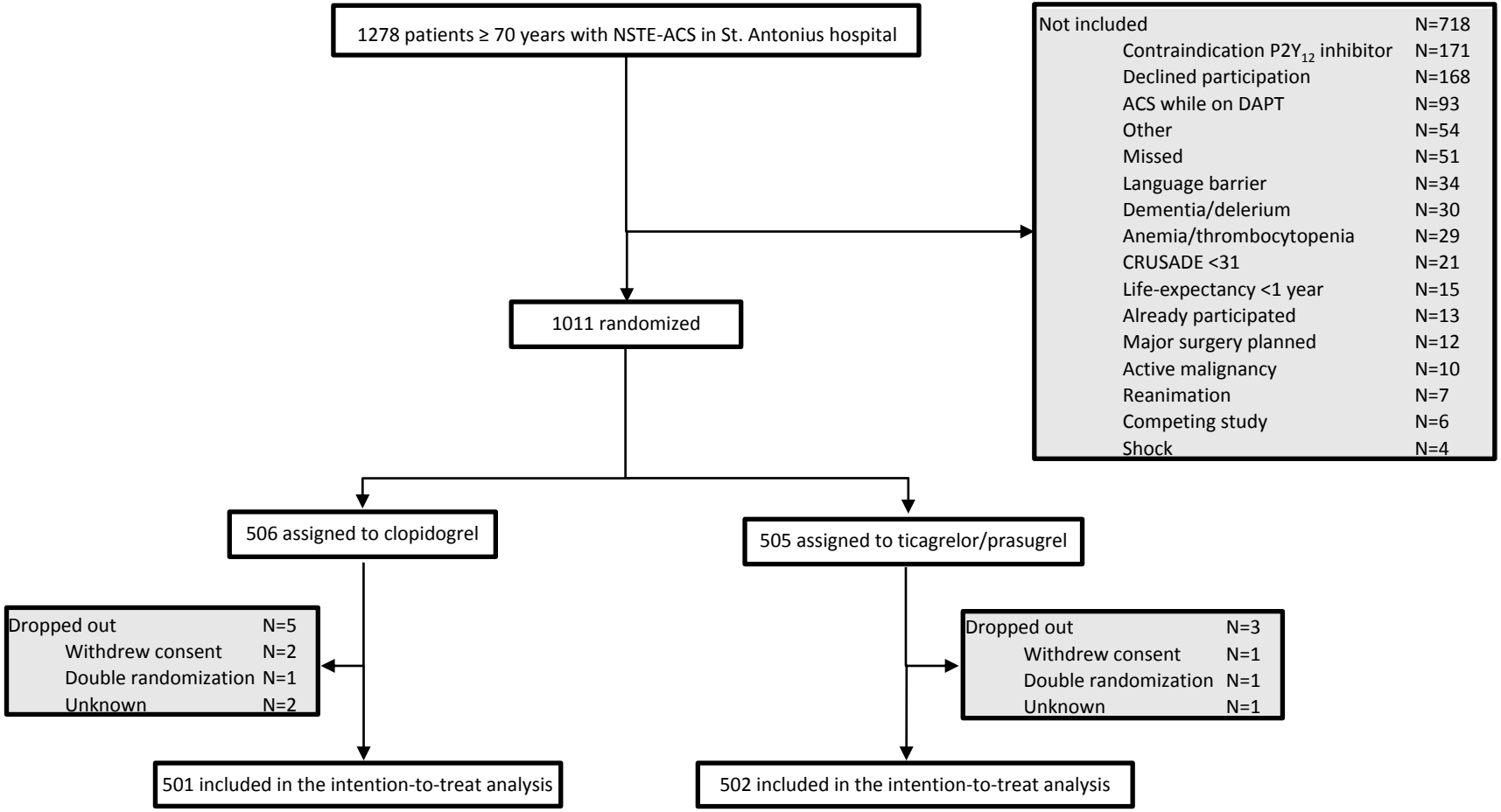
Additional information (1I)

97,6% already received a P2Y12 inhibitor before randomization

- Clopidogrel: 71% had to switch after randomization → 30% reloaded
- Ticagrelor/prasugrel: 29% had to switch after randomization → 14% reloaded

Loading dosages of clopidogrel

- 300mg: 41%
- 600mg: 57%


1278 patients ≥ 70 years with NSTE-ACS in St. Antonius hospital
Not included N=718
Contraindication P2Y12 inhibitor N=171
Declined participation N=168
ACS while on DAPT N=93
Other N=54
Missed N=51
Language barrier N=34
Dementia/delerium N=30
Anemia/thrombocytopenia N=29
CRUSADE <31 N=21
Life-expectancy <1 year N=15
Already participated N=13
Major surgery planned N=12
Active malignancy N=10
Reanimation N=7
Competing study N=6
Shock N=4
1011 randomized
506 assigned to clopidogrel
505 assigned to ticagrelor/prasugrel
Dropped out N=5
Withdrew consent N=2
Double randomization N=1
Unknown N=2
Dropped out N=3
Withdrew consent N=1
Double randomization N=1
Unknown N=1
501 included in the intention-to-treat analysis
502 included in the intention-to-treat analysis