CHANGE DAPT

Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents

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On behalf of the CHANGE DAPT Study Investigators

ESC CONGRESS BARCELONA 2017 #esccongress www.escardio.org/ESC2017

Conflicts of Interest

Speaker's name: Clemens von Birgelen

I have the following potential conflicts of interest to report:

- ❑ **Institutional research grants or research support** were received from **AstraZeneca, Biotronik, Boston Scientific, and Medtronic.**

- ❑ **Speakers honoraria:**

  Honoraria are requested to be directly donated to the humanitarian non-governmental organization **"Médecins Sans Frontières (MSF)/ Doctors Without Borders",** best known for its projects in war-torn regions and developing countries affected by endemic diseases.

  - www.msf.org
  - www.doctorswithoutborders.org

Background

- Contemporary guidelines[1,2] recommend ticagrelor over clopidogrel as part of the primary dual antiplatelet therapy (DAPT) regimen for *all* patients with acute coronary syndromes (ACS).
- This is based on the PLATO[3] trial, in which ticagrelor-treated *moderate-to-high risk* ACS pts. had:
  - Fewer ischemic events (i.e. lower vascular death and MI rate);
  - More major bleedings, unrelated to coronary artery bypass grafting (CABG).
- However, in the PLATO[3] trial:
  - Many patients were treated without any revascularization (medical therapy only) or by CABG;
  - Patients treated by PCI (approximately 65 % PLATO pts.) received either bare metal stents (> 60 %) or - mostly older-generation - drug-eluting stents (DES) (< 40 %).
- In current clinical routine, most ACS patients are treated with newer-generation DES, which have demonstrated in various studies improvements in clinical outcome as compared to early DES.

1. Steg et al. **Eur Heart J** 2012; 33: 2569-2619
2. Roffi et al. **Eur Heart J** 2016; 37: 267-315
3. Wallentin et al. **N Engl J Med** 2009; 361: 1045-57

Aim

To evaluate, in a consecutive series of real-world ACS patients treated by PCI with newer-generation DES, the impact of the guideline-recommended change in primary DAPT regimen (i.e. *from clopidogrel- to ticagrelor-based DAPT*) on 1-year clinical outcome.

Twente & Thoraxcentrum Twente

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BARCELONA 2017

Twente is the name of a region in the Eastern Netherlands, well-known for its beautiful landscapes, stately castles, ground-breaking technology, and infectiously innovative spirit.

Thoraxcentrum Twente, is located in the heart of Enschede, the largest city of the region. The research department of TC Twente conducts the **TWENTE trials** in cooperation with other medical centers and **University of Twente**.

Source of images: on the left hand side Wikipedia, on the right hand side MST, Enschede, NL

CHANGE DAPT

Investigator-initiated observational study

Inclusion criteria

- Age ≥ 18 years
- Presented with ACS
- Treated by PCI with newer-generation DES

Exclusion criteria

- Known pregnancy
- Life expectancy < 1 year
- Planned surgery, necessitating interruption of DAPT during first 6 months
- Known intolerance to DES
- Use of oral anticoagulation therapy

Consecutive ACS patients, treated by PCI at Thoraxcentrum Twente, the Netherlands

Primary DAPT regimen changed on May 1, 2014

Clopidogrel Period (CP)
December 21, 2012 – April 30, 2014

Ticagrelor Period (TP)
May 1, 2014 – August 25, 2015

Outcome at 1-year follow-up:

- **Primary endpoint: Net Adverse Clinical and Cerebral Events (NACCE)**
  All-cause death, any MI, stroke, or major bleeding (BARC class 3 or 5 and/or TIMI major)
- **Secondary endpoints:**
  Individual components of NACCE – any revascularization – stent thrombosis – composite of cardiac death, MI, or stroke

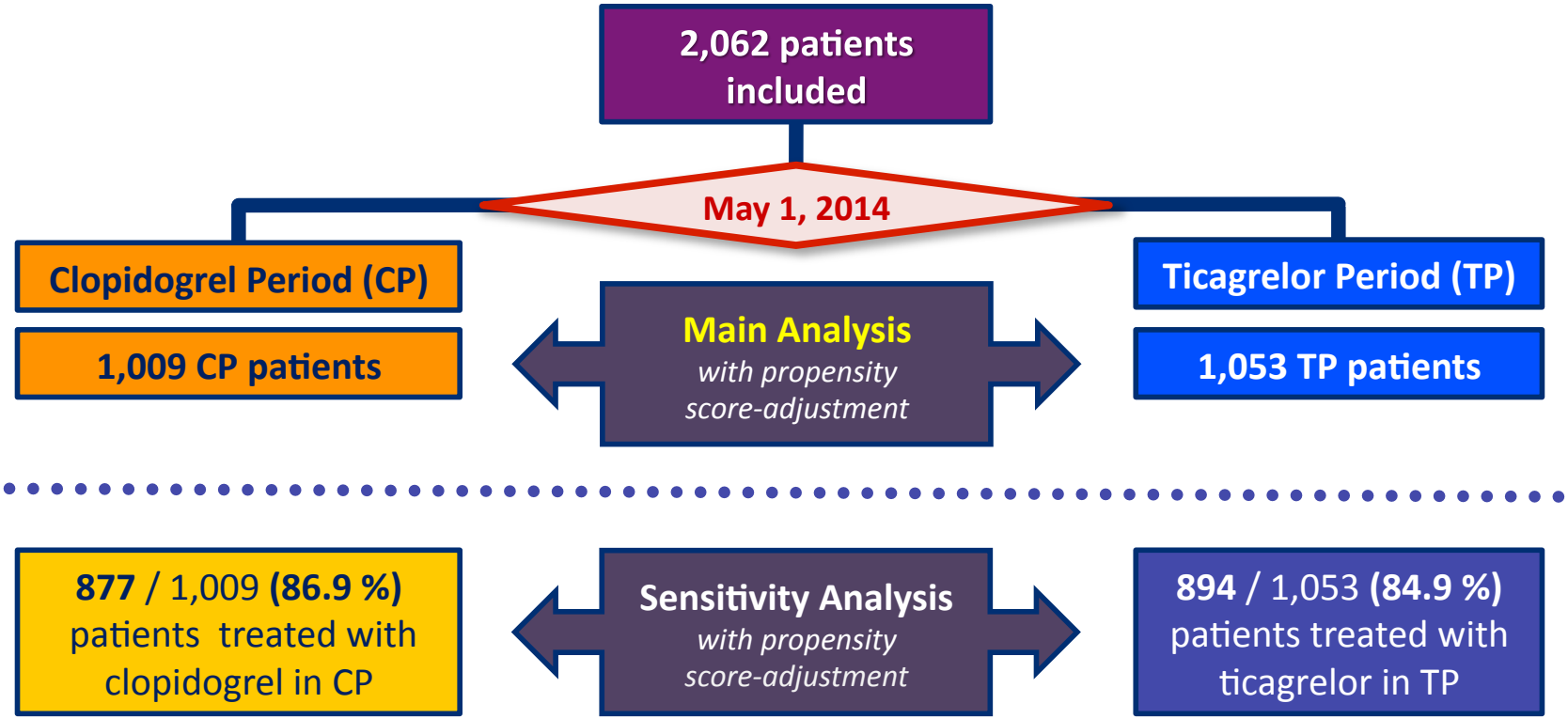
Definitions of clinical endpoints according to (Bleeding) Academic Research Consortium and Thrombolysis in Myocardial Infarction criteria. Clinicaltrials.gov: NCT03197298

Sample Size for Assessment of Non-Inferiority Hypothesis

- The sample size was calculated assuming a NACCE rate of 6.5% at 1-year follow-up based on data of the OPTIMIZE[1], TWENTE[2], and DUTCH PEERS[3] trials, with the non-inferiority margin set at 2.7%, as in OPTIMIZE[1].
- A sample size of 1,031 patients per group (i.e. treatment period) would yield a power of at least 80% to detect non-inferiority with a one-sided alpha level of 0.05.

1. Feres et al. **JAMA** 2013; 310:2510-22
2. von Birgelen et al. **JACC** 2012; 59:1350-61
3. von Birgelen et al. **Lancet** 2014; 383:413-23

Study Flow and Analyses



Clopidogrel in CP and ticagrelor in TP = clopidogrel in CP and ticagrelor in TP, respectively, at discharge or at the time of NACCE before discharge

Baseline Characteristics

	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	P
Age (years)	62.9 ± 11.6	63.9 ± 12.1	0.04
Male sex	702 (69.6%)	748 (71.0%)	0.47
BMI (kg/m^2)	27.4 ± 4.3	27.7 ± 4.4	0.13
Clinical history			
Hypertension	428 (42.4%)	440 (41.8%)	0.77
Hypercholesterolemia	360 (35.7%)	384 (36.5%)	0.71
Diabetes mellitus	158 (15.7%)	186 (17.7%)	0.22
Peripheral artery disease	89 (8.8%)	58 (5.5%)	0.003
Chronic obstructive pulmonary disease	78 (7.7%)	83 (7.9%)	0.90
Previous myocardial infarction	146 (14.5%)	151 (14.3%)	0.93
Previous percutaneous coronary intervention	166 (16.5%)	174 (16.5%)	0.97
Previous coronary artery bypass surgery	72 (7.1%)	63 (6.0%)	0.29
Previous stroke	32 (3.2%)	31 (2.9%)	0.76
Previous gastro-intestinal bleeding	11 (1.1%)	15 (1.4%)	0.50
Renal insufficiency	40 (4.0%)	38 (3.6%)	0.67
Clinical presentation			
ST-elevation myocardial infarction	452 (44.8%)	434 (41.2%)	0.10
Non-ST-elevation myocardial infarction	256 (25.4%)	292 (27.7%)	0.23
Unstable angina	301 (29.8%)	327 (31.1%)	0.55

Values are n (%) or mean ± standard deviation

Procedural Characteristics

	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	P
Vascular access			< 0.001
Radial	179 (17.7%)	470 (44.6%)	-
Femoral	830 (82.3%)	583 (55.4%)	-
Vessel disease			0.35
1	550 (54.4%)	603 (57.3%)	-
2	310 (30.7%)	294 (27.9%)	-
3	149 (14.8%)	156 (14.8%)	-
Multivessel treatment	176 (17.4%)	181 (17.2%)	0.88
Glycoprotein IIb/IIIa-inhibitor use	441 (43.7%)	260 (24.7%)	< 0.001
Stent type			0.21
Sirolimus-eluting cobalt chromium stent	268 (26.6%)	290 (27.5%)	-
Zotarolimus-eluting cobalt chromium stent	426 (42.2%)	455 (43.2%)	-
Everolimus-eluting platinum chromium stent	307 (30.4%)	306 (29.1%)	-
Other newer-generation DES	8 (0.8%)	2 (0.2%)	-

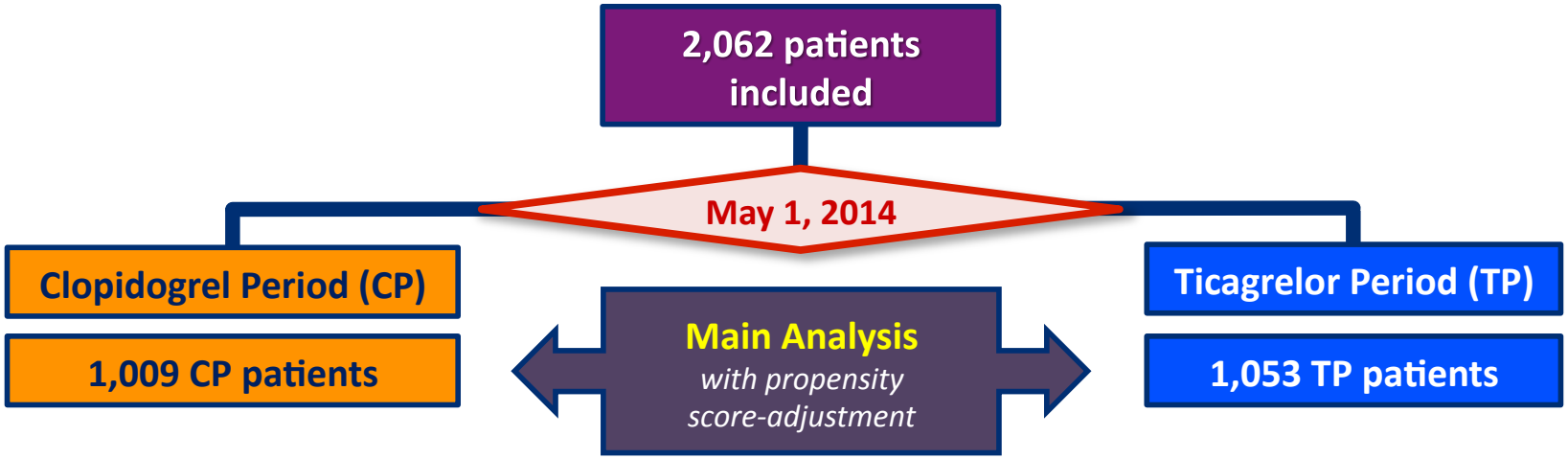
Values are n (%)

Medication

	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	P
At discharge			
Clopidogrel	877 (86.9%)	159 (15.1%)	-
Ticagrelor	132 (13.1%)	894 (84.9%)	-
Aspirin	1,009 (100%)	1,053 (100%)	-
Non-steroidal anti-inflammatory drugs	20 (2.0%)	16 (1.5%)	0.42
Proton pump inhibitors	430 (42.6%)	580 (55.1%)	< 0.001
At 1-year follow-up			
DAPT	916 (90.8%)	947 (89.9%)	0.69
with Clopidogrel	794 (78.7%)	184 (17.5%)	-
with Ticagrelor	122 (12.1%)	763 (72.5%)	-
Aspirin	944 (93.6%)	982 (93.3%)	0.66
Oral anticoagulant + $P2Y_{12}$-inhibitor	42 (4.2%)	30 (2.9%)	0.20

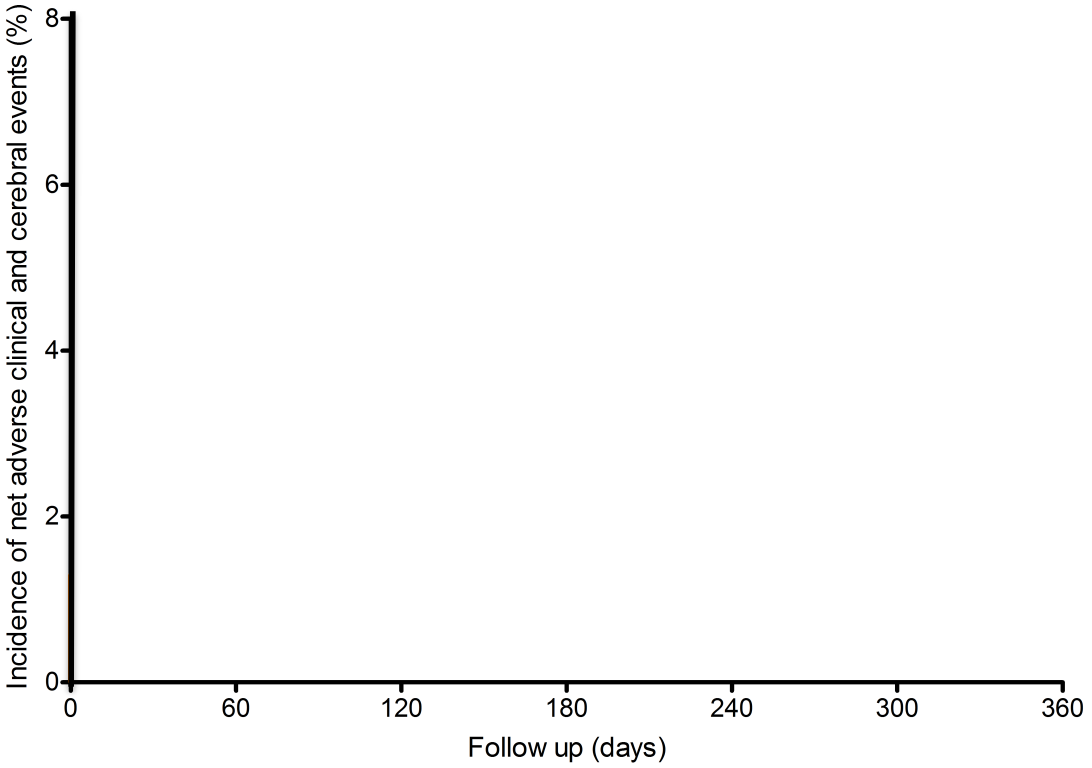
Values are n (%)

Study Flow and Analyses



NACCE at 1-Year Follow-up

(All-cause death, any MI, stroke, or major bleeding)



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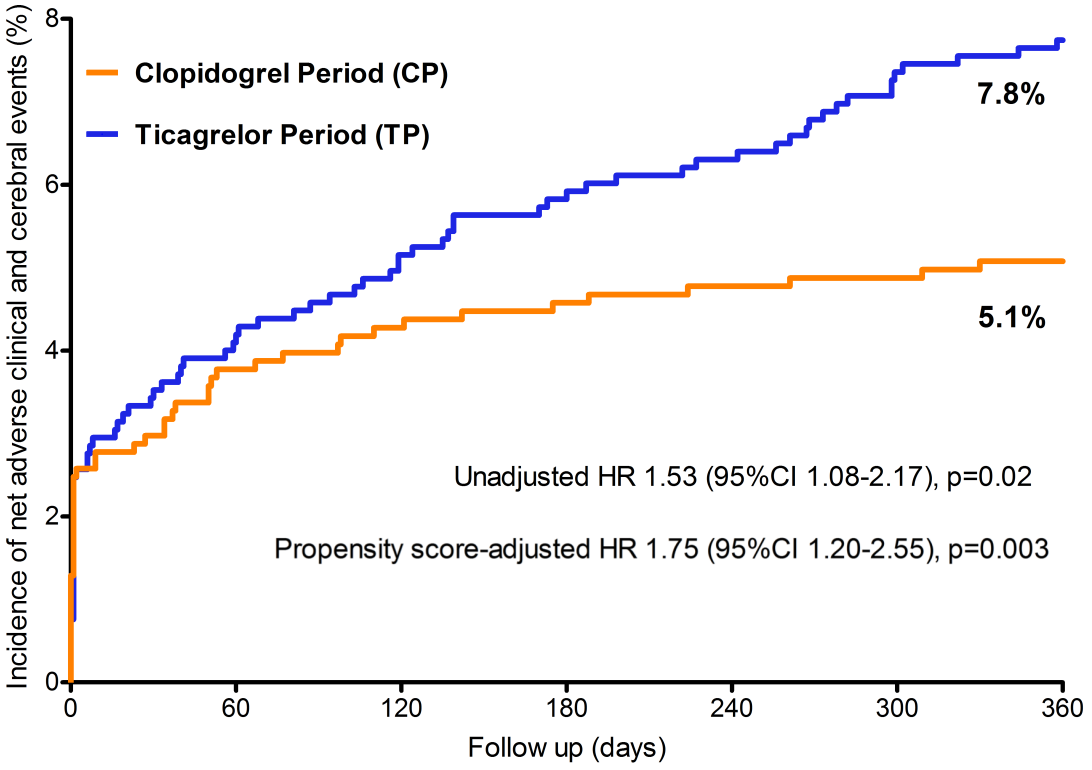


- **Follow-up rate: 99.3% for CP and TP**

NACCE at 1-Year Follow-up

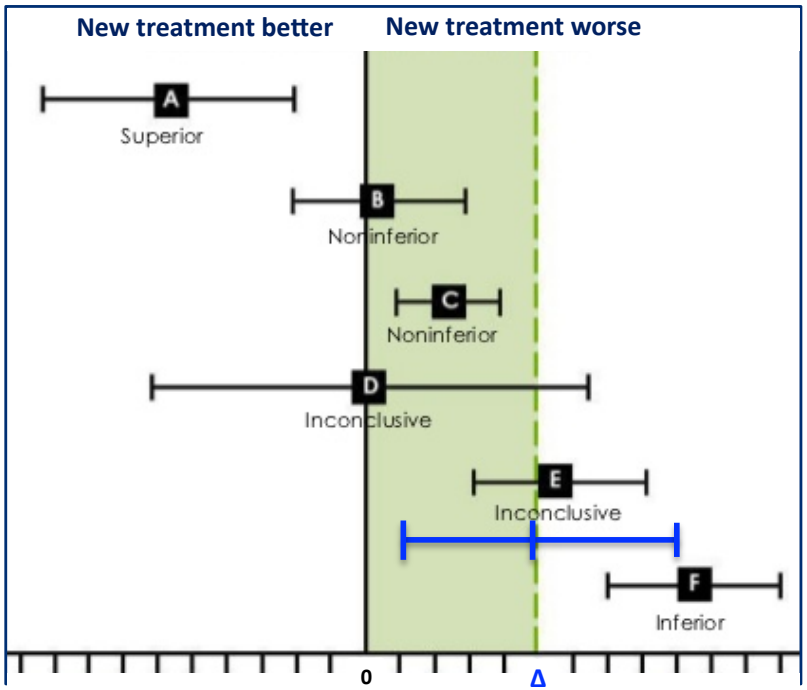
(All-cause death, any MI, stroke, or major bleeding)

CP 5.1% ⟷ **TP 7.8%**

Risk difference: 2.64 %
Upper one-sided 95% CI: 4.77

$P_{non\text{-}inferiority} = 0.48$

Inconclusive regarding the non-inferiority hypothesis

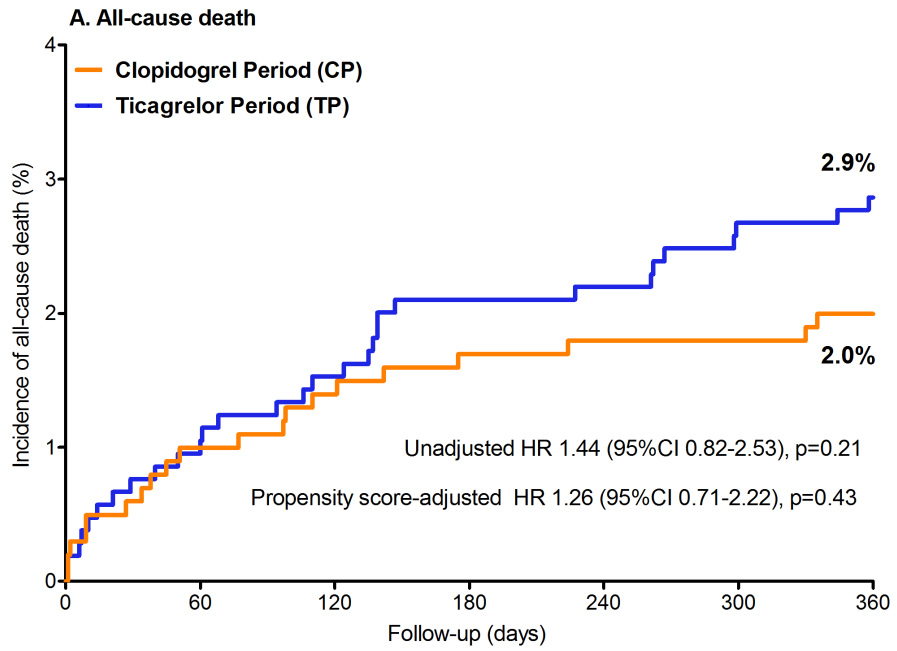


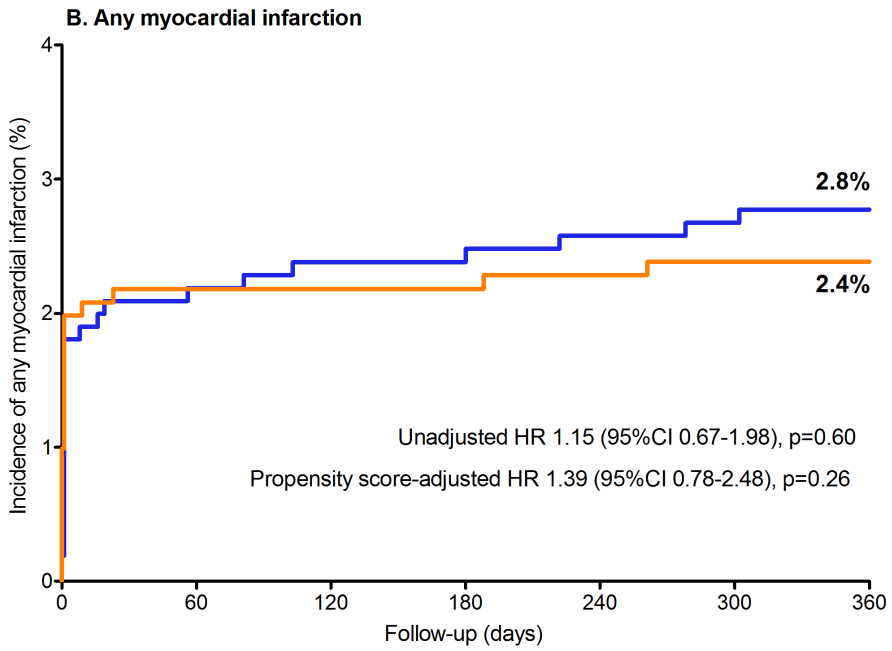
Non-inferiority margin (Δ): 2.7%
Risk difference: 2.64%
95% CI: 0.52 ——— 4.77

Scheme modified from: H. Sturgeon, PharmD; SlideShare

Components of NACCE at 1-Year Follow-up

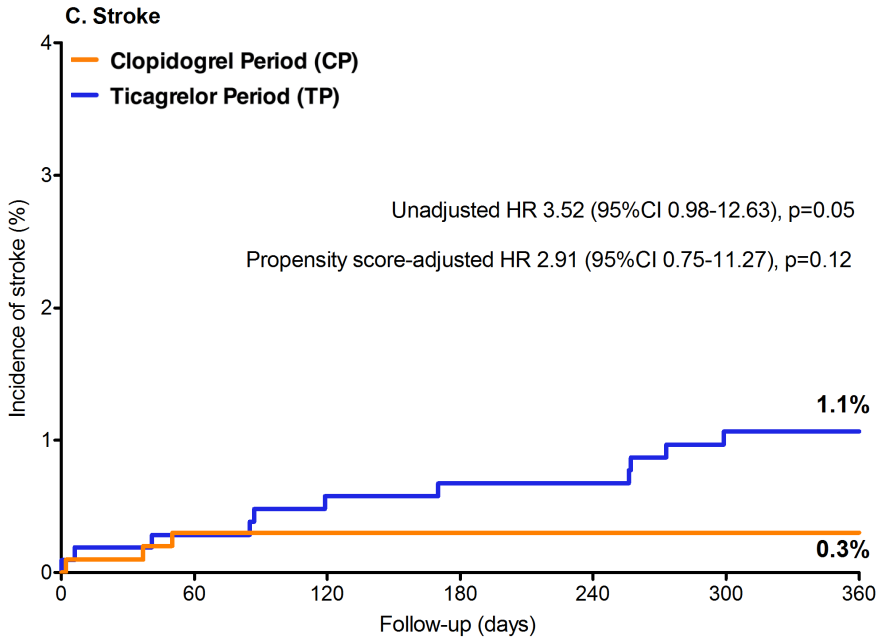
(A) All-cause death and (B) Any myocardial infarction

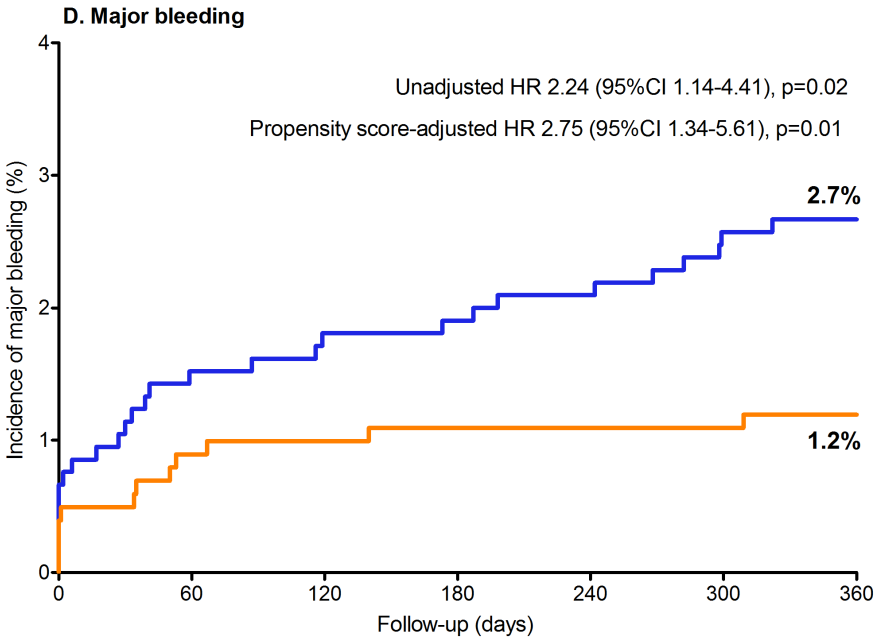




Components of NACCE at 1-Year Follow-up

(C) Stroke and (D) Major bleeding



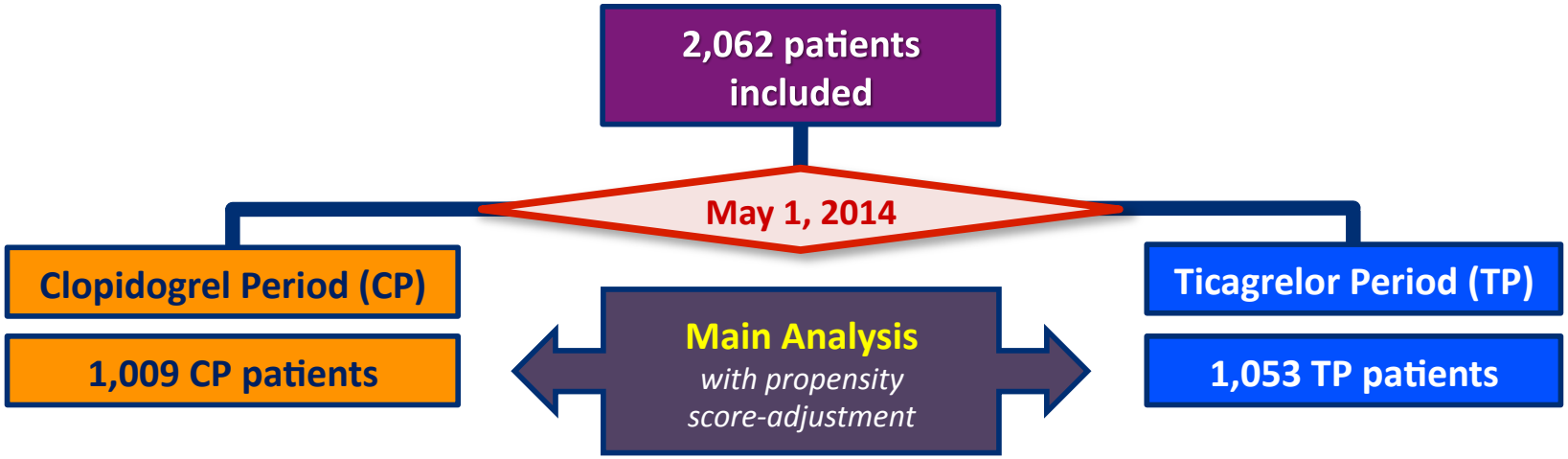


1-Year Clinical Outcome

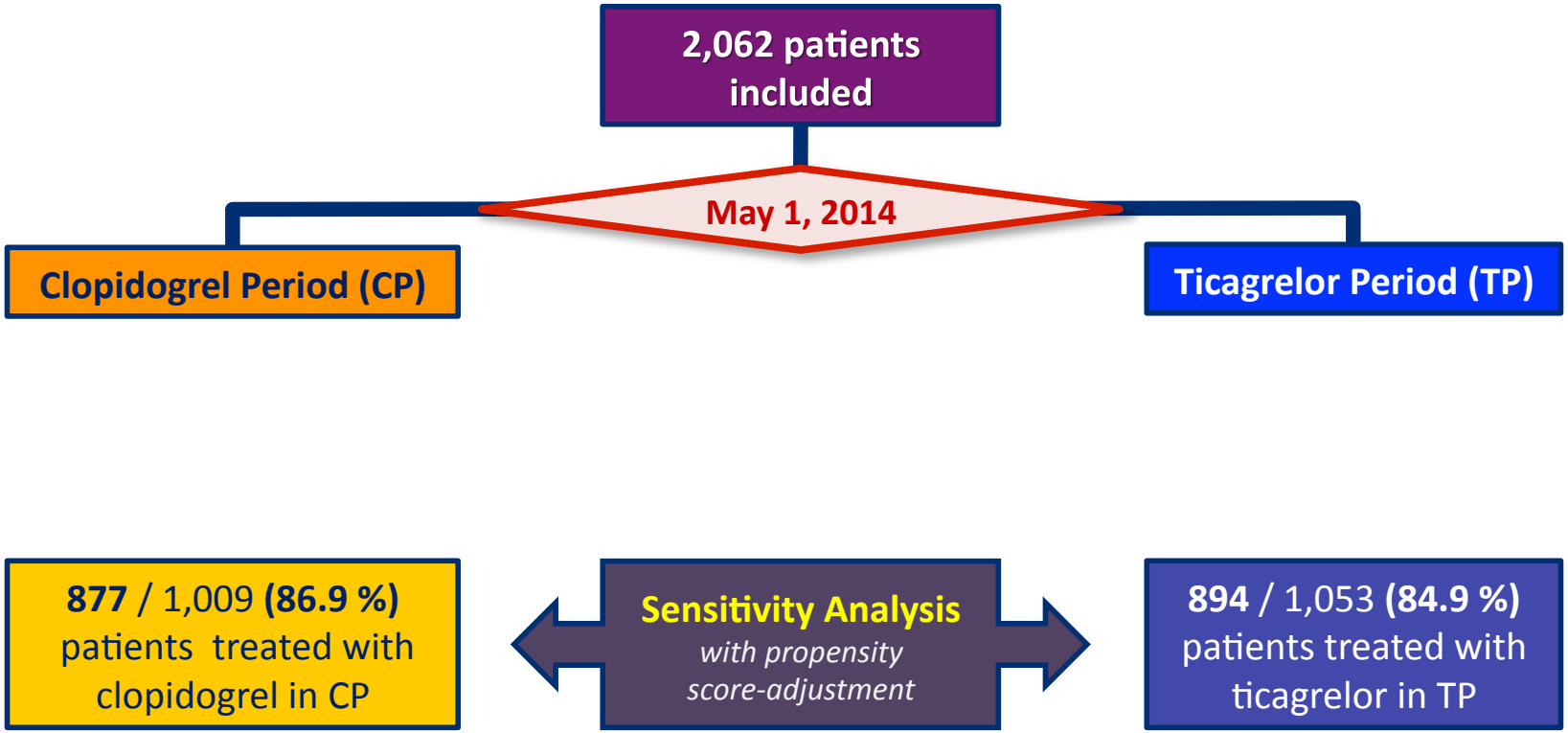
	CP (n=1,009)	TP (n=1,053)	Propensity Score-Adjusted HR (95%CI)	P
NACCE	51 (5.1%)	81 (7.8%)	1.75 (1.20-2.55)	0.003
All-cause death	20 (2.0%)	30 (2.9%)	1.61 (0.88-2.95)	0.12
Any myocardial infarction (MI)	24 (2.4%)	29 (2.8%)	1.39 (0.78-2.48)	0.26
Stroke	3 (0.3%)	11 (1.1%)	2.91 (0.75-11.27)	0.12
Major bleeding	12 (1.2%)	28 (2.7%)	2.75 (1.34-5.61)	0.01
Cardiac death, MI, or stroke	37 (3.7%)	49 (4.7%)	1.33 (0.84-2.11)	0.22
Definite or probable stent thrombosis	6 (0.6%)	8 (0.8%)	1.03 (0.33-3.27)	0.96

Values are n (%)

Study Flow and Analyses

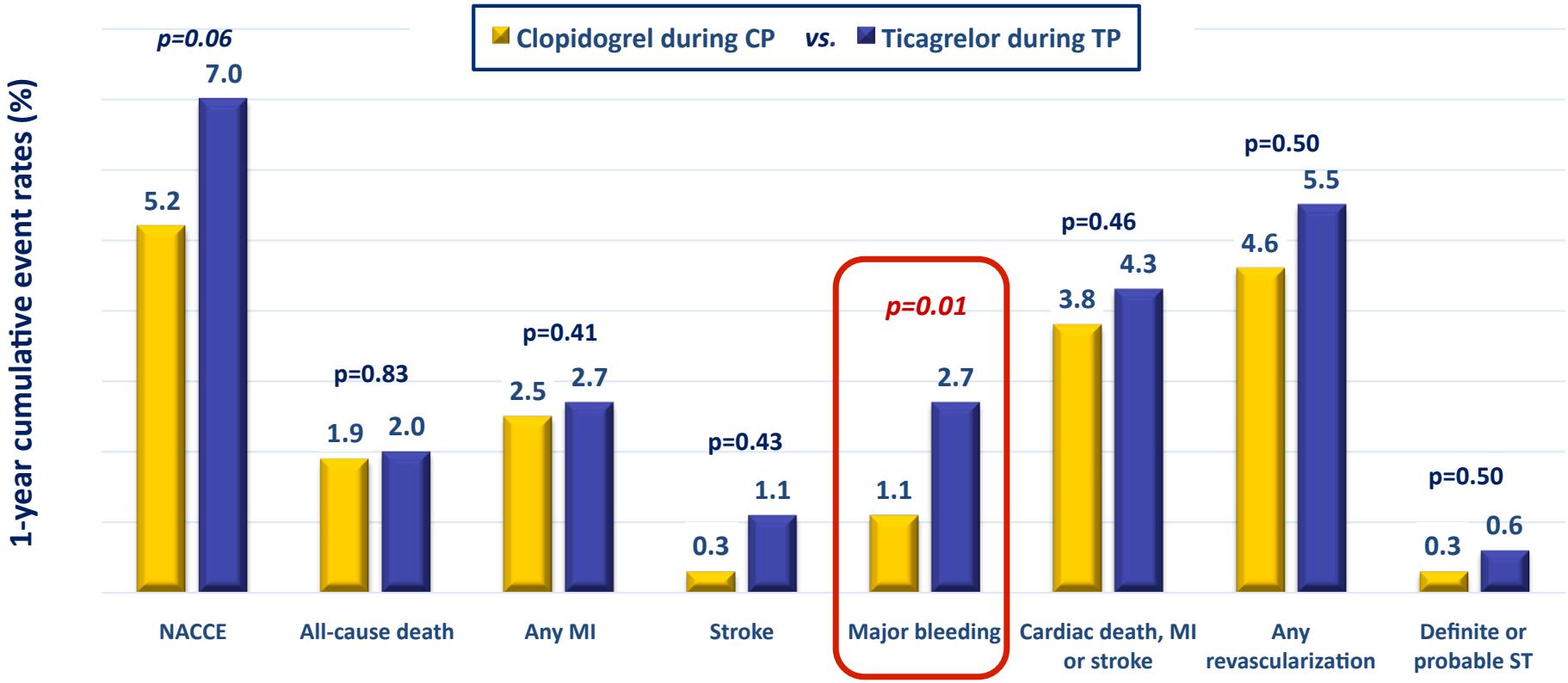


Study Flow and Analyses



Clopidogrel in CP and ticagrelor in TP = clopidogrel in CP and ticagrelor in TP, respectively, at discharge or at the time of NACCE before discharge

Sensitivity Analysis, Propensity Score-Adjusted



Pts. on clopidogrel during CP (yellow) versus pts. on ticagrelor during TP (blue), at discharge or at time of in-hospital NACCE.
CP=clopidogrel period; MI=myocardial infarction; ST=stent thrombosis; TP=ticagrelor period.
P-values are propensity score-adjusted.

Discussion I

- **The CHANGE DAPT study is (among) the first to assess guideline-recommended changes in primary DAPT regimen in a *consecutive series* of real-world ACS patients, who were *all* treated by PCI with exclusive use of newer-generation DES.**
- **Our data support recent findings of the randomized TOPIC[1] trial and preliminary data from Västa Götaland County in Sweden, based on the SCAAR[2] registry.**
- **In contrast with our results, the large SWEDEHEART[3,4] registry revealed findings that were similar to the randomized PLATO trial.**
  However, in the SWEDEHEART registry:
  - **Ticagrelor was more often used in patients at lower risk of bleeding and death (indicated by lower CRUSADE and GRACE scores)[4]; and**
  - **Ticagrelor-treated patients were more often assessed by angiography and were more often treated by PCI[3,4].**

1. Cuisset et al. **Eur Heart J** 2017; May 16. doi: 10.1093/eurheartj/ehx175
2. Elmerovic et al. Presented at **EuroPCR 2017**, Paris, France
3. Sahlén et al. **Eur Heart J** 2016; 37:3335-42
4. Sahlén et al. **Eur Heart J Cardiovasc Pharmacother** 2016;2:5-12

Discussion II

- **The lack of benefit in ischemic outcomes during TP may be due to:**
  - **The inclusion of *all* ACS types (while PLATO included only moderate-to-high risk ACS);**
  - **The assessment of *PCI-treated* patients only with exclusive use of *newer-generation* DES and overall favourable outcomes;**
  - **The *"real-world"* setting which might imply a lower medication adherence that could partly be related to side effects[1].**

- **The increased major bleeding risk during TP was observed despite:**
  - ***More trans-radial procedures;***
  - ***Less use of glycoprotein IIb/IIIa-inhibitors; and***
  - ***More prescriptions of proton pump inhibitors*.**

1. Bergmeijer et al. **Cardiology** 2017;138:164-8

Discussion III – Limitations

- This study present non-randomized data; however, randomized trials often lack external validity, while registries may better reflect routine clinical practice.
- Residual confounding cannot be excluded; however, propensity score-adjustment and the sensitivity analysis support the findings.
- Event rates were lower than in phase-III trials, which might partly be explained by ascertainment bias. On the other hand, event rates in our centre/trials are generally low,[1-3] which has been related to very high rates of stent postdilation (≥80%), and follow-up rates were very high (>99%).
- The study was not powered for assessing differences in outcome parameters with low event rates (e.g. stent thrombosis or stroke).
- The findings should not be generalized to patients treated *without* PCI.

1. **Lancet** 2014;383:413-23
2. **Lancet** 2016;388:2607-17
3. **JAMA Cardiol** 2017;2:268-76

Conclusions

In consecutive ACS patients treated by PCI with newer-generation DES, the guideline-recommended change in primary DAPT regimen to ticagrelor-based DAPT was associated with an increased event risk. This was primarily driven by a higher rate of major bleeding, while no benefit in ischemic outcomes was observed.

CHANGE DAPT

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CHANGE DAPT

eep
editorial expedited publication

CLINICAL RESEARCH

EuroIntervention 2017;13-online publish-ahead-of-print August 2017

Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT

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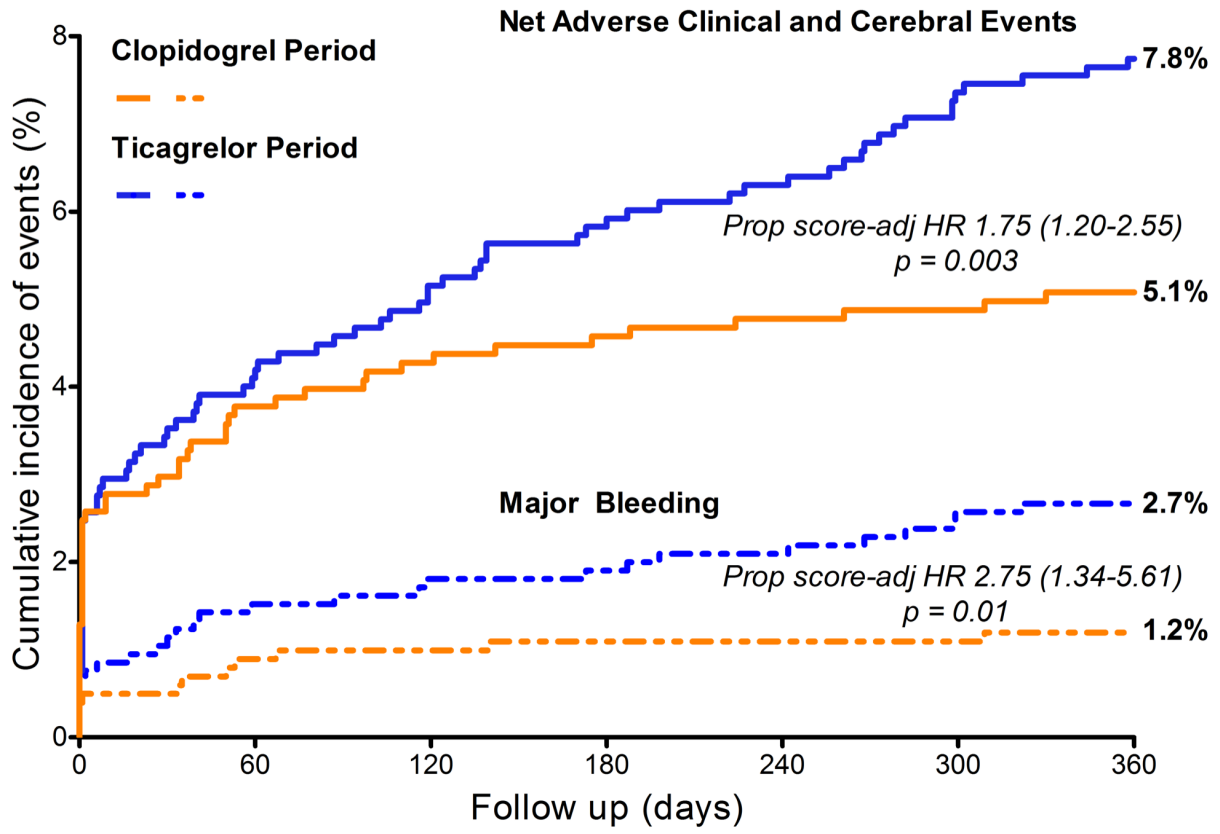
Zocca P. *et al.* **EuroIntervention** 2017; *in press* – online published ahead of print August 29, 2017

CHANGE DAPT

Backup Slides

CHANGE DAPT

Investigator-initiated observational study in 2,062 consecutive ACS patients, treated by PCI with newer-generation DES



von Birgelen C., presented September 29, 2017; ESC, Barcelona, Spain.

Zocca P. *et al.* **EuroIntervention** – *in press; online published ahead of print August 29, 2017.*

Clinicaltrials.gov: NCT03197298

Reasons for deviation from primary DAPT regimen

	Ticagrelor at discharge during CP n=132/1,009 (13.1%)	Clopidogrel at discharge during TP n=159/1,053 (15.1%)
The other $P2Y_{12}$-inhibitor was initiated in a referring hospital	113 (85.6%)	61 (38.4%)
At discretion of the treating physician without written documentation	6 (4.5%)	51 (32.1%)
Pre-admission use of the other $P2Y_{12}$-inhibitor	0 (0.0%)	23 (14.5%)
Side effects or allergy	12 (9.1%)	6 (3.8%)
Comorbidity	0 (0.0%)	12 (7.5%)
Interaction with pre-admission medication	0 (0.0%)	2 (1.3%)
To promote medication adherence	0 (0.0%)	3 (1.9%)
History of stent thrombosis	1 (0.8%)	0 (0.0%)
History of bleeding	0 (0.0%)	1 (0.6%)

Values are n (%)

CHANGE DAPT

Investigator-initiated observational study

Inclusion criteria

- Age ≥ 18 years
- Presented with ACS
- Treated by PCI with newer-generation DES

2,062 consecutive ACS patients, treated by PCI at Thoraxcentrum Twente, the Netherlands

Exclusion criteria

- Known pregnancy
- Life expectancy < 1 year
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n = 1,009

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Definitions of clinical endpoints according to (Bleeding) Academic Research Consortium and Thrombolysis in Myocardial Infarction criteria. Clinicaltrials.gov: NCT03197298

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