Re-defining the Role of Ticagrelor for Long-term DAPT ; How to Apply PEGASUS TIMI-54 to Real World Practice

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- Review why we need long-term DAPT in MI patients
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There is an unmet need for improved secondary prevention in patients with a prior MI

- Approximately **50%** of major coronary events occur in those with a previous hospital discharge diagnosis of ischaemic heart disease

In 2016, the European Society of Cardiology issued a "Call to action", in which they highlight the high risk of subsequent CV events in patients with a history of MI, and the unmet need for improved secondary prevention.

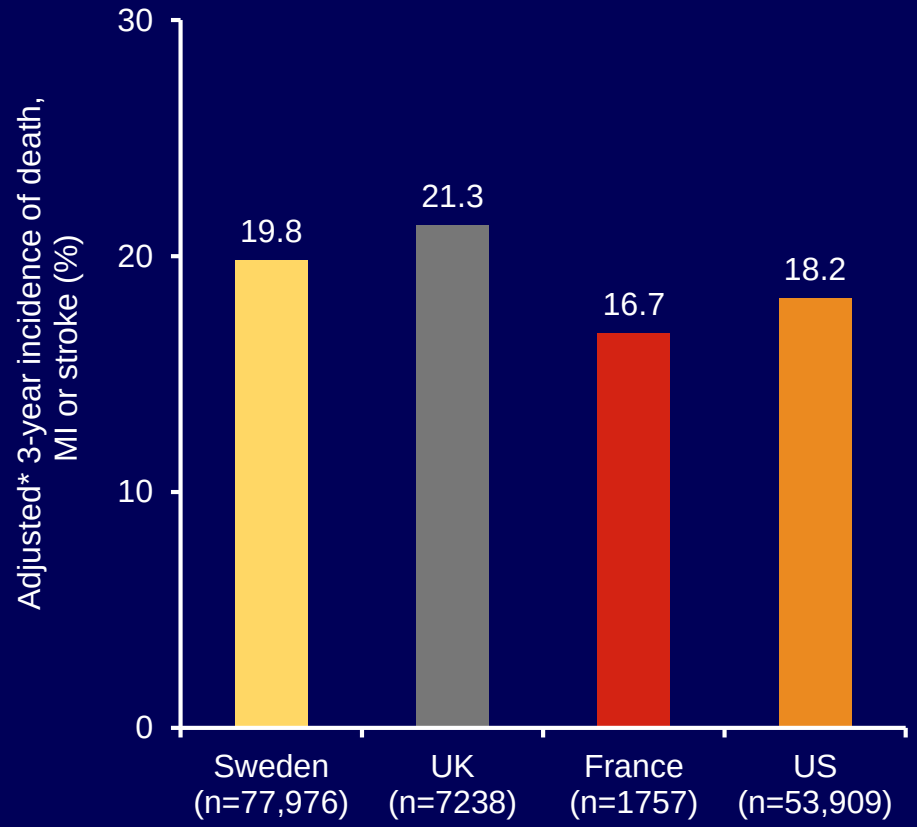
"Prevention after MI is crucial to reduce risk and suffering"

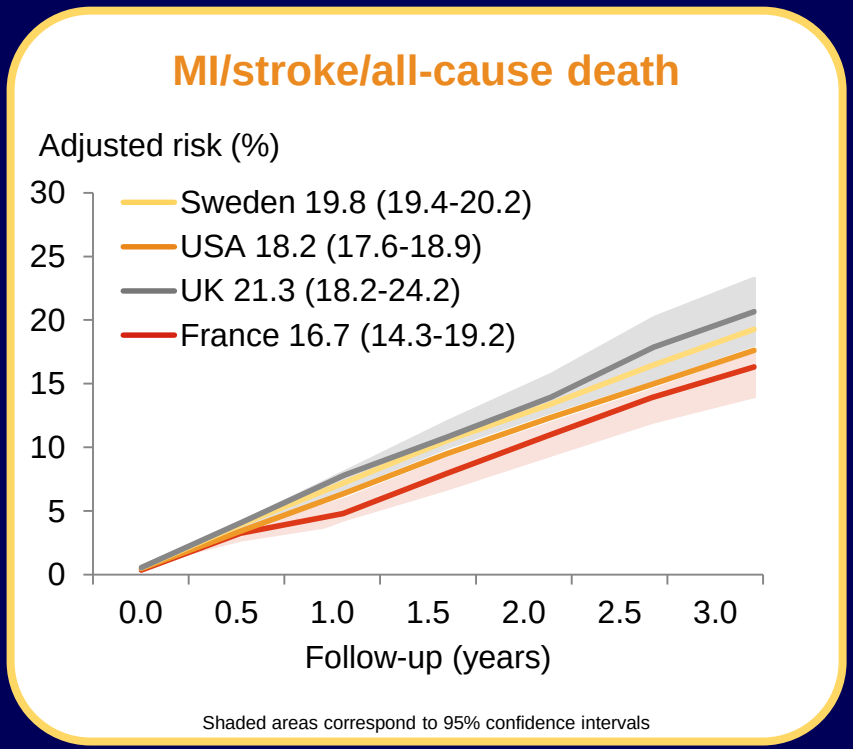
Piepoli MF *et al. Eur J Prevent Cardiol* 2016;23:1994–2006

Produced in framework of ESC Prevention of CVD Programme (led by EACPR in collaboration with ACCA and CCNAP); supported by unrestricted educational grants

~1 in 5 patients who are event free for the first year post-MI, will suffer an MI, stroke or death within 3 years

APOLLO 4-country analysis: adjusted incidence*[Rapsomaniki 2014]





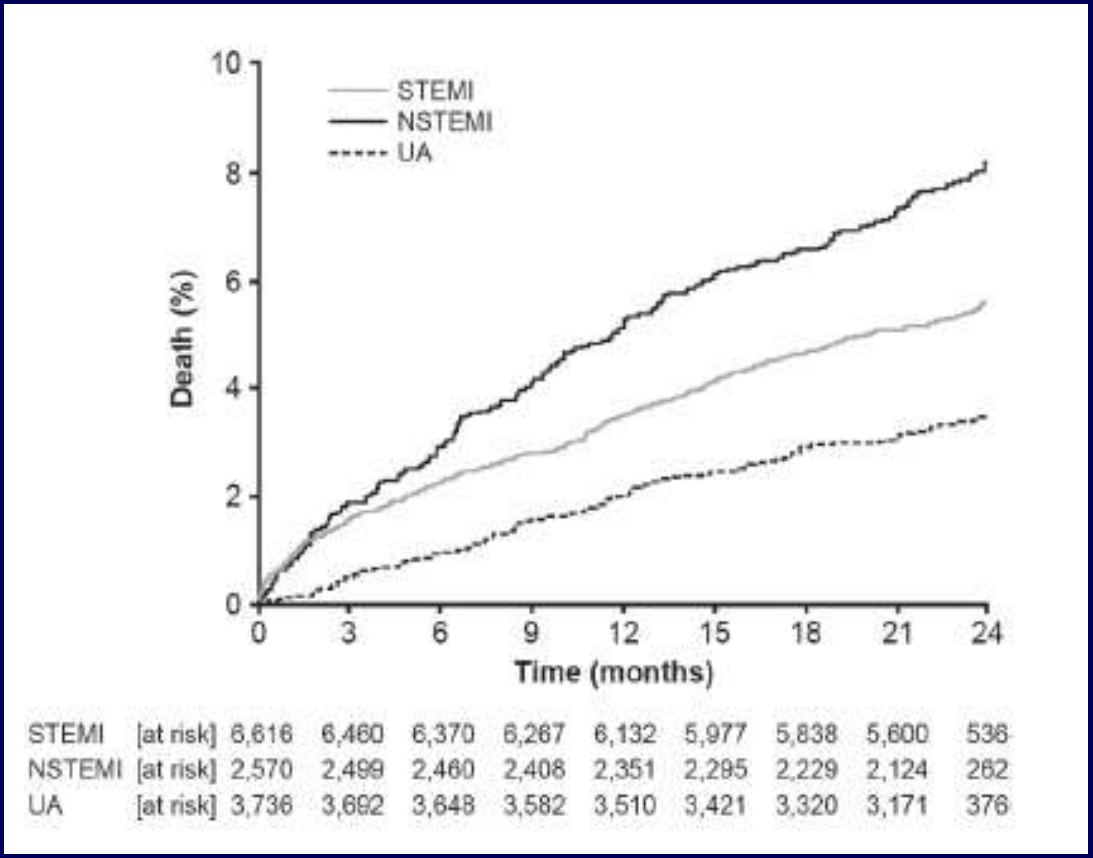
MI, myocardial infarction.

*Adjusted for differences in study populations; MI, myocardial infarction. Shaded areas / figures in brackets [95%CI]

1. Rapsomaniki E *et al*. ESC Late Breaking Registry presentation 2014.

Asian ACS patients also occur consistently ischemic risk, especially in Myocardial infraction

EPICOR-Asia was a multinational multicenter, observational, prospective, longitudinal cohort study in a real-life setting, 12,922 hospital survivors of an ACS event from 219 centres in Asia.



- **Conclusion: Mortality and vascular event rates are still of concerns in Asian ACS patients**
- **Participating countries and regions included China, Hong Kong, India, Malaysis, Singapore, South Korea, Thailand and Vietnam**

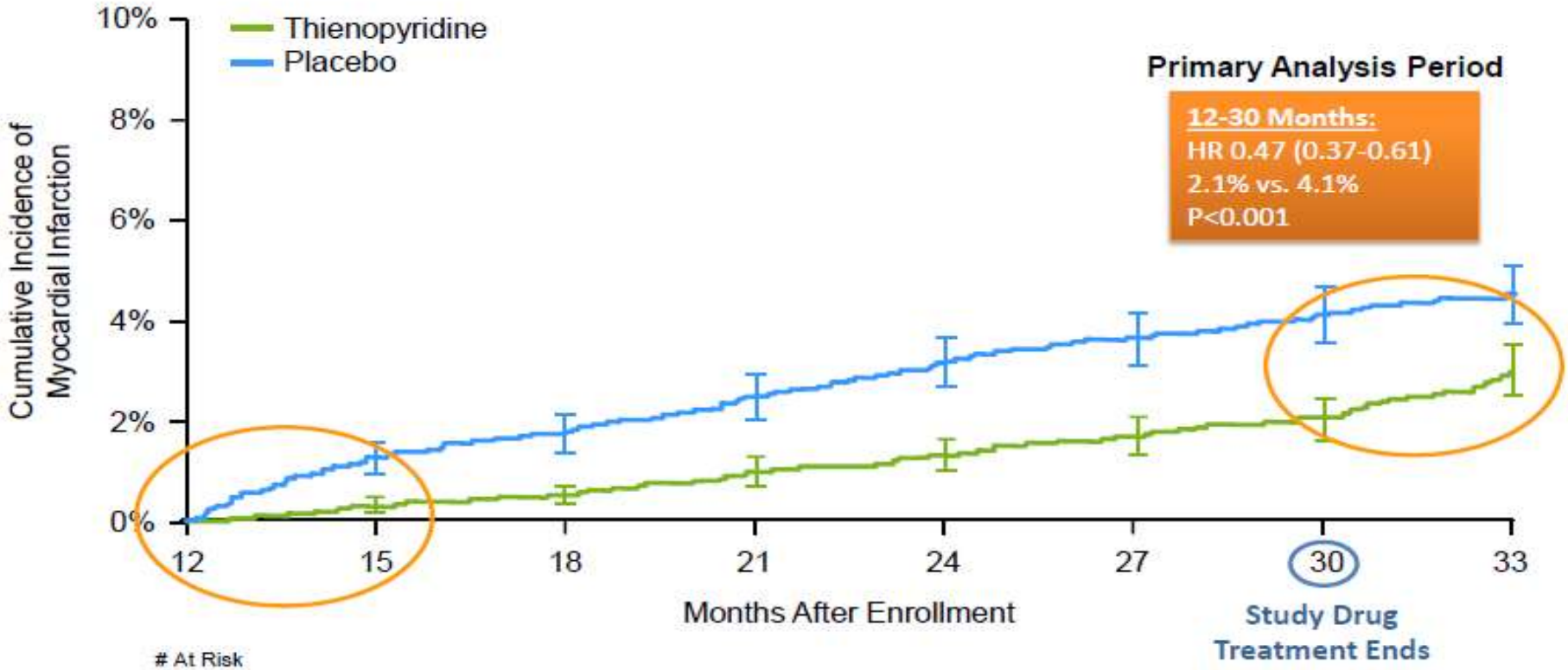
1. **Huo Yong, et al JACC March 17, 2015 Volume 65,**

Review why we need long-term DAPT in MI patients

Rebound Phenomenon after withdrawal P2Y12 inhibitors

Myocardial Infarction

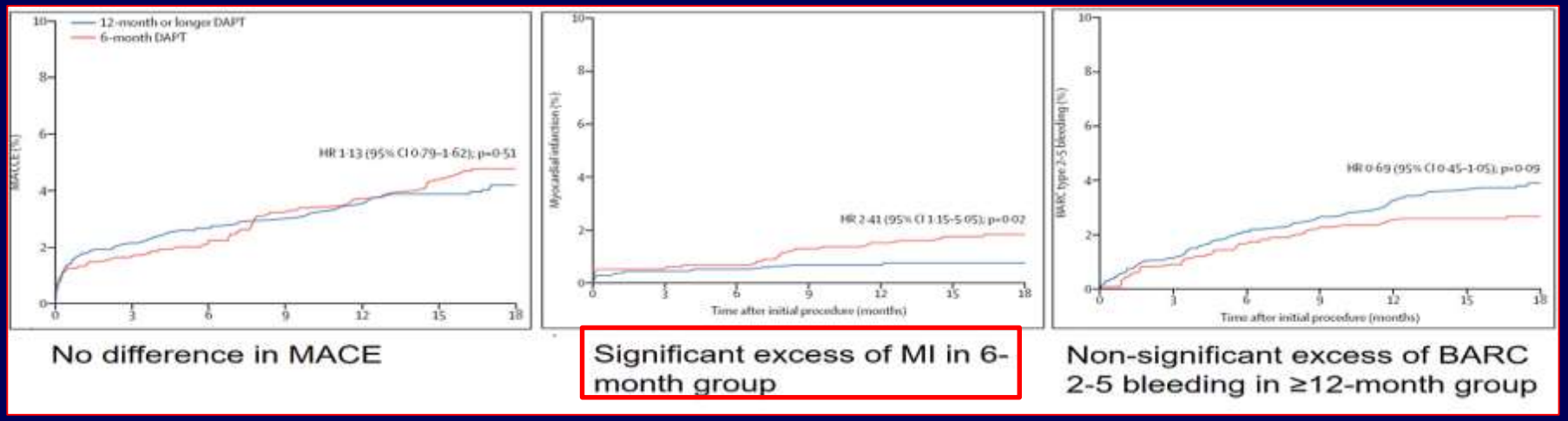
DAPT STUDY



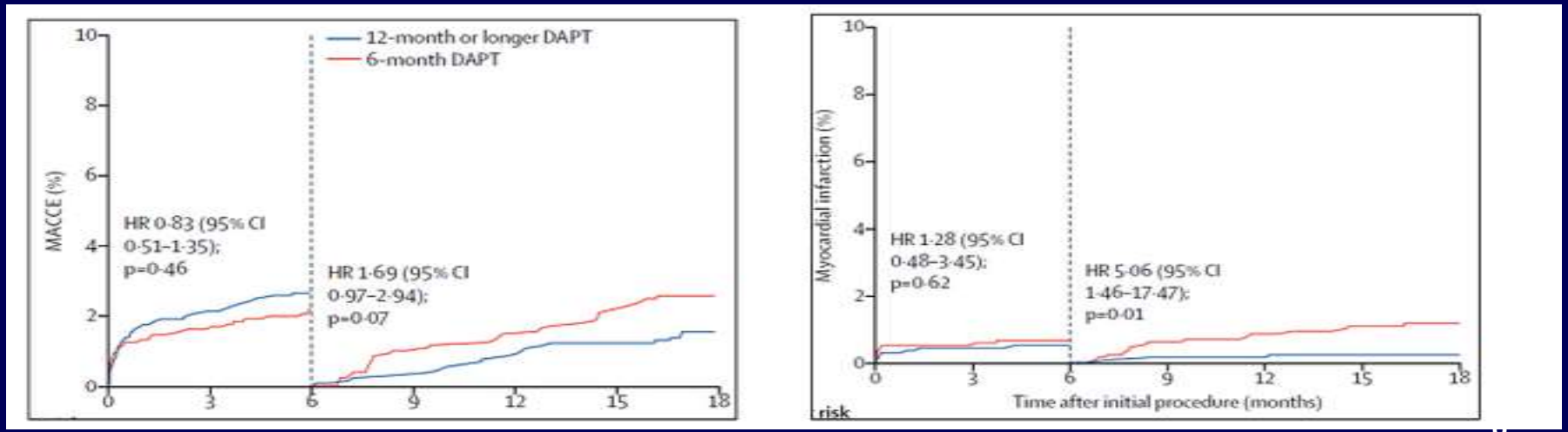
# At Risk							
Thienopyridine 5020	4920	4849	4789	4717	4634	4580	3051
Placebo 4941	4804	4727	4653	4565	4501	4440	3012

DAPT in ACS: SMART-DATE

- **Non-inferiority for MACE of 6 months DAPT vs ≥ 12 months DAPT was met, however significant excess of MI in 6months DAPT group**



- **Landmark analysis shows definite tendency to higher MACE and MI rate in ASA group beyond 6 months**



Hahn JY et al. Lancet. 2018 Mar 31;391(10127):1274-1284

DAPT in ACS: SMART-DATE

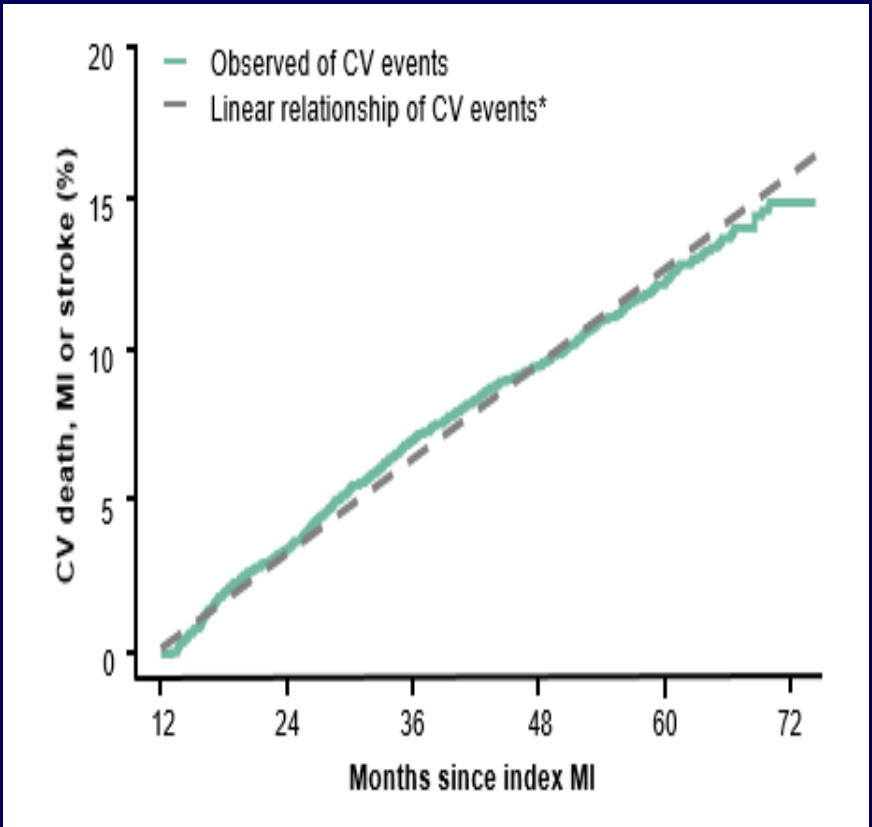
	DAPT-6 group (n=1357)	DAPT-12 group (n=1355)	HR (95% CI)	p value
MACCE	63 (4.7%)	56 (4.2%)	1.13 (0.79-1.62)	0.51
Death	35 (2.6%)	39 (2.9%)	0.90 (0.57-1.42)	0.90
Myocardial infarction	24 (1.8%)	10 (0.8%)	2.41 (1.15-5.05)	0.02
Target vessel MI	14 (1.1%)	7 (0.5%)	2.01 (0.81-4.97)	0.13
Non-target vessel MI	10 (0.8%)	3 (0.2%)	3.35 (0.92-12.2)	0.07
Cerebrovascular accident (stroke)	11 (0.8%)	12 (0.9%)	0.92 (0.41-2.08)	0.84
Cardiac death	18 (1.4%)	24 (1.8%)	0.75 (0.41-1.38)	0.36
Cardiac death or MI	39 (2.9%)	32 (2.4%)	1.22 (0.77-1.95)	0.40
Stent thrombosis	15 (1.1%)	10 (0.7%)	1.50 (0.68-3.35)	0.32
Bleeding BARC type 2-5	35 (2.7%)	51 (3.9%)	0.69 (0.45-1.05)	0.09
Major bleeding (BARC type 3,4,or 5)	6 (0.5%)	10 (0.8%)	0.60 (0.22-1.65)	0.33
Net adverse clinical and cerebral events	96 (7.2%)	99 (7.4%)	0.97 (0.73-1.29)	0.84

Hahn JY et al. Lancet. 2018 Mar 31;391(10127):1274-1284

What is the standard of care in post MI patients; Clo. DAPT or ASA?

Patients with a prior MI are associated with a high and persistent ischemic risk, as observed in PEGASUS TIMI-54

Patients with a prior MI remained at persistent risk of ischaemic events for at least 5 years after their index MI



- **Patients were randomized ≥1 year from qualifying MI, therefore no events within the first year were observed**
- **In the PEGASUS-TIMI 54 study, the rate of CV death, MI or stroke for patients with a prior MI receiving ASA monotherapy remained constant throughout the duration of the trial, at an annualized rate of ~3%**
- **28% of patients were ≥5 years since their qualifying index event at the end of the analysis (median follow-up 33-months from randomization), highlighting the persistency of ischaemic risk in patients with a prior MI**

*Based on left-truncated analysis

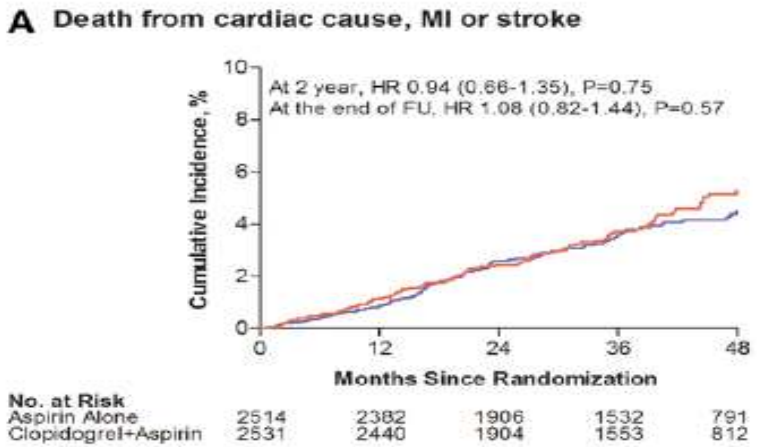
Bonaca MP *et al. J Am Coll Cardiol* 2017;70:1368–1375

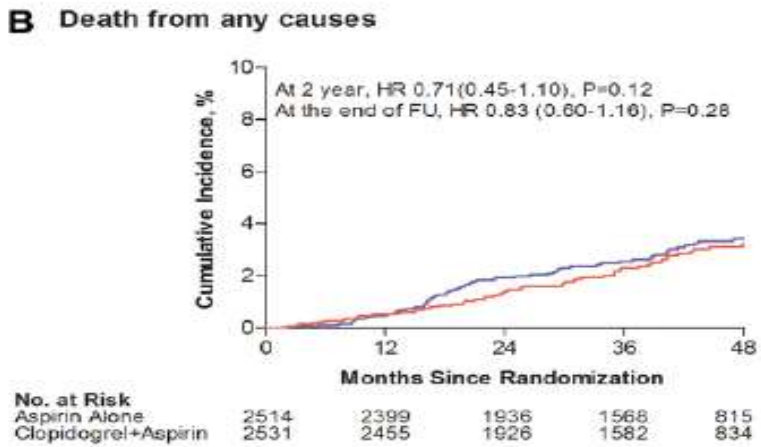
This analysis was a prespecified sub-analysis of the patients from the PEGASUS-TIMI 54 trial who received placebo

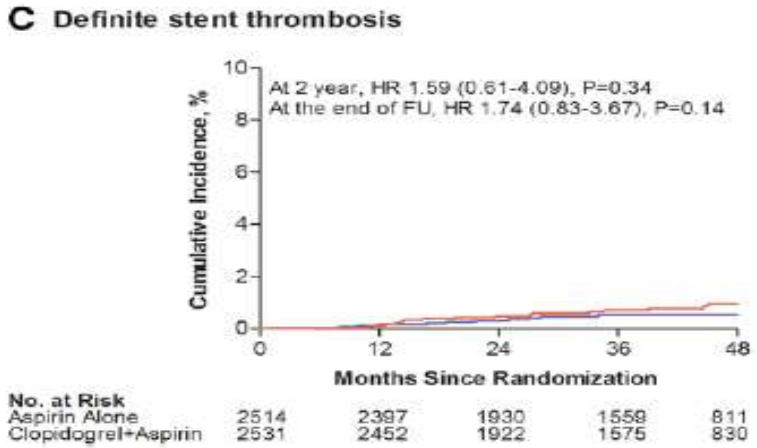
Clopidogrel is not enough for long-term DAPT

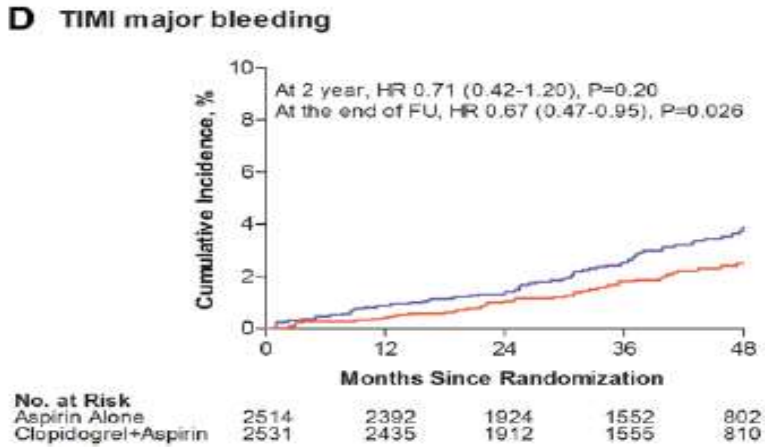
DES-LATE A Randomized, Controlled Trial in Korea (n=5045)

Among patients who were on 12-month dual antiplatelet therapy without complications, an additional 24months of dual antiplatelet therapy with **clopidogrel versus aspirin alone did not reduce the risk of the composite end point** of death from cardiac causes, myocardial infarction, or stroke **in Korean patients**



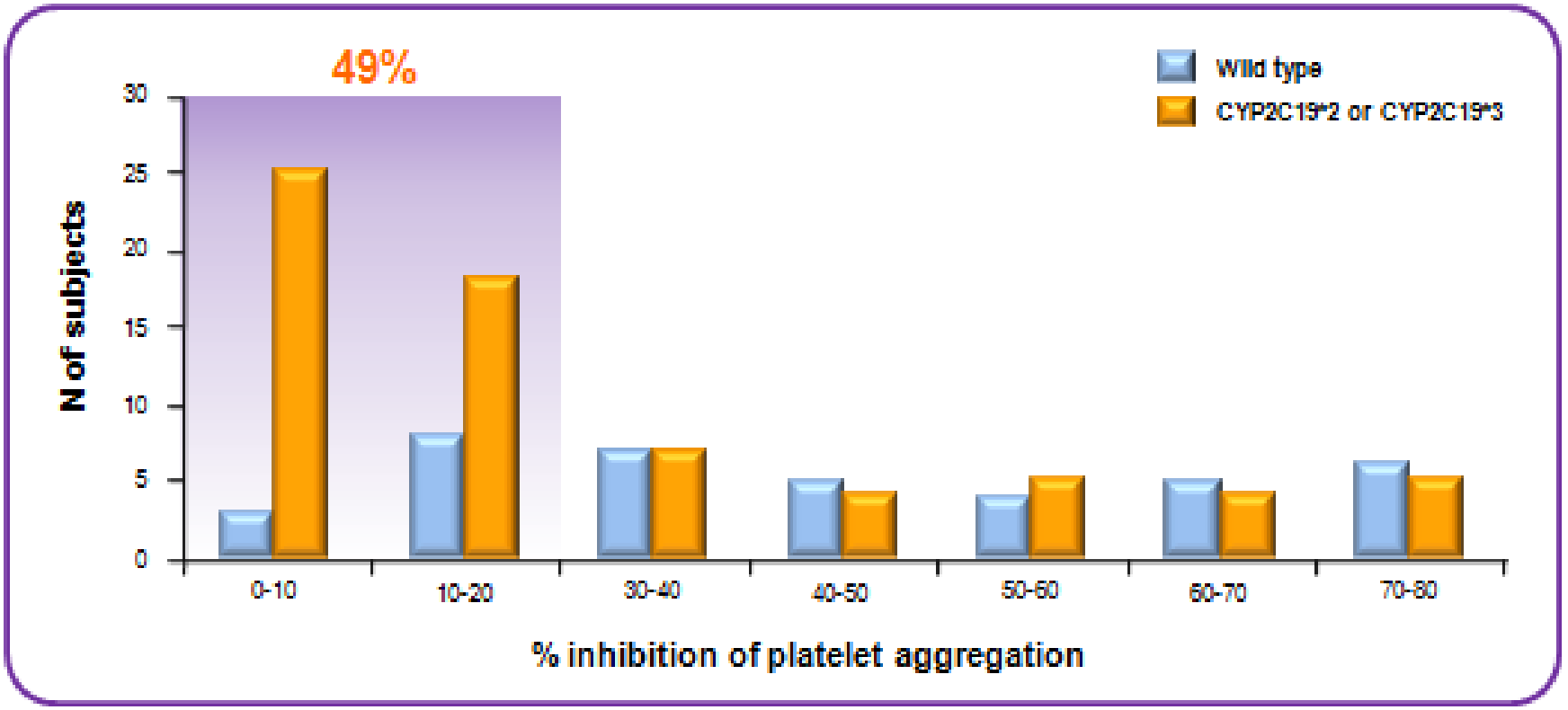






1.CW Lee et al. Circulation. 2014;129:304-312.

About 50% of patients with clopidgorel were reported as non-responders in Korea



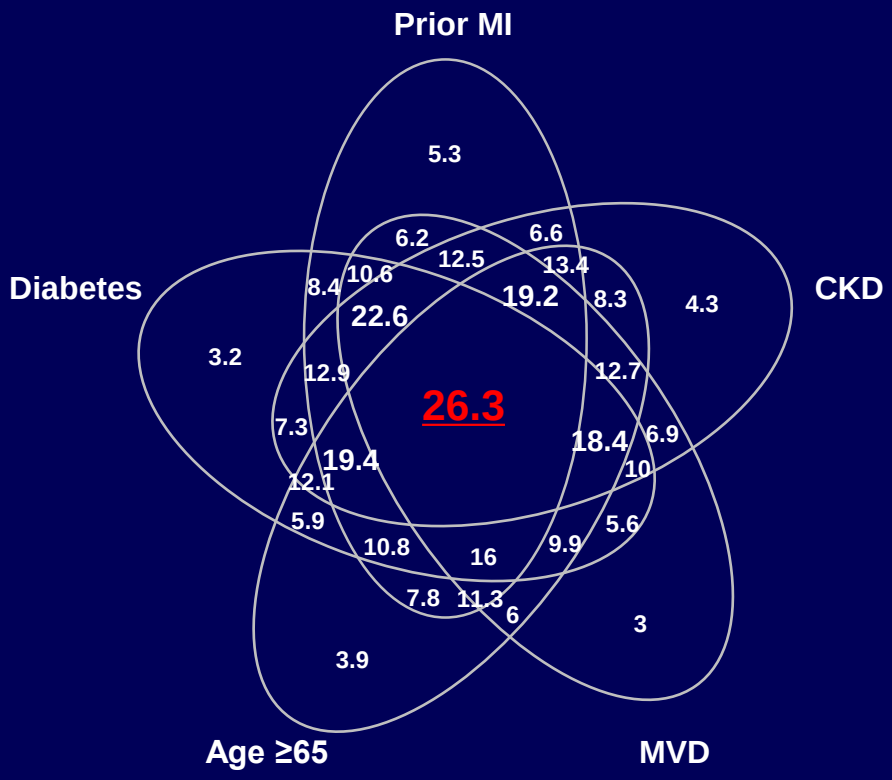
114 ACS patients at the Samsung Medical Center between June 2008 and July 2009 were evaluated. All the patients underwent coronary angiography and received a daily dose of 75mg(105 patients) or 150mg(9 patients) of Clopidogrel for more than a month. The ages of the patients ranged 35 to 87 yr(median age, 63 yr). All the patients were undergoing dual antiplatelet, 32 received an additional dose of cilostazol. The degree of inhibition of platelets was assessed using the VerifyNow assay (Accumetrics, USA). The patients who showed less than 20% inhibition of platelets were defined as non-responders to Clopidogrel treatment. Steady state plasma concentrations of Clopidogrel were measured using HPLC/tandem mass spectrometry. CYP2C19 genotyping was also performed.

KJ Park et al. Korean J Lab Med 2011;31:91-94

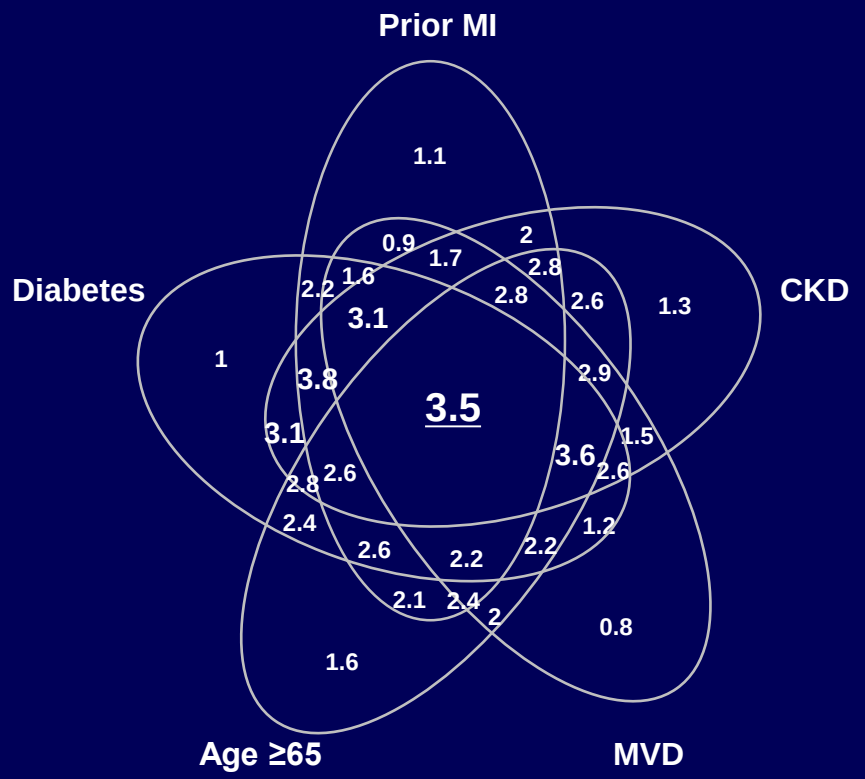
Re-defining risk of HRPMI patients and how to apply PEGASUS TIMI 54 to Real world Practice

Combination of risk factors leads to more incidence of CV events

Incidence (events per 100 person-years) of MI, stroke of CV death*

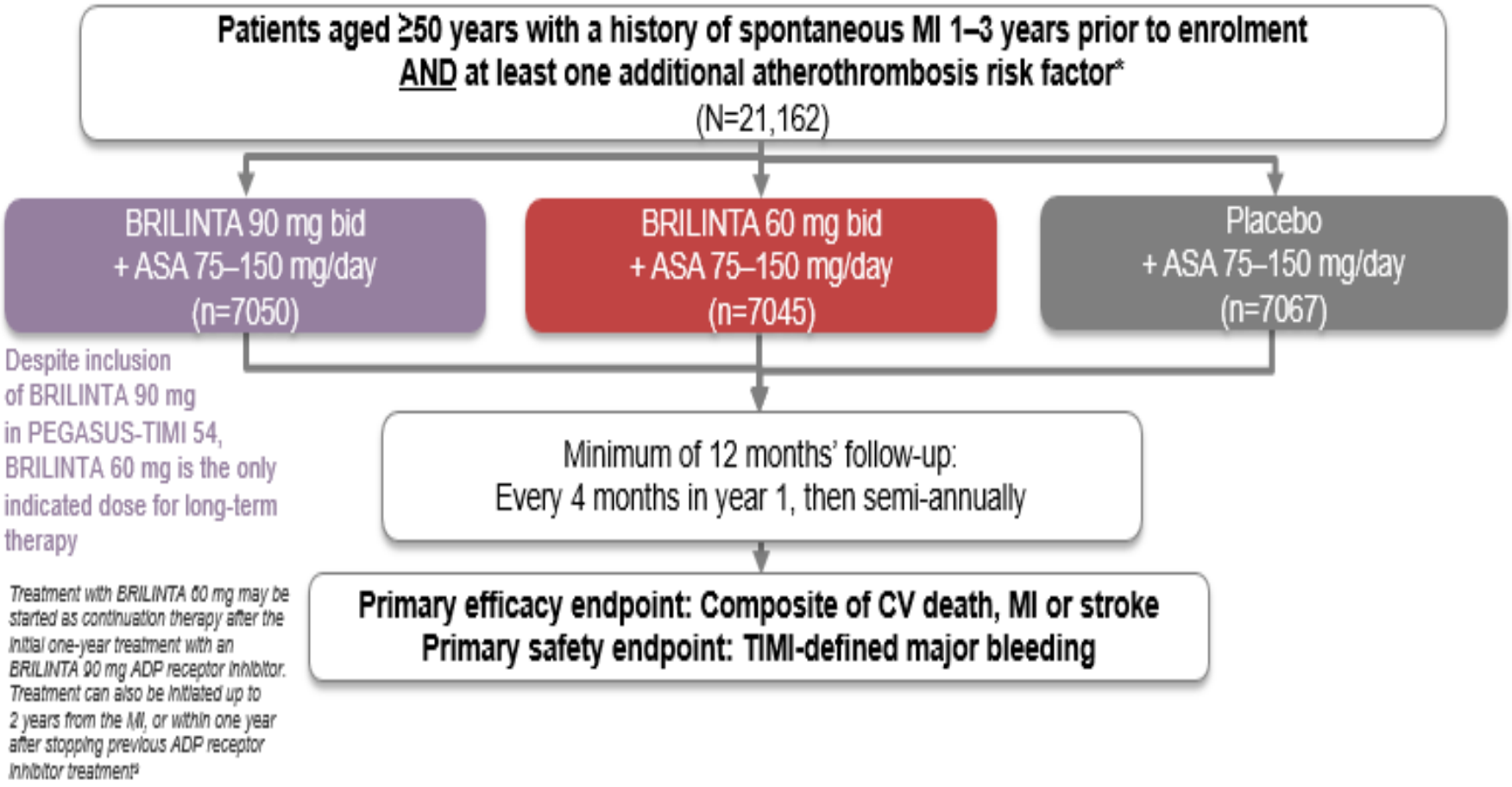


Incidence (events per 100 person-years) of major bleeding*



- CKD = chronic kidney disease; CV = cardiovascular; MI = myocardial infarction; MVD = multivessel disease
- Lindholm D et al. *Eur Heart J.* 2018;39 (suppl):265. Abs 1398.

PEGASUS-TIMI 54 study design[1,2]



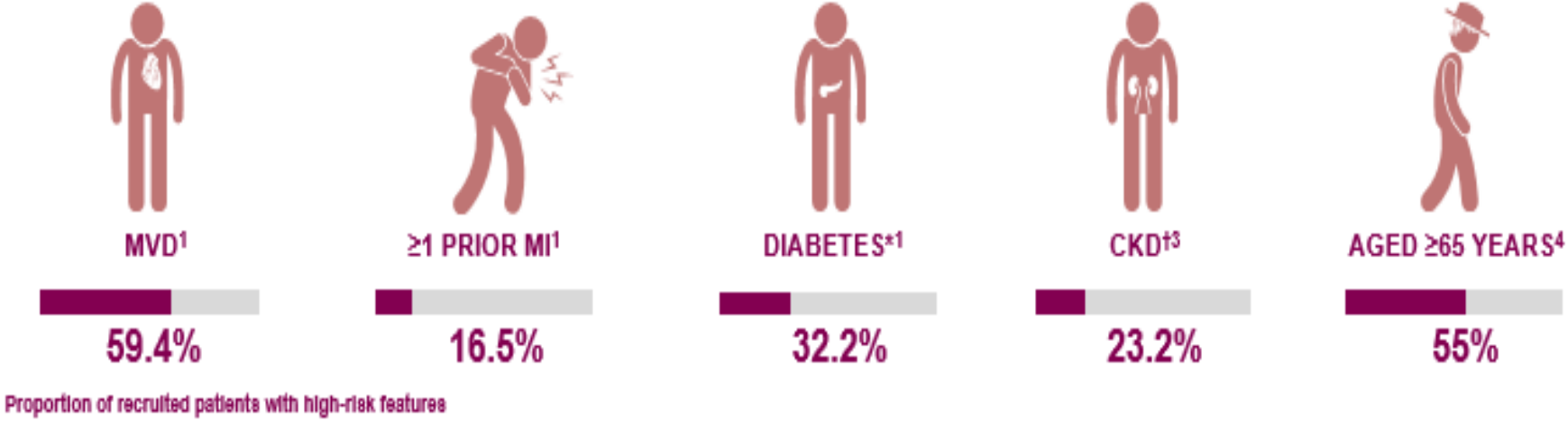
*Age ≥65 years, diabetes mellitus requiring medication, ≥prior MI, multivessel CAD or chronic non-end-stage renal disease defined as CrCl < 60mL/min

1. Bonaca MP *et al. Am Heart J* 2014;167:437–444; 2. Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800; 3. **AstraZeneca. BRILIQUE Summary of Product Characteristics**

PEGASUS TIMI-54 study enrolled prior MI patients with high ischemic risk factors

PEGASUS inclusion criteria:

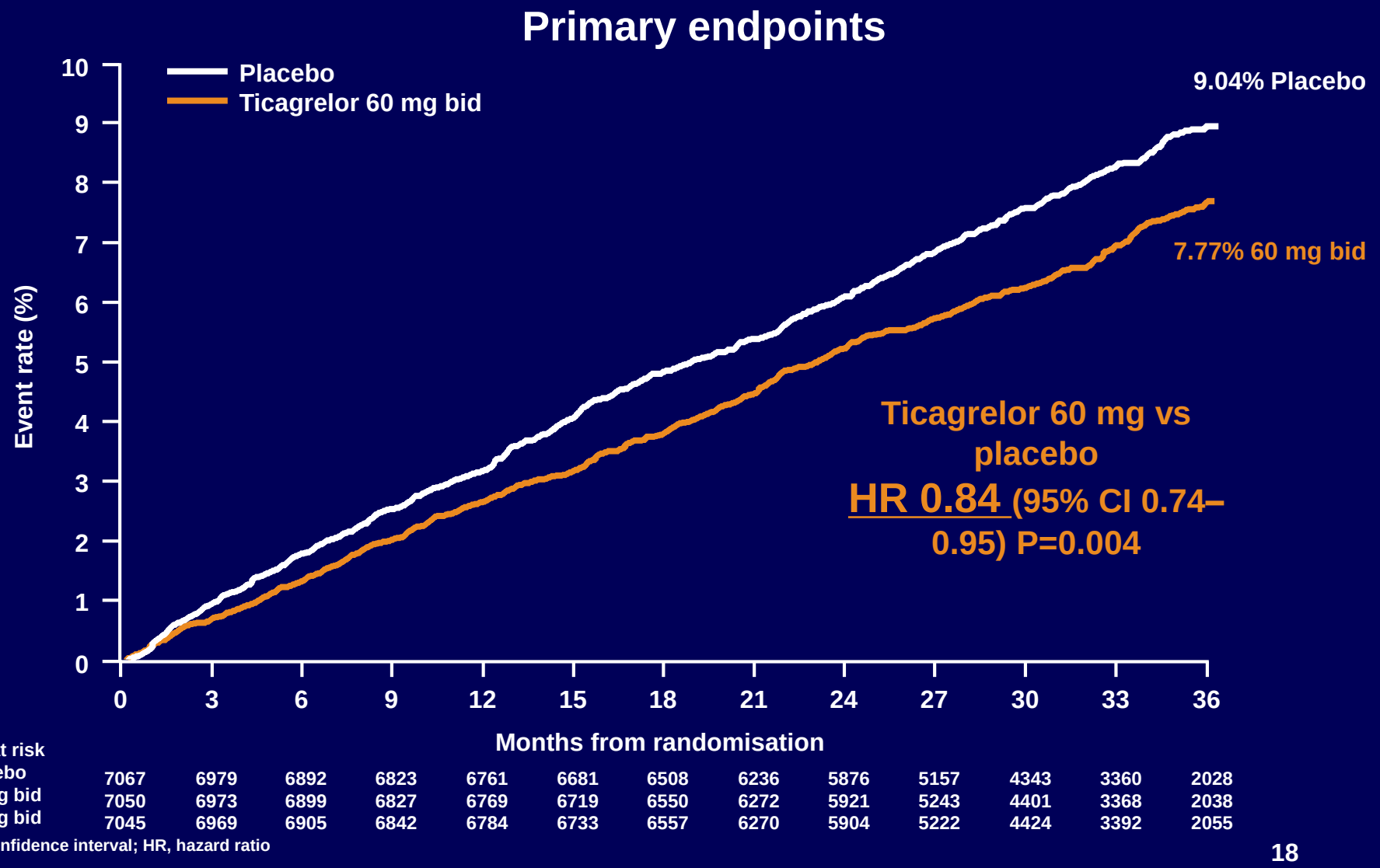
- Age ≥50 years old; prescribed and tolerating ASA at the time of enrolment
- History of a spontaneous MI 1–3 years prior to enrolment
- One of the following additional high-risk features:[1–4]



*Age ≥65 years, diabetes mellitus requiring medication, ≥prior MI, multivessel CAD or chronic non-end-stage renal disease defined as CrCl < 60mL/min

1. Bonaca MP *et al. Am Heart J* 2014;167:437–444; 2. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 3. **AstraZeneca. BRILIQUE Summary of Product Characteristics**

Ticagrelor 60mg is the only proven OAP to reduce CV events over 3years in HRPMI vs ASA alone

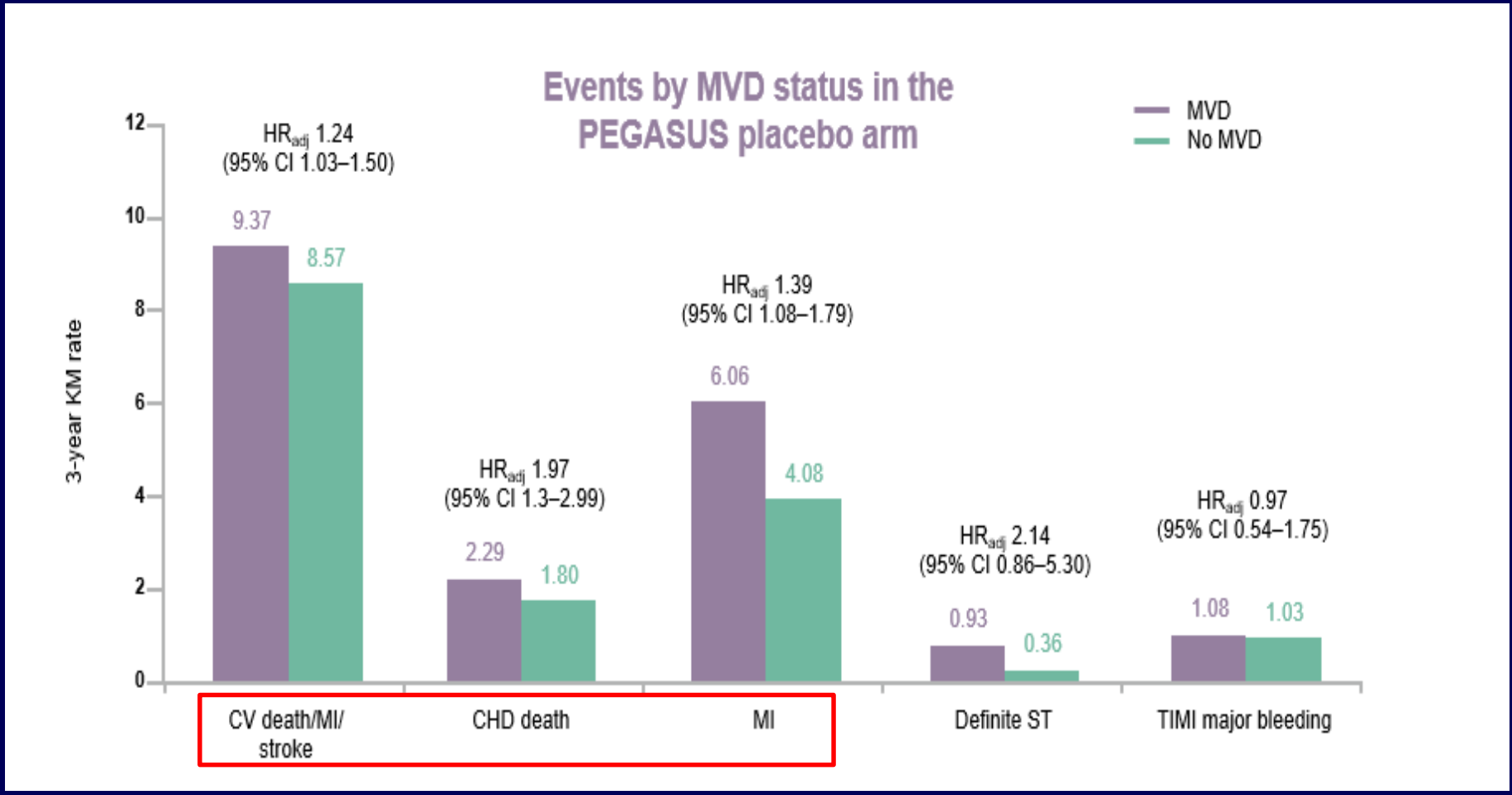


CI, confidence interval; HR, hazard ratio

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

PEGASUS sub-analysis showed Patients with MVD are at a greater risk of ischemic events

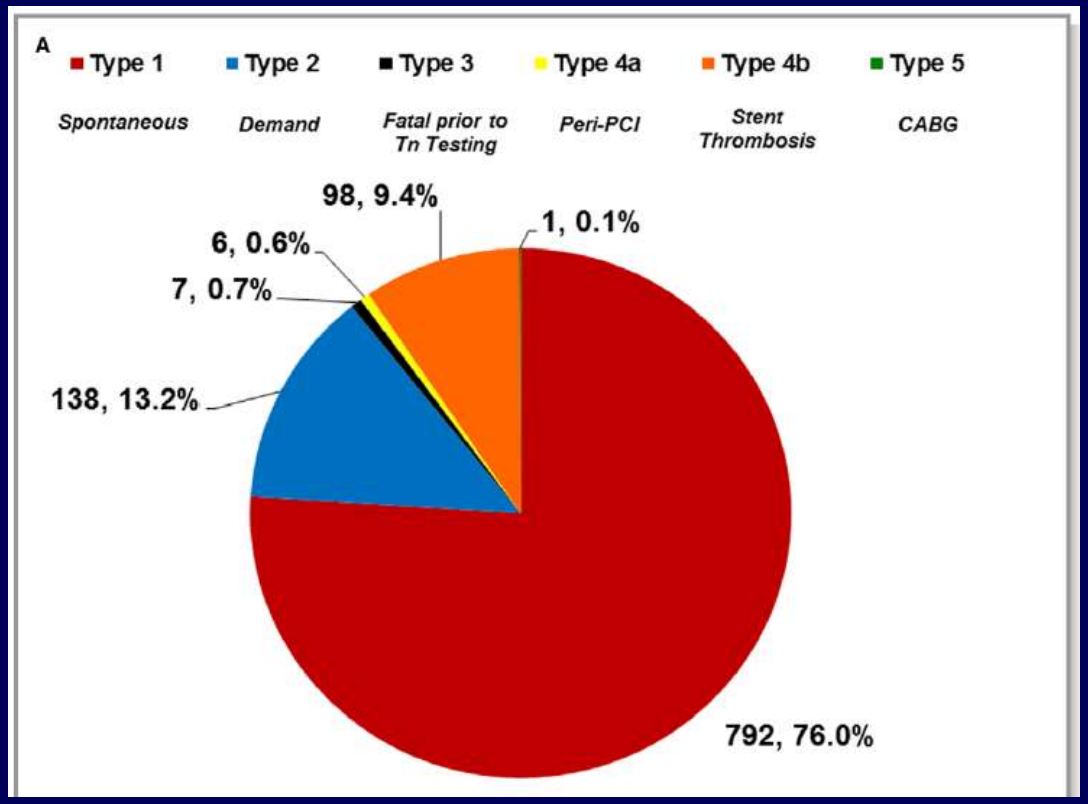
An analysis of PEGASUS patients receiving placebo demonstrated the risk of recurrent ischemic events is present regardless of MVD status, but is greater in patients with MVD than those without



Bansilal S et al. J Am Coll Cardiol 2018;71:489–496

PEGASUS sub-analysis shows that majority of MI type is a spontaneous MI

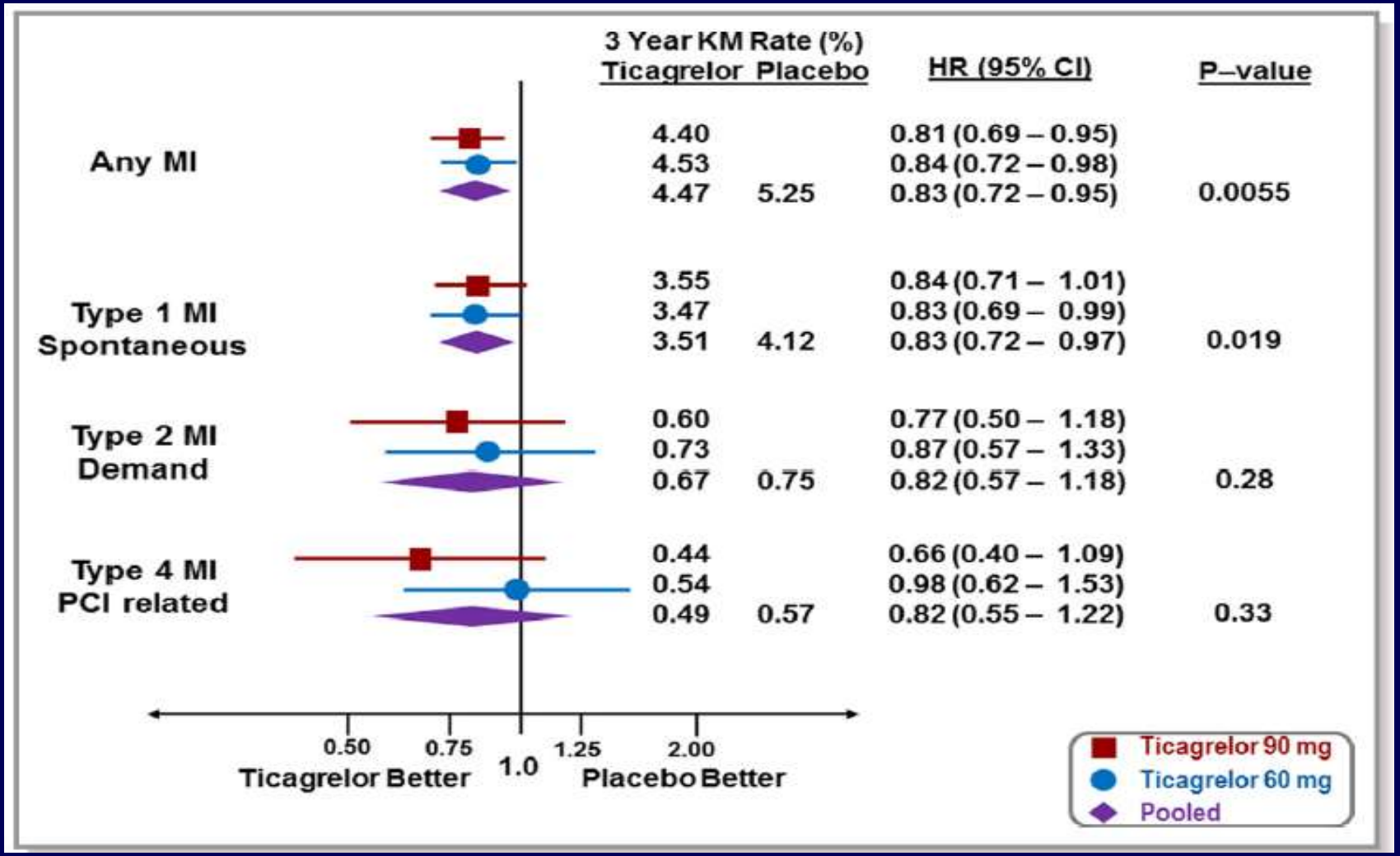
- Study design: MIs were adjudicated by a blinded clinical events committee and categorized by subtype and fold elevation of peak cardiac troponin over the upper limit of normal. A total of 1042 MIs occurred in 898 of the 21 162 randomized patients over a median follow-up of 33 months



- The majority of the MIs (76%) were spontaneous (Type 1), Demand MI (Type 2) and stent thrombosis (Type 4b) accounting for 13% and 9%, respectively; sudden death (Type 3), percutaneous coronary intervention–related (Type 4a) and coronary artery bypass graft–related (Type 5) each accounted for <1%.

Bonaca MP *et al* J Am Heart Assoc. 2018;7: e009260. DOI: 10.1161/JAHA.118.009260

Ticagrelor reduces the MI consistently regardless of MI sub-types compared to ASA



Bonaca MP *et al* J Am Heart Assoc. 2018;7: e009260. DOI: 10.1161/JAHA.118.009260

T2DM patients have high tendency of increasing CV events; MI and all cause death

- Study design: Patients with their first MI recorded in the U.K. General Practice Research Database in 1997–2008 were classified as T2DM, diagnosed before or within 28 days after the date of the first recorded MI ,or non-T2DM. Patients diagnosed within 28 days after the index date were assumed to have developed T2DM at baseline

Table 2—Crude recurrence rate and rate ratio of the primary outcome (subsequent MI) and secondary outcomes (all-cause death and a composite outcome of all-cause death or subsequent MI) in the primary and sensitivity cohorts of patients with and without T2DM (per 1,000 person-years)

	n	Events	Person-years	Recurrence rate (95% CI)	Rate ratio (95% CI)
Primary cohort*					
Subsequent MI†					
Both sexes					
T2DM	7,411	1,198	36,499	32.8 (31.0–34.7)	1.44 (1.35–1.53)
Non-T2DM	48,726	6,114	268,137	22.8 (22.2–23.4)	1.0 (ref.)
Men					
T2DM	4,695	735	24,189	30.4 (28.2–32.7)	1.36 (1.26–1.47)
Non-T2DM	31,825	4,038	180,719	22.3 (21.7–23.0)	1.0 (ref.)
Women					
T2DM	2,716	463	12,310	37.6 (34.3–41.2)	1.58 (1.43–1.75)
Non-T2DM	16,901	2,076	87,418	23.7 (22.7–24.8)	1.0 (ref.)
All-cause death†					
Both sexes					
T2DM	7,411	3,412	40,781	83.7 (80.9–86.5)	1.61 (1.55–1.67)
Non-T2DM	48,726	15,400	295,465	52.1 (51.3–53.0)	1.0 (ref.)
Men					
T2DM	4,695	2,040	26,985	75.6 (72.4–79.0)	1.66 (1.58–1.74)
Non-T2DM	31,825	9,075	199,355	45.5 (44.6–46.5)	1.0 (ref.)
Women					
T2DM	2,716	1,372	13,796	99.5 (94.3–104.9)	1.51 (1.42–1.60)
Non-T2DM	16,901	6,325	96,110	65.8 (64.2–67.5)	1.0 (ref.)
All-cause death or subsequent MI†					
Both sexes					
T2DM	7,411	3,886	36,499	106.5 (103.1–109.9)	1.52 (1.47–1.58)
Non-T2DM	48,726	18,755	268,137	69.9 (68.9–71.0)	1.0 (ref.)
Men					
T2DM	4,695	2,344	24,189	96.9 (93.0–100.9)	1.53 (1.46–1.60)
Non-T2DM	31,825	11,434	180,719	63.3 (62.1–64.4)	1.0 (ref.)
Women					
T2DM	2,716	1,542	12,310	125.3 (119.1–131.7)	1.50 (1.42–1.58)
Non-T2DM	16,901	7,321	87,418	83.7 (81.8–85.7)	1.0 (ref.)

Ref: Huifang Liang et al. Diabetes Care 2014;37:1329–1337

PEGASUS-TIMI 54: Efficacy and Safety of Ticagrelor 60 mg vs ASA in Patients with Diabetes

	Ticagrelor 60 mg bid	Placebo	Hazard ratio (95% CI)	P value
Efficacy	N=2308	N=2257		
CV death, MI or stroke (%)	10.00	11.60	0.83 (0.69–1.004)	0.0547
CV death (%)	3.79	4.97	0.74 (0.55–0.99)	0.0428*
MI (%)	5.97	6.51	0.90 (0.70–1.15)	0.39
Stroke (%)	1.77	2.46	0.69 (0.46–1.06)	0.0906
All-cause death (%)	6.18	7.11	0.84 (0.66–1.06)	0.15
CHD death (%)	2.14	3.35	0.64 (0.43–0.94)	0.0214*
Safety	N=2281	N=2238		
TIMI major bleeding (%)	2.51	0.98	2.47 (1.40–4.35)	0.0018*
TIMI major or minor bleeding (%)	3.22	1.32	2.39 (1.45–3.94)	0.0007*

*Indicates nominal P value
3-year Kaplan Meier event rates are presented
Bhatt DL *et al. J Am Coll Cardiol. 2016 Jun 14;67(23):2732-40*

THEMIS Study Design (New RCT on Ticagrelor)

THEMIS is a multinational, randomized, double-blinded Phase III trial to compare BRILINTA bid vs. placebo for the prevention of CV events in patients with T2DM at high risk of CV events*†[1,2]

Duration of follow-up: up to 58 months (1,385 events occurred)

Patients with T2DM at high risk of CV events* (n~19,300)

R

BRILINTA 60 mg bid†
Low-dose ASA (≤150 mg) od unless contraindicated or not tolerated

Placebo†
Low-dose ASA (≤150 mg) od unless contraindicated or not tolerated

Primary efficacy endpoint: time to first occurrence of MACE (CV death, MI or stroke)

Secondary efficacy endpoints: CV death, MI, ischaemic stroke, all-cause death

Primary safety endpoint: TIMI Major bleeding

Top Line Results: Q1 2019

Result presentation: TBD 2019

Inclusion criteria: T2DM patients ≥50 years of age treated with ≥6 months glucose lowering therapy, with either documented CAD or previous revascularization of a coronary artery

Key exclusion criteria:

- History of MI or stroke
- Planned use of blood clotting agents or ASA >150 mg od
- Planned coronary/cerebrovascular/peripheral artery revascularization
- Known bleeding disorders
- Treatment with OAC or LMWH
- History of ICH (any time) or GI bleeding (last 6 months)
- Major surgery within last 30 days
- Severe liver disease or CKD requiring dialysis

*High risk of CV events defined as: history of PCI/CABG, or angiographic evidence of ≥50% lumen stenosis of at least one coronary artery; †BRILINTA 60 mg: initially, BRILINTA 90 mg or corresponding placebo was the selected dose, but reduced to BRILINTA 60 mg or corresponding placebo in Clinical Study Protocol Amendment No. 1

ASA, acetylsalicylic acid; bid, twice daily; CABG, coronary artery bypass graft; CKD, chronic kidney disease; GI, gastrointestinal; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; OAC, oral anticoagulation; od, once daily; PCI, percutaneous coronary intervention; R, randomization

1. Held P *et al. Future Cardiol.* 2016;12:405–18; 2. NCT01991795. https://clinicaltrials.gov/show/NCT01991795. Accessed: October 2018

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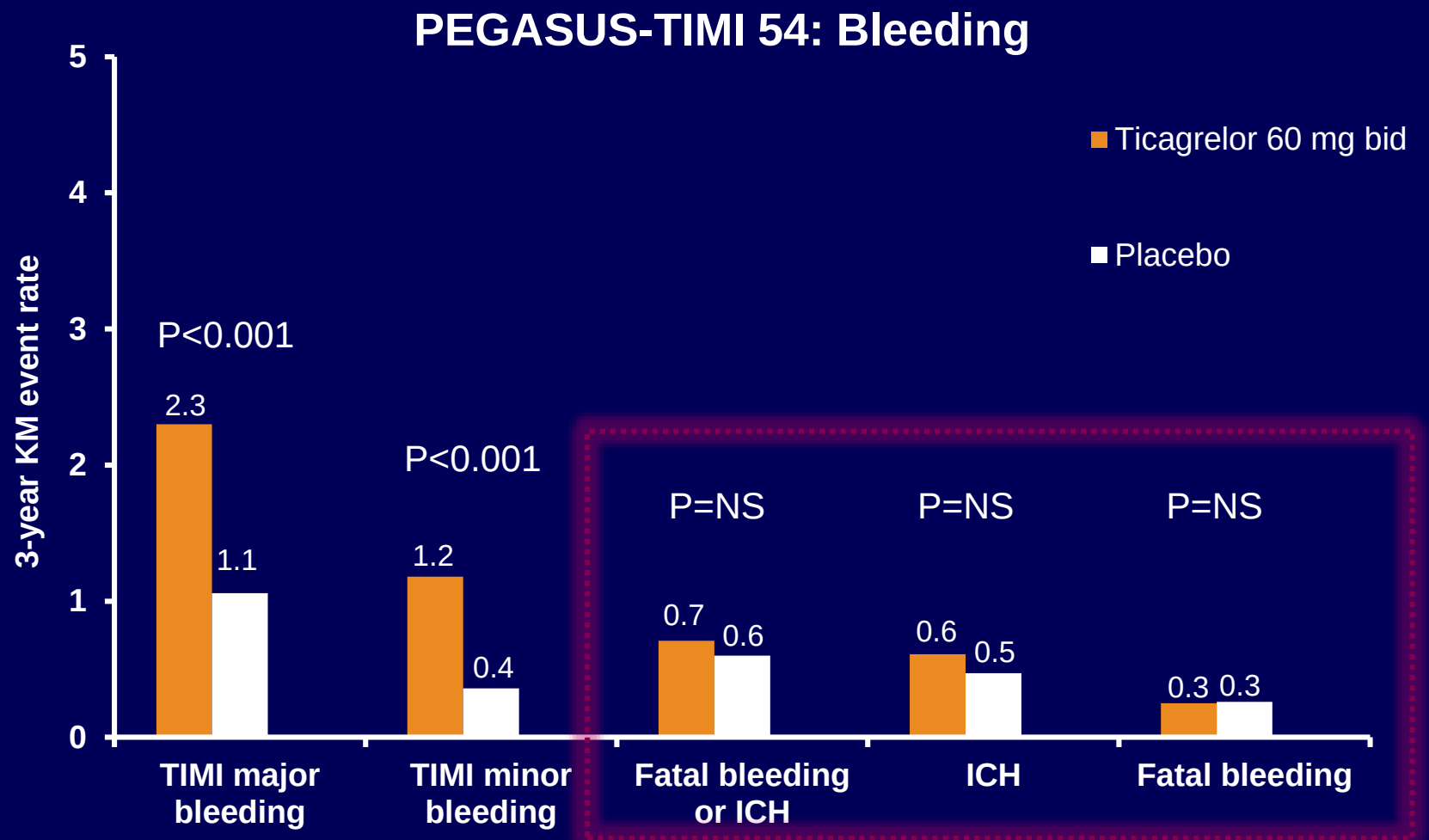
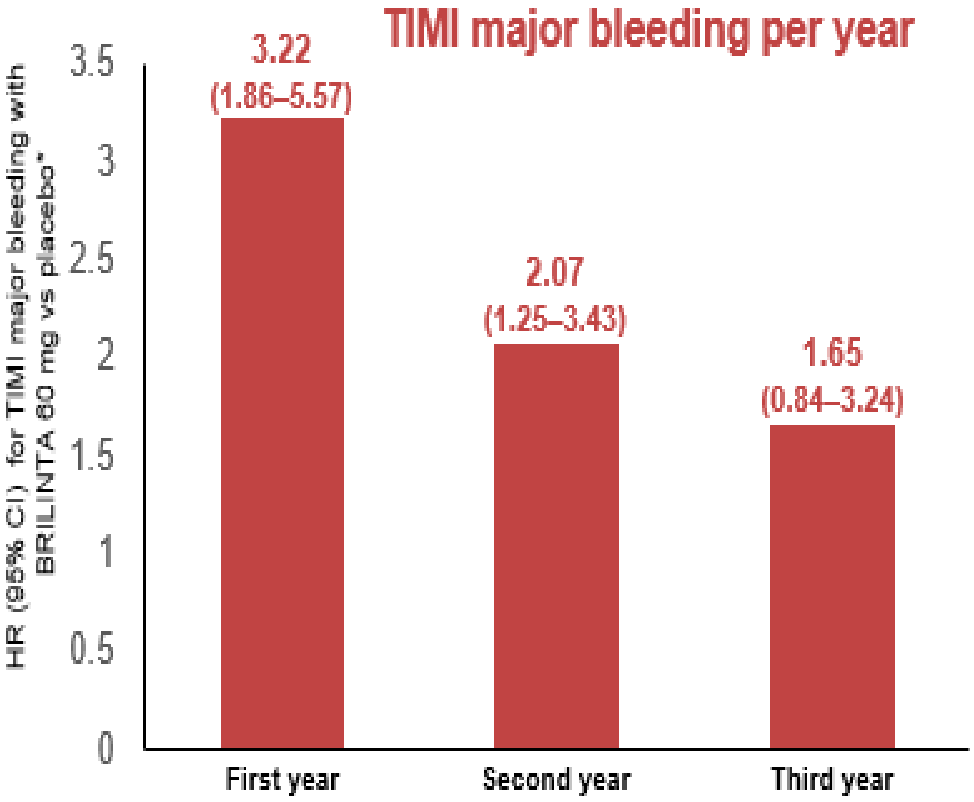
Ticagrelor 60mg did not increase intracranial haemorrhage or fatal bleeding compared to ASA, despite of increasing TIMI major bleeding



Rates are presented as 3-year Kaplan-Meier estimates
P<0.026 indicates statistical significance

Bonaca MP et al. N Engl J Med 2015;372:1791–1800

BRILINTA 60 mg* was associated with an expected increased risk of major bleeding for each year, but showed a trend towards less bleeding over the duration of PEGASUS trial

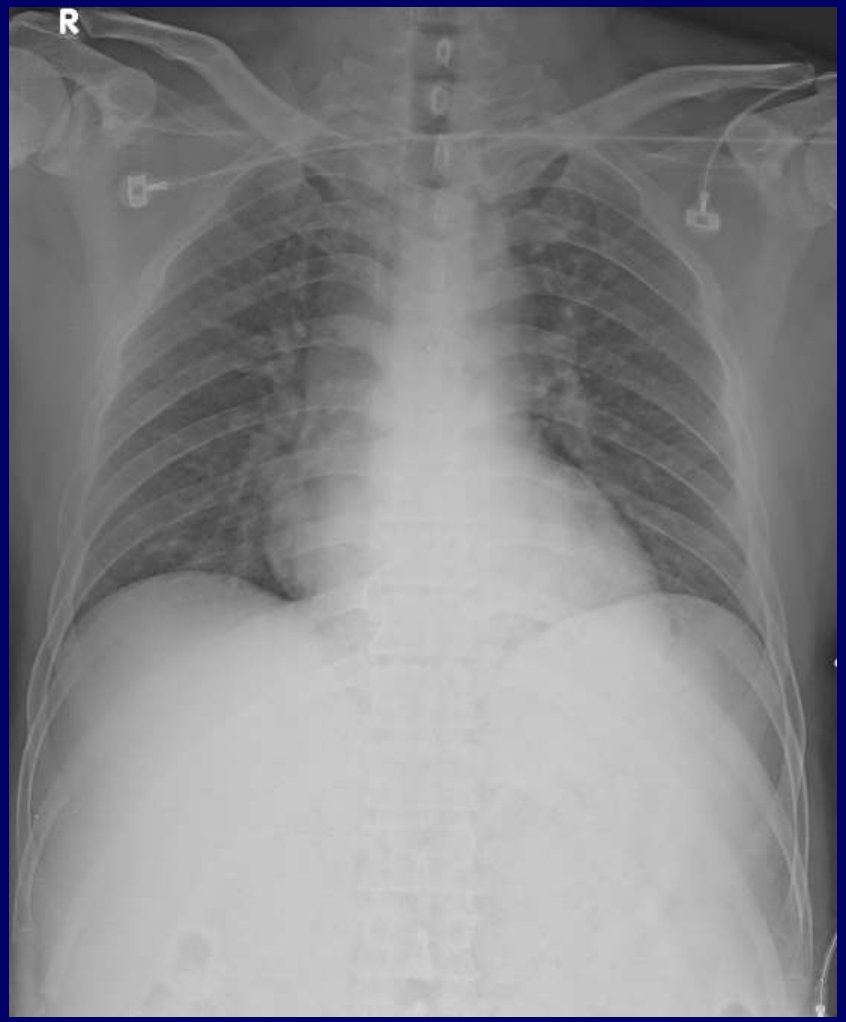


No significant increase in ICH or fatal bleeding was observed for BRILINTA 60 mg + ASA (vs ASA alone) during any of the 3 years of follow-up

Bonaca, M.P. et al. J Am Coll Cardiol. 2017;70(11):1368–75.

Ticagrelor Case

- Male/ 42 years old
- Ongoing Chest pain for 30 minutes (2016.03 → ER)
- Underlying disease :
  - Dyslipidemia
  - Medication : None
- 180/110mmHg
- Regular heart beats without murmur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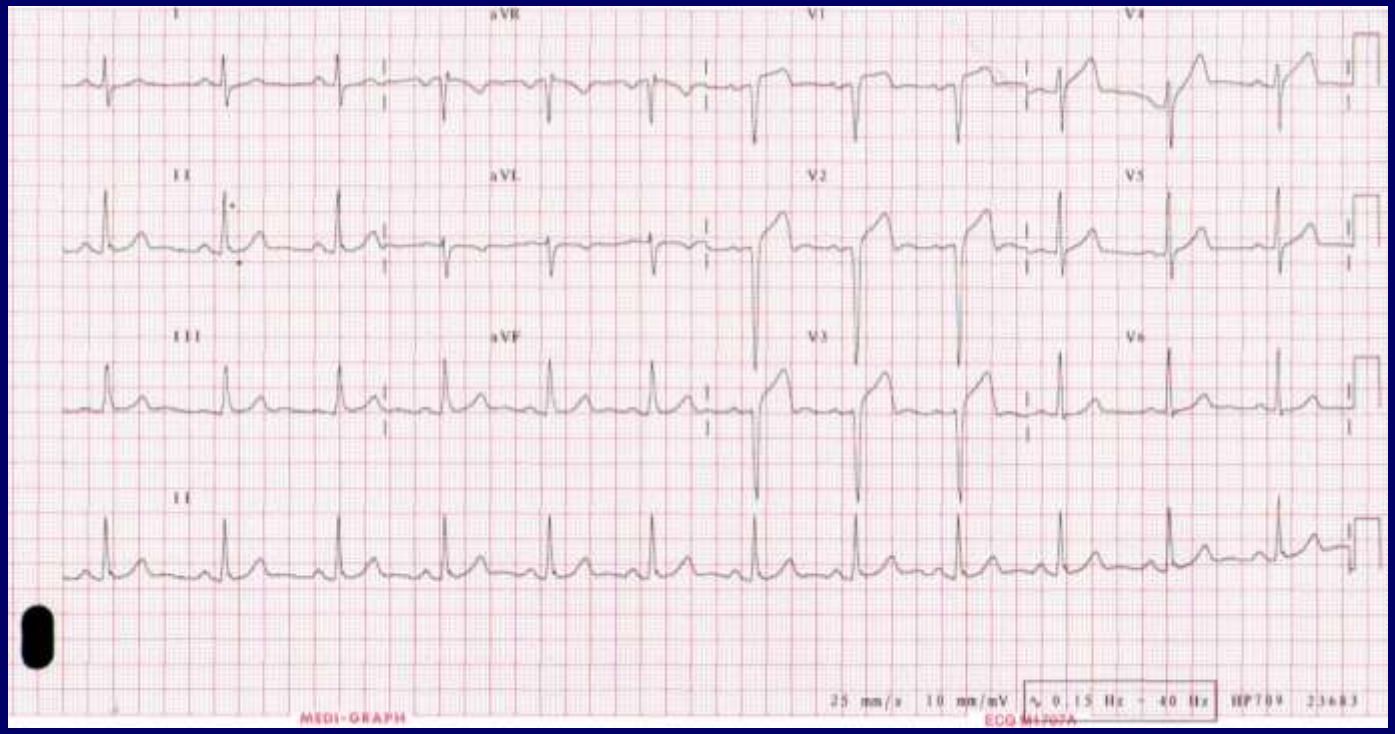
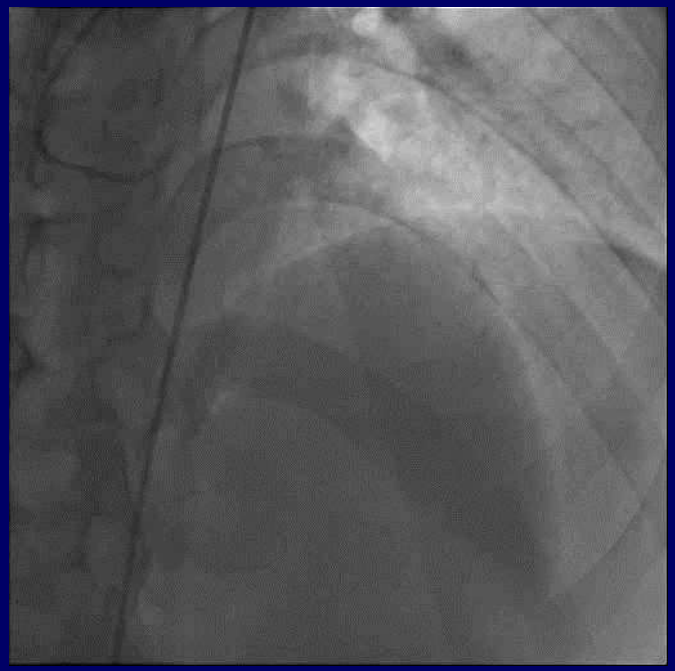
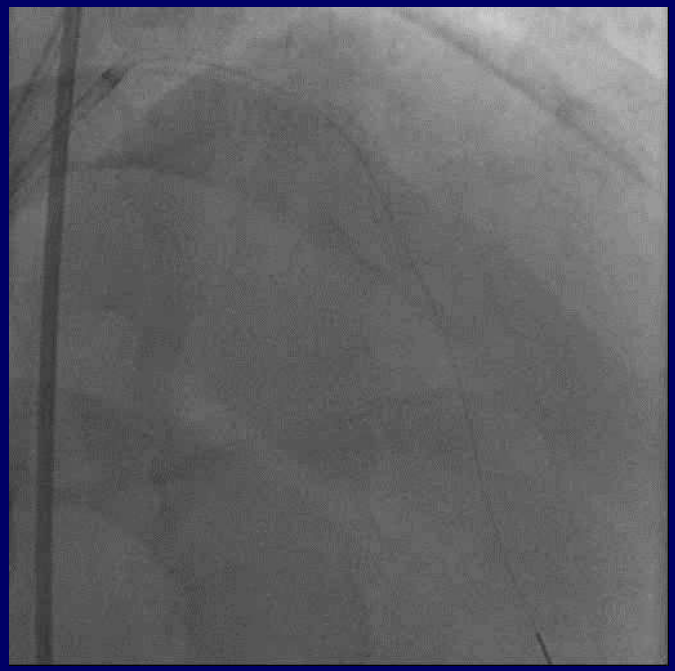
EKG

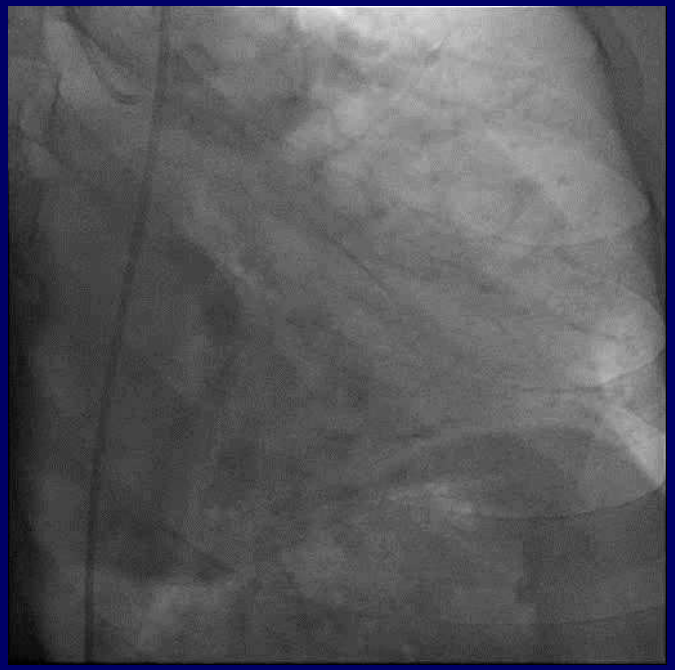

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
25 mm/s
10 mm/mV
0.15 Hz - 40 Hz
MEDI-GRAPH

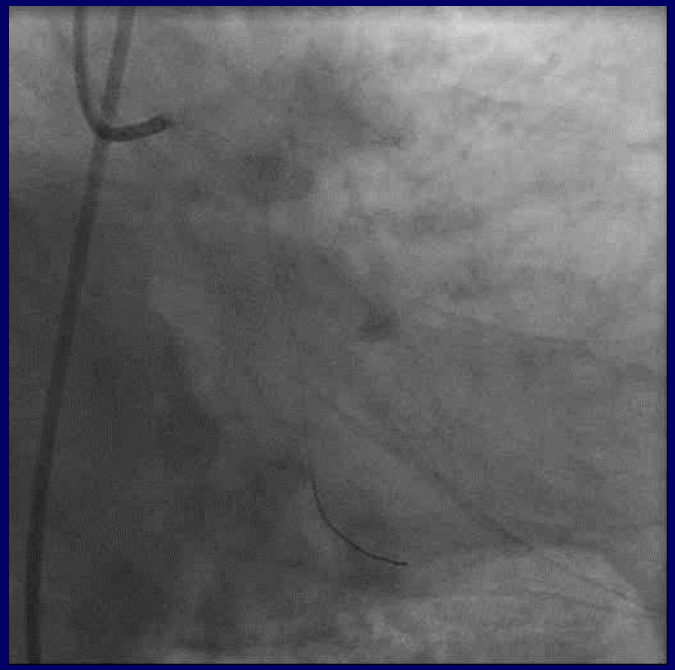
pLAD PCI for STEMI





PTCA for LCX

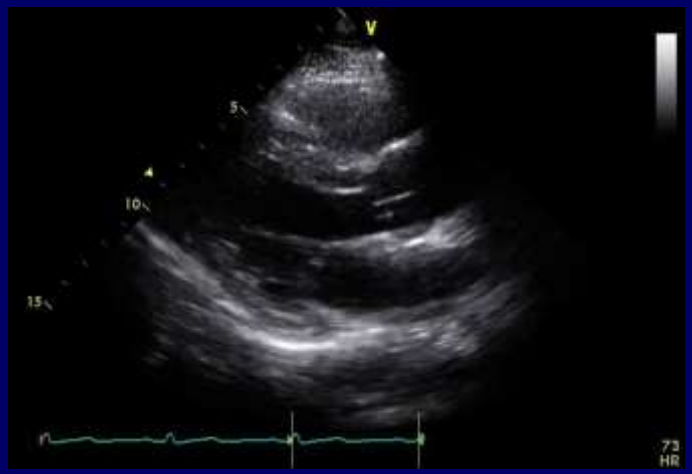


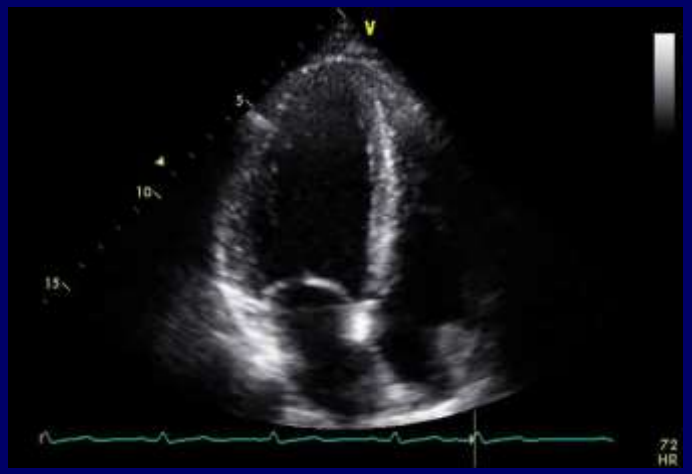


Laboratory findings

- CBC 14.7g/dL -7900/㎕ – 255K
- Electrolyte
  - Na 140mmol/L - K 3.9 mmol/L – Cl 102 mmol/L
- BUN/Cr 14/1.0 mg/dL
- AST/ALT 24/41 IU/L
- CK-MB/Troponin I 1.43 → 80 /0.109 ng/ml
- HbA1c 5.9%
- Total Cholesterol 337mg/dL, TG 214mg/dL
  LDL 194mg/dL, HDL 31mg/dL

TTE

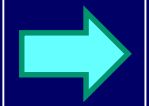




Discharge Medication

For 1 year after PCI

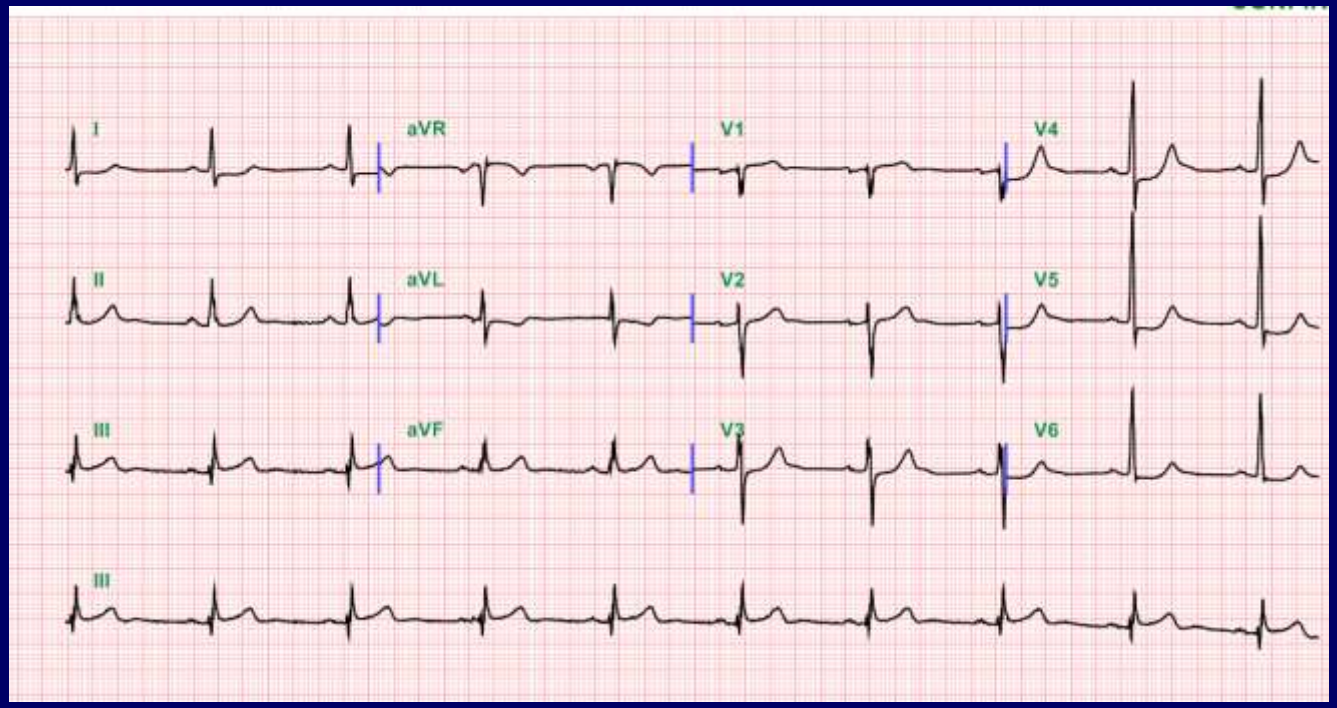
- Aspirin 100mg qd
- Ticagrelor 90mg bid
- Pitavastatin 4mg qd
- Valsartan 80mg qd
- Nebivolol 2.5mg qd



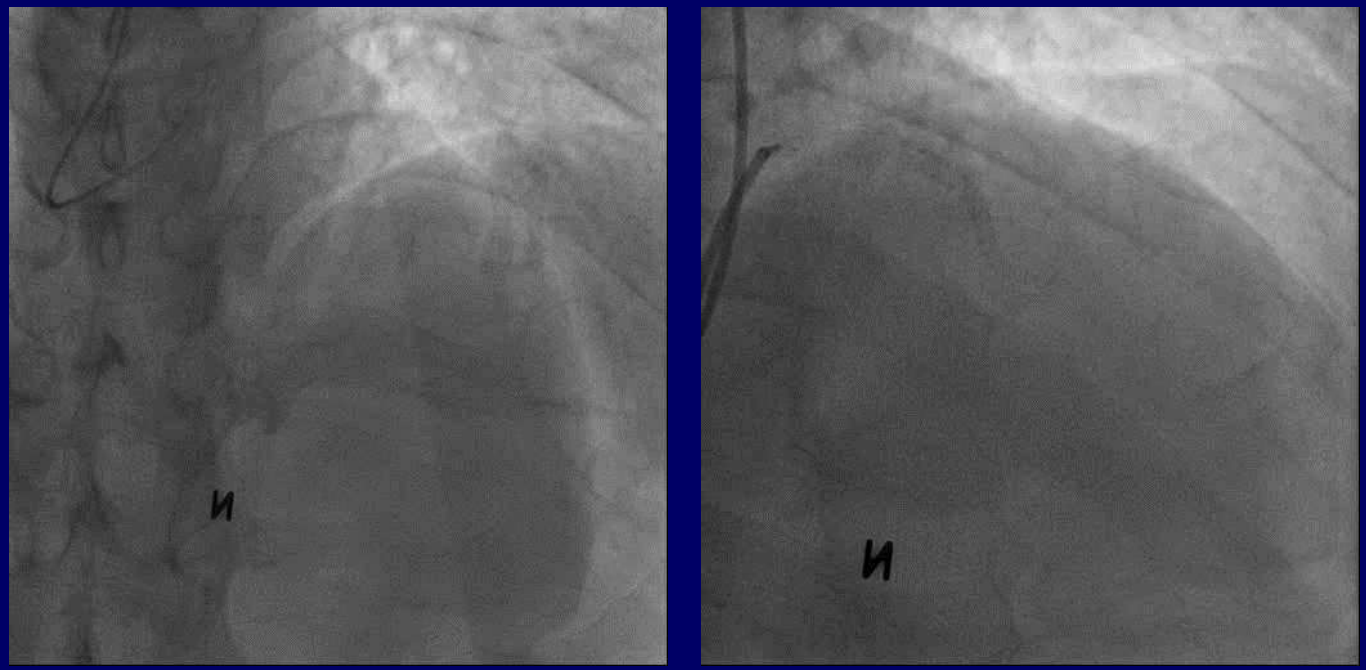
1 year after PCI

- Aspirin 100mg qd
- Clopidogrel 75mg qd
- Pitavastatin 4mg qd
- Valsartan 80mg qd
- Nebivolol 2.5mg qd

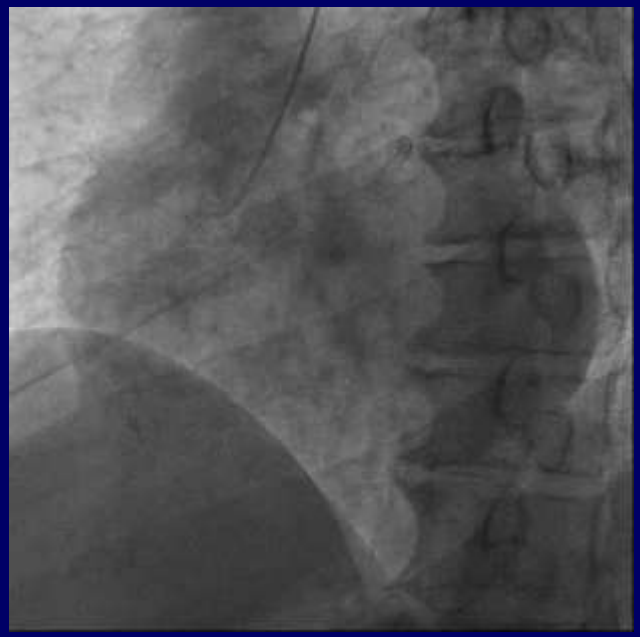
2017.11. 1. Chest Pain Again !

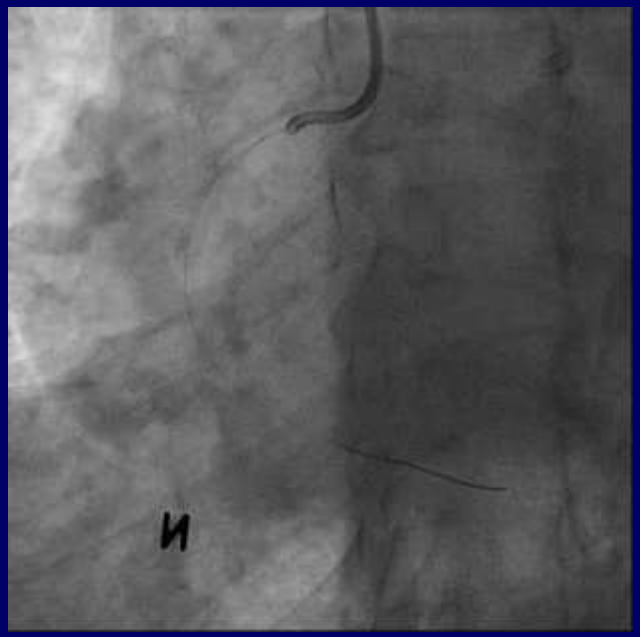


PCI for pLAD ISR



PCI for mRCA

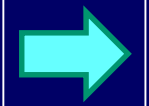




Discharge Medication After 2nd PCI

For 1 year after 2nd PCI

- Aspirin 100mg qd
- **Ticagrelor 90mg bid**
- Rosuvastatin 20mg qd
- Valsartan 80mg qd
- Nebivolol 2.5mg qd
- Diamicron 60mg
- Diabex XR 500mg



1 year after 2nd PCI

- Aspirin 100mg qd
- **Ticagrelor 60mg bid**
- Rosuvastatin 20mg qd
- Valsartan 80mg qd
- Nebivolol 2.5mg qd
- Diamicron 60mg
- Diabex XR 500mg

Summary

- In patients with MI, the risk of a recurrent atherothrombotic event is high and persistent; therefore, patients need protection from CV events
- Combination of risk factors leads to more incidence of CV events
- BRILINTA 60 mg is the only P2Y12 inhibitor proven to reduce atherothrombotic events over 3 years in higher-risk post-MI patients
- BRILINTA 60mg is not only proven in high risk post-MI patients but also expected to expand its use in DM patients, so consistent positive results will change the treatment paradigm in patients with CAD

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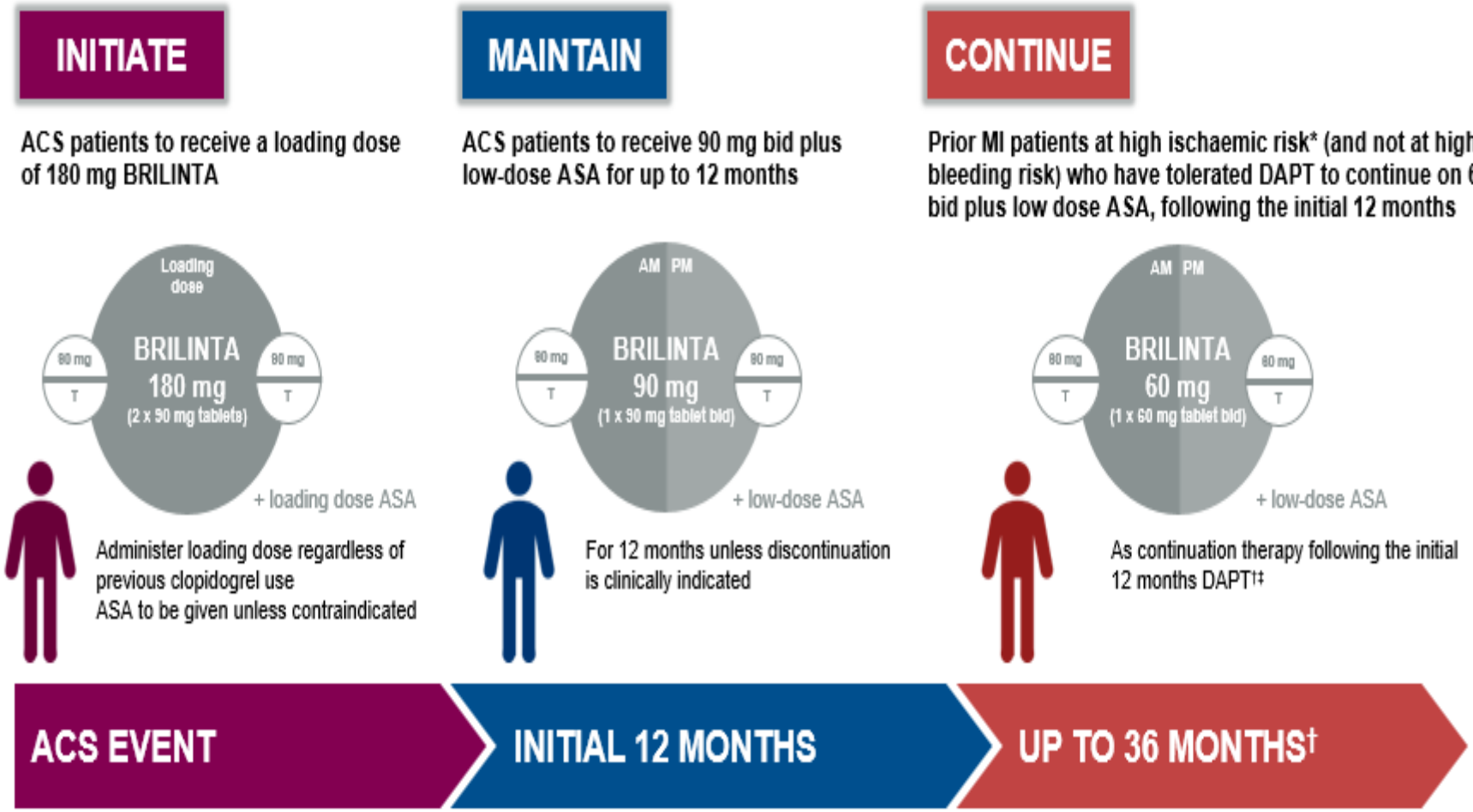
Take home message

BRILINTA is effective in ACS, and provides long-term CV benefits for post-MI patients *[1–3]



*Patients aged ≥50 years with a prior history of MI within 1–3 years and ≥1 additional atherothrombotic risk factor (age ≥65 years, >1 prior MI, multi-vessel disease, diabetes requiring medication, chronic non-end-stage renal dysfunction defined by CrCl <60 mL/min); †There are limited data on the efficacy and safety of BRILINTA beyond 3 years of extended treatment; ‡Or initiated ≤2 years from MI or ≤1 year from previous $P2Y_{12}$ inhibitor treatment

1. AstraZeneca. BRILIQUE Summary of Product Characteristics; 2. Wallentin L *et al. N Engl J* Med 2009;361:1045–1057; 3. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800