

Practical consideration for long DAPT based on patients and lesion selection

Tullio Palmerini
University of Bologna
Italy

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria

Company

- Eli Lilly, Abbott
- Abbott

DAPT trials: 18 RCTs

≤6 months vs ≥ 1 year (n=13)

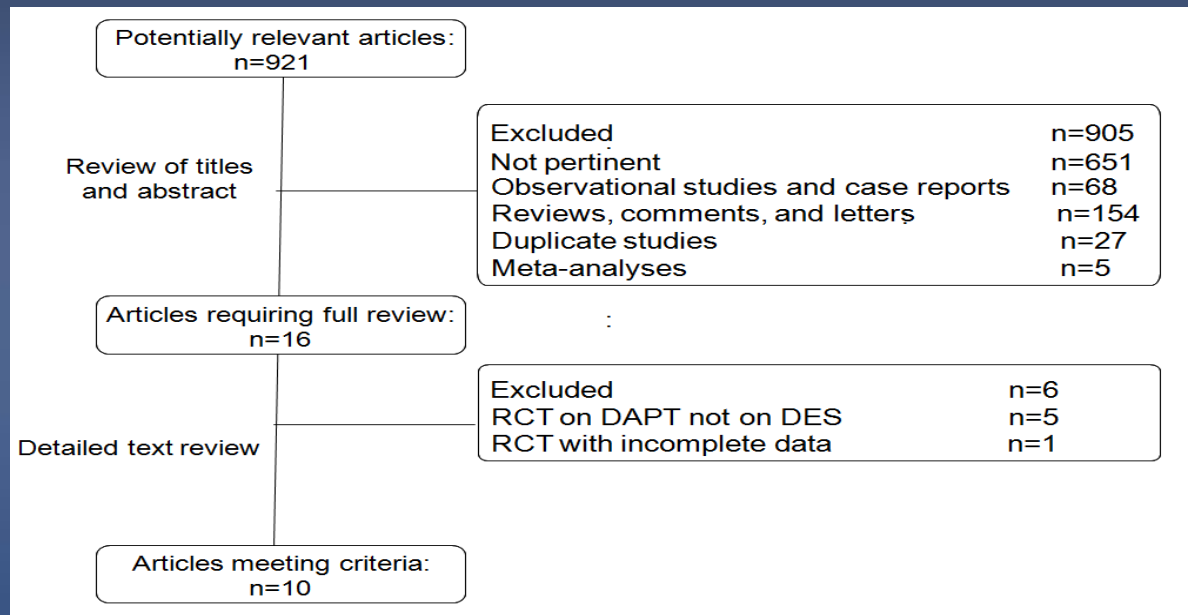
- RESET
 - OPTIMIZE
 - REDUCE
 - EXCELLENT
 - ISAR SAFE
 - SECURITY
 - I LOVE IT
 - IVUS XPL
 - PRODIGY
 - ITALICS
 - NIPPON
 - DAPT STEMI
 - STOP DAPT 2
- 3 RCT: 3 months vs 1 year
- 5 RCT 6 months vs 1 year
- 4 RCT 6 months vs > 1 year
- 1 month vs > 1 year

1 year vs > 1 year (n=5)

- DAPT trial
- DES LATE
- ARCTIC INTERRUPTION
- OPTIDUAL
- Dadjou et al

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone



10 RCT
31,666 pts

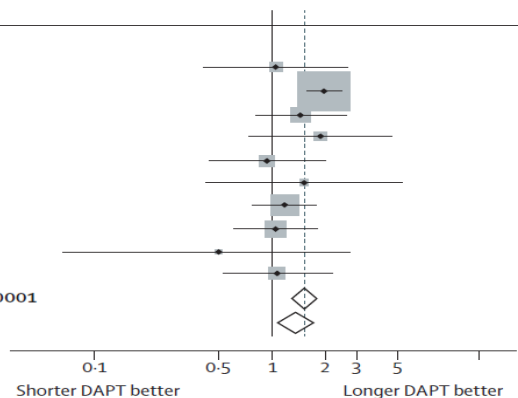
Lancet 2015

Prolonged DAPT: MI and ST

C Myocardial infarction

Study

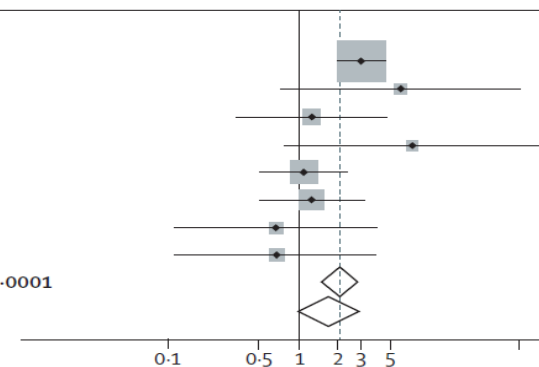
ARCTIC-Interruption, 2014²⁵
 DAPT, 2014¹³
 DES-LATE, 2014¹¹
 EXCELLENT, 2012⁸
 ISAR-SAFE, 2014²⁶
 ITALIC, 2014¹⁷
 OPTIMIZE, 2013⁷
 PRODIGY, 2012¹⁰
 RESET, 2012⁹
 SECURITY, 2014¹⁶
 I-V: ($I^2=29.3\%$, $p=0.17$); p value for ES<0.0001
 D+L: p value for ES=0.01



A Definite or probable stent thrombosis

Study

DAPT, 2014¹³
 EXCELLENT, 2012⁸
 ISAR SAFE, 2014²⁶
 ITALIC, 2014¹⁷
 OPTIMIZE, 2013⁷
 PRODIGY, 2012¹⁰
 RESET, 2012⁹
 SECURITY, 2014¹⁶
 I-V: ($I^2=43.7\%$, $p=0.09$); p value for ES<0.0001
 D+L: p value for ES=0.06

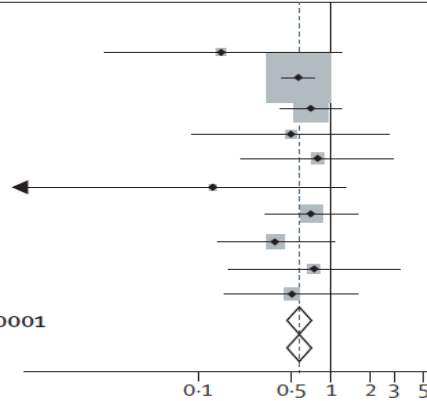


DAPT and bleeding

A Major bleeding

Study

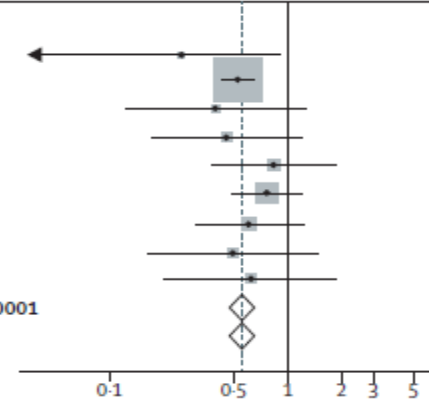
ARCTIC-Interruption, 2014²⁵
 DAPT, 2014¹³
 DES-LATE, 2014¹¹
 EXCELLENT, 2012⁸
 ISAR SAFE, 2014²⁶
 ITALIC, 2014¹⁷
 OPTIMIZE, 2013⁷
 PRODIGY, 2012¹⁰
 RESET, 2012⁹
 SECURITY, 2014¹⁶
 I-V: ($I^2=0.0\%$, $p=0.83$); p value for ES<0.0001
 D+L: p value for ES<0.0001



B Any bleeding

Study

ARCTIC-Interruption, 2014²⁵
 DAPT, 2014¹³
 EXCELLENT, 2012⁸
 ISAR SAFE, 2014²⁶
 ITALIC, 2014¹⁷
 OPTIMIZE, 2013⁷
 PRODIGY, 2012¹⁰
 RESET, 2012⁹
 SECURITY, 2014¹⁶
 I-V: ($I^2=0.0\%$, $p=0.72$); p value for ES<0.0001
 D+L: p value for ES<0.0001



Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting

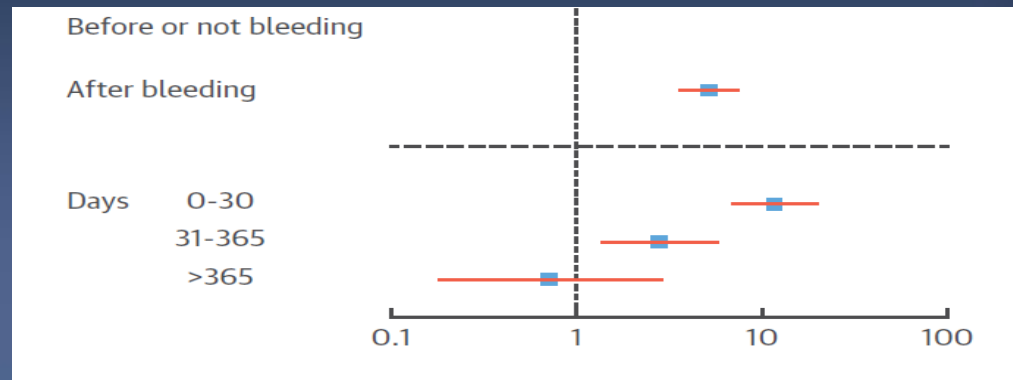
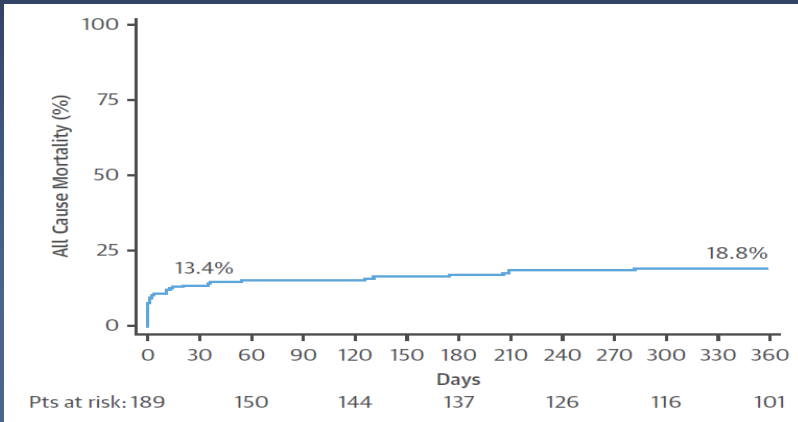


Tullio Palmerini, MD,^a Letizia Bacchi Reggiani, MStat,^a Diego Della Riva, MD,^a Mattia Romanello, MD,^a Fausto Feres, MD,^b Alexandre Abizaid, MD,^b Martine Gilard, MD,^c Marie-Claude Morice, MD,^d Marco Valgimigli, MD, PhD,^e Myeong-Ki Hong, MD, PhD,^f Byeong-Keuk Kim, MD, PhD,^f Yangsoo Jang, MD, PhD,^f Hyo-Soo Kim, MD, PhD,^g Kyung Woo Park, MD,^g Antonio Colombo, MD,^h Alaide Chieffo, MD,^h Jung-Min Ahn, MD,ⁱ Seung-Jung Park, MD,ⁱ Stefanie Schüpke, MD,^j Adnan Kastrati, MD,^j Gilles Montalescot, MD,^k Philippe Gabriel Steg, MD,^l Abdourahmane Diallo, MD,^m Eric Vicaut, MD,^m Gerard Helft, MD,ⁿ Giuseppe Biondi-Zoccai, MD, MStat,^o Bo Xu, MD,^p Yaling Han, MD,^q Philippe Genereux, MD,^r Deepak L. Bhatt, MD, MPH,^s Gregg W. Stone, MD^r

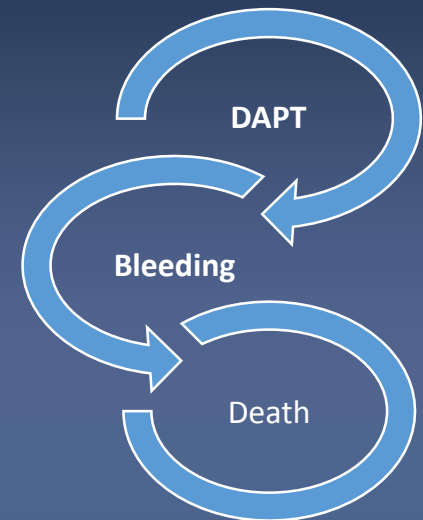
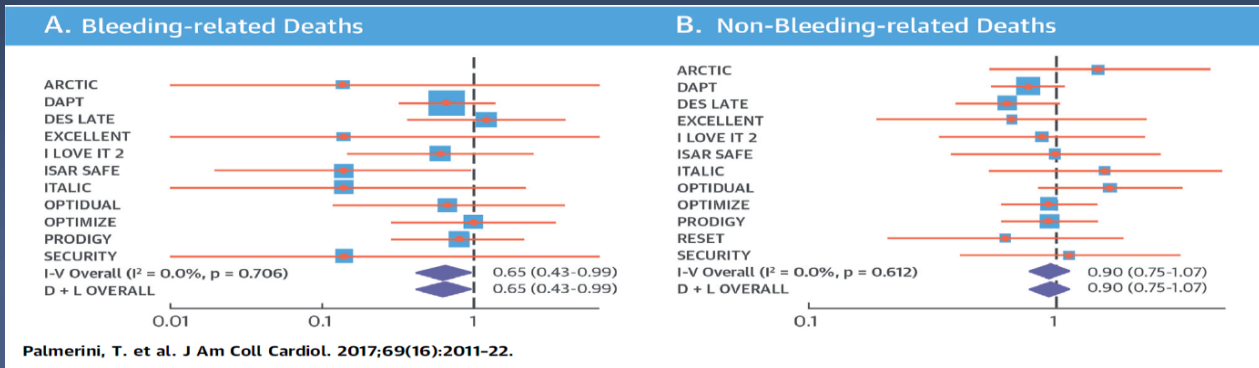
12 randomized studies with 34880 patients

IPD for 6 randomized studies with 11473 patients

Bleeding and mortality



Mechanistic link between DAPT bleeding and mortality



Ischemic vs bleeding risk

- Old age
- Recurrent ischemia
- Recurrent ST
- Complex CAD and PCI
- Diabetes
- PAD
- CKD
- ACS

- Old age
- Prone bleed lesion
- Previous bleeding
- Anemia
- Thrombocytopenia
- Cortison or FANS
- CKD
- Leukocyte count

Shorter vs longer DAPT: the importance of tailoring DAPT

- Clinical presentation

- Diabetes

DAPT Consortium (joint international collaboration)

IPD of 6 randomized trials

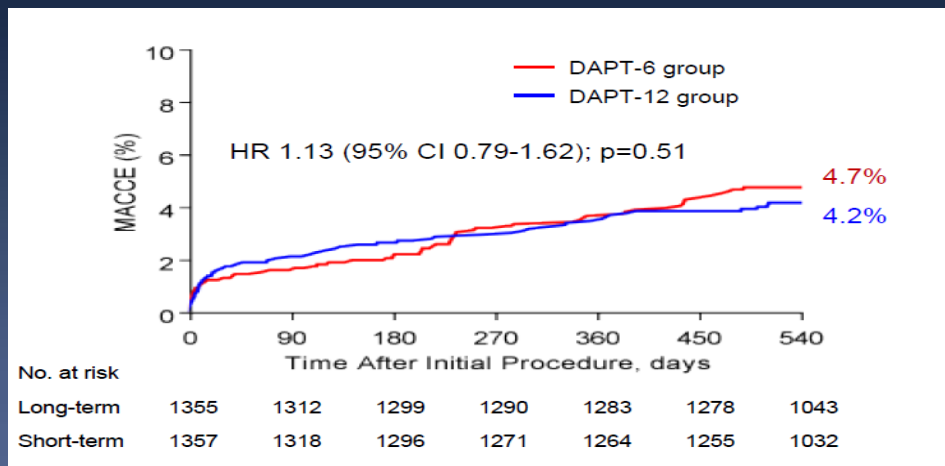
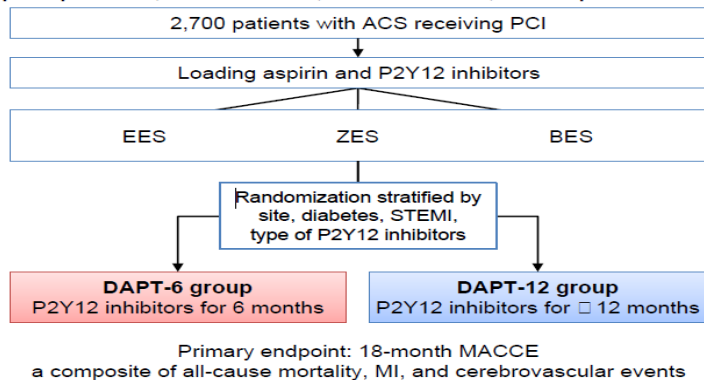
Exploring risk and benefit of DAPT in major subgroups

- Age

- Complexity of CAD

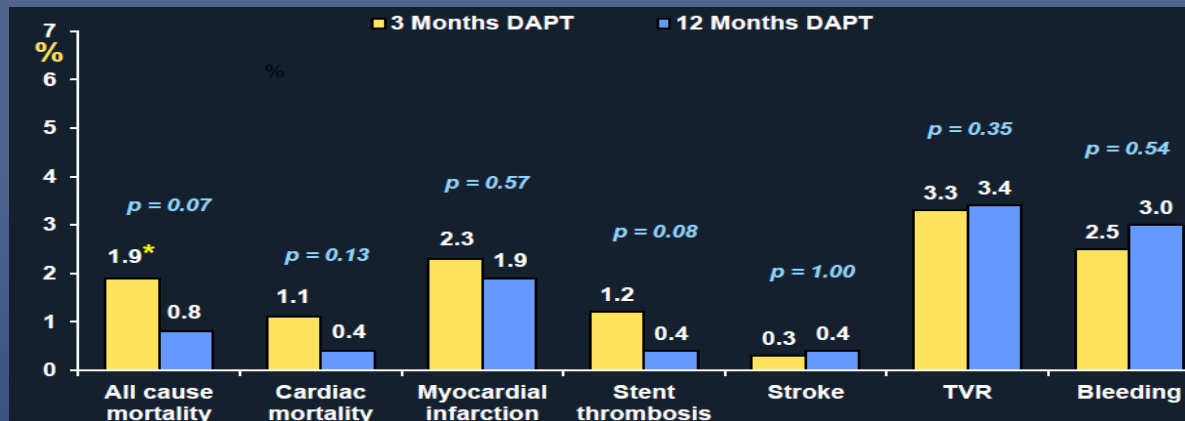
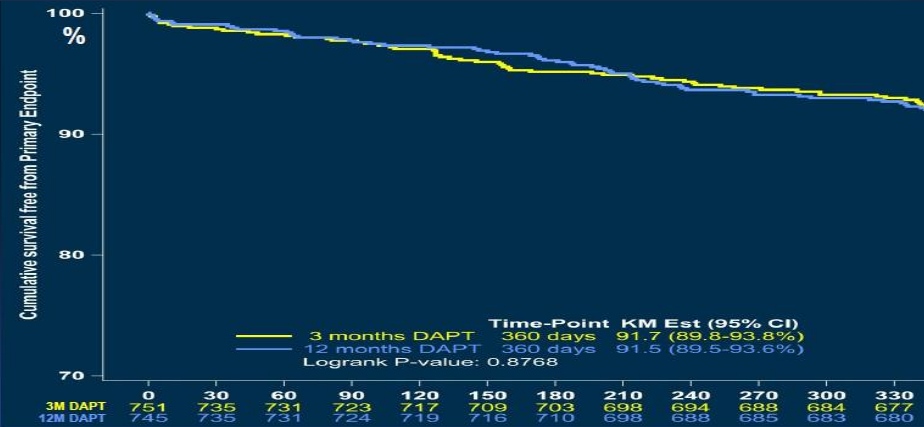
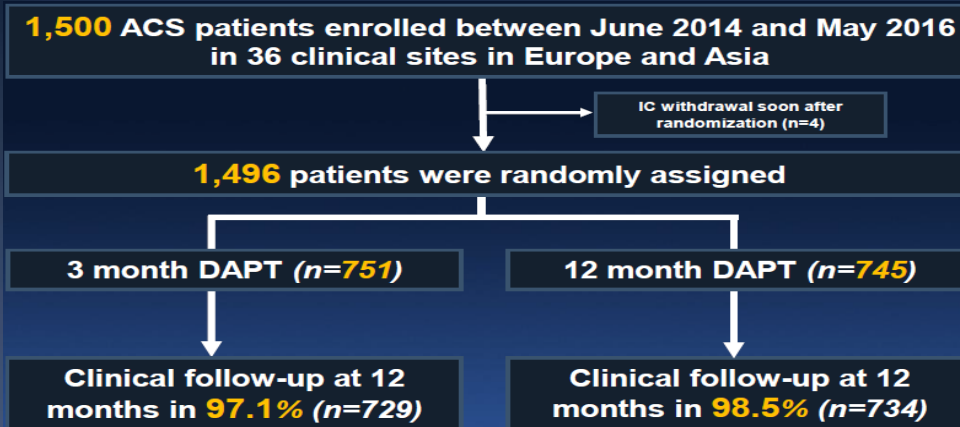
SMART DATE: 6-month vs 1-year DAPT

A prospective, multicenter, randomized, and open-label trial



| | 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 |

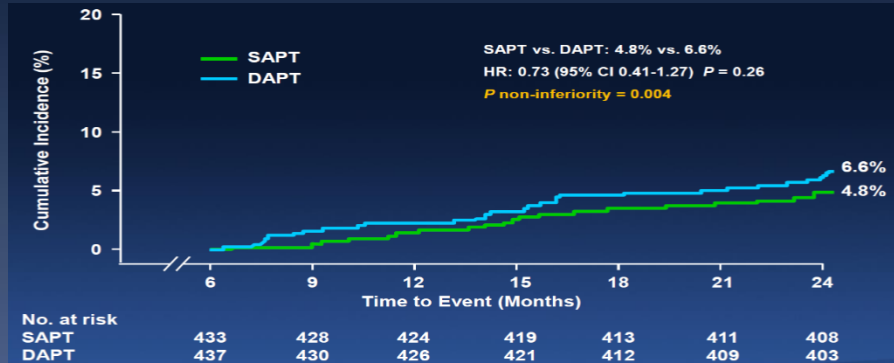
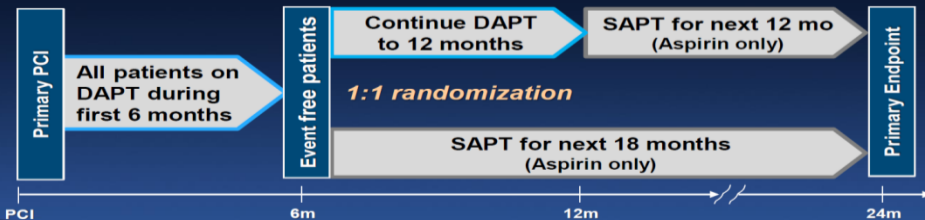
REDUCE: 3-month vs 1-year DAPT



DAPT STEMI: 6-month vs 18 month DAPT

Prospective, International, Randomized, Non-inferiority Trial
STEMI Patients undergoing primary PCI with a second-generation
Zotarolimus-eluting stent (Resolute Integrity)

Enrollment took place in 17 centers in The Netherlands, Poland, Switzerland and Norway



Of the expected 1000 patients only 870 were finally randomized
The observed event rate (4.8%) was lower than the expected event rate (15%)
The non-inferiority margin was relatively wide
Any revascularization was a component of the primary endpoint

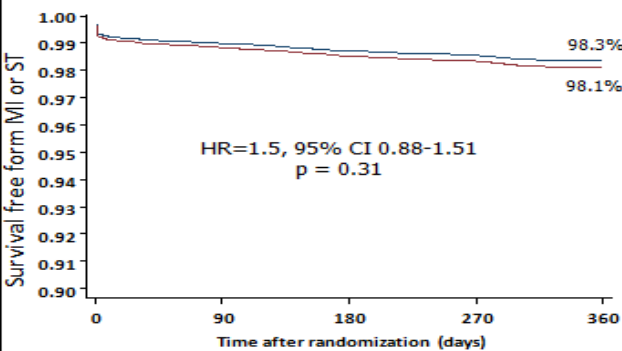


Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients

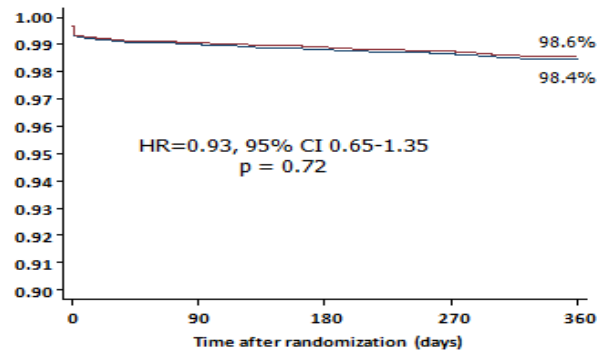
Tullio Palmerini¹, Diego Della Riva¹, Umberto Benedetto², Letizia Bacchi Reggiani¹, Fausto Feres³, Alexandre Abizaid³, Martine Gilard⁴, Marie-Claude Morice⁵, Marco Valgimigli⁶, Myeong-Ki Hong⁷, Byeong-Keuk Kim⁷, Yangsoo Jang⁷, Hyo-Soo Kim⁸, Kyung Woo Park⁸, Antonio Colombo⁹, Alaide Chieffo⁹, Diego Sangiorgi¹, Giuseppe Biondi-Zoccai¹⁰, Philippe Généreux¹¹, Gianni D. Angelini², Maria Pufulete², Jonathon White¹¹, Deepak L. Bhatt¹², and Gregg W. Stone^{11*}

DAPT duration and clinical presentation

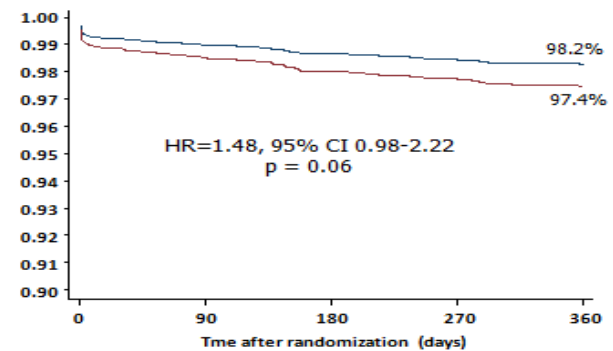
All patients



Stable CAD patients

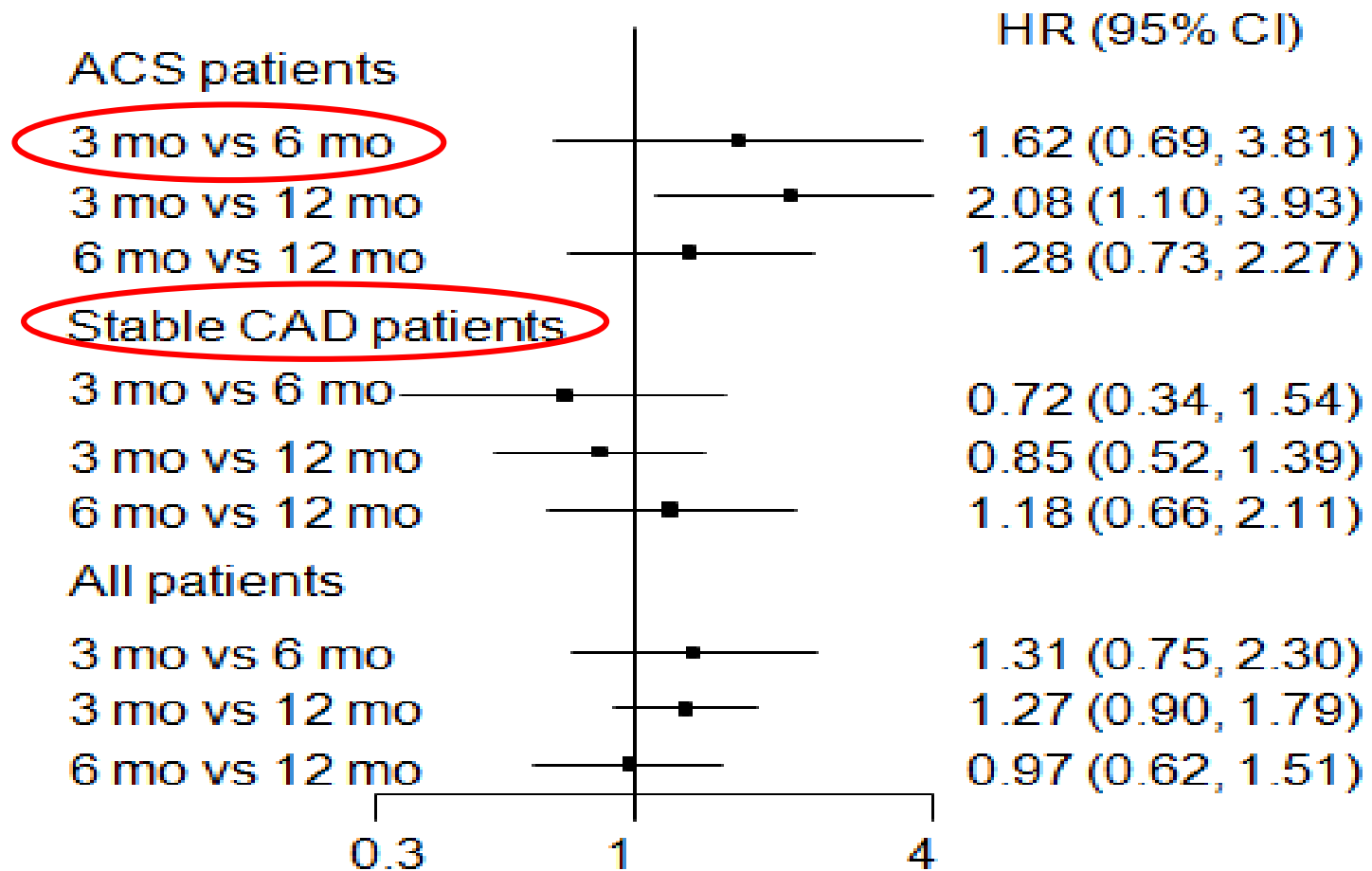


ACS patients



— Long DAPT — Short DAPT

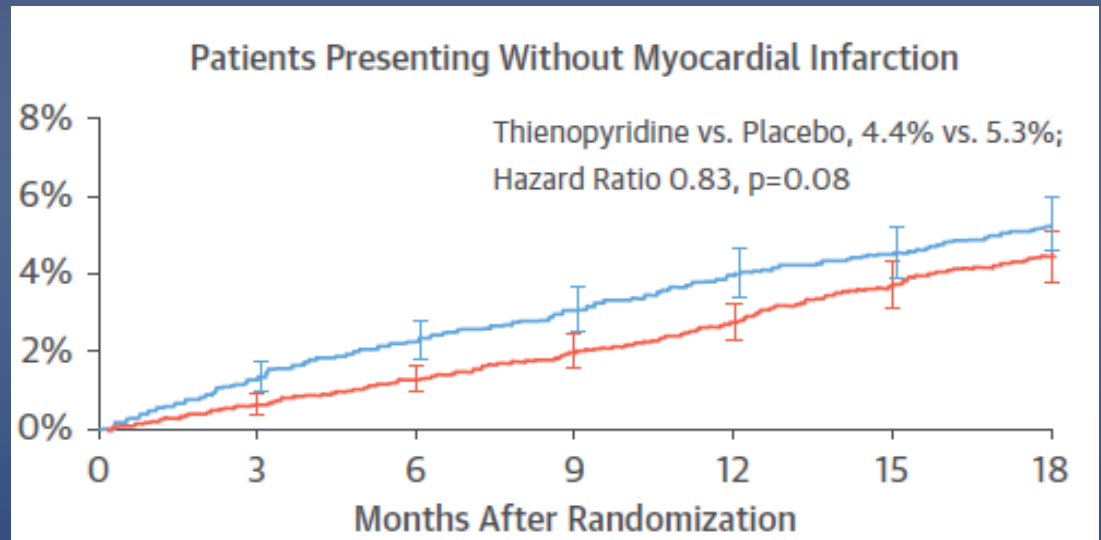
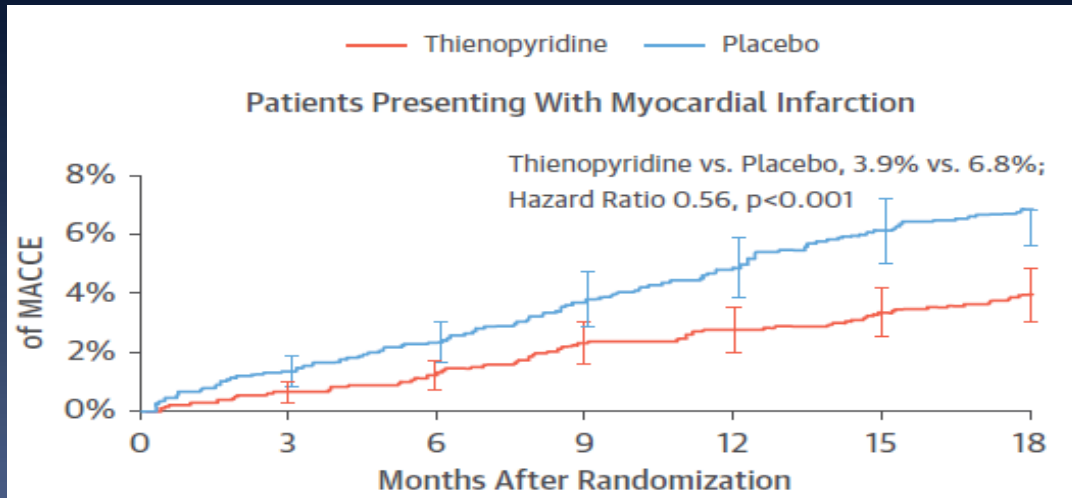
MI, ST



Summary of evidence

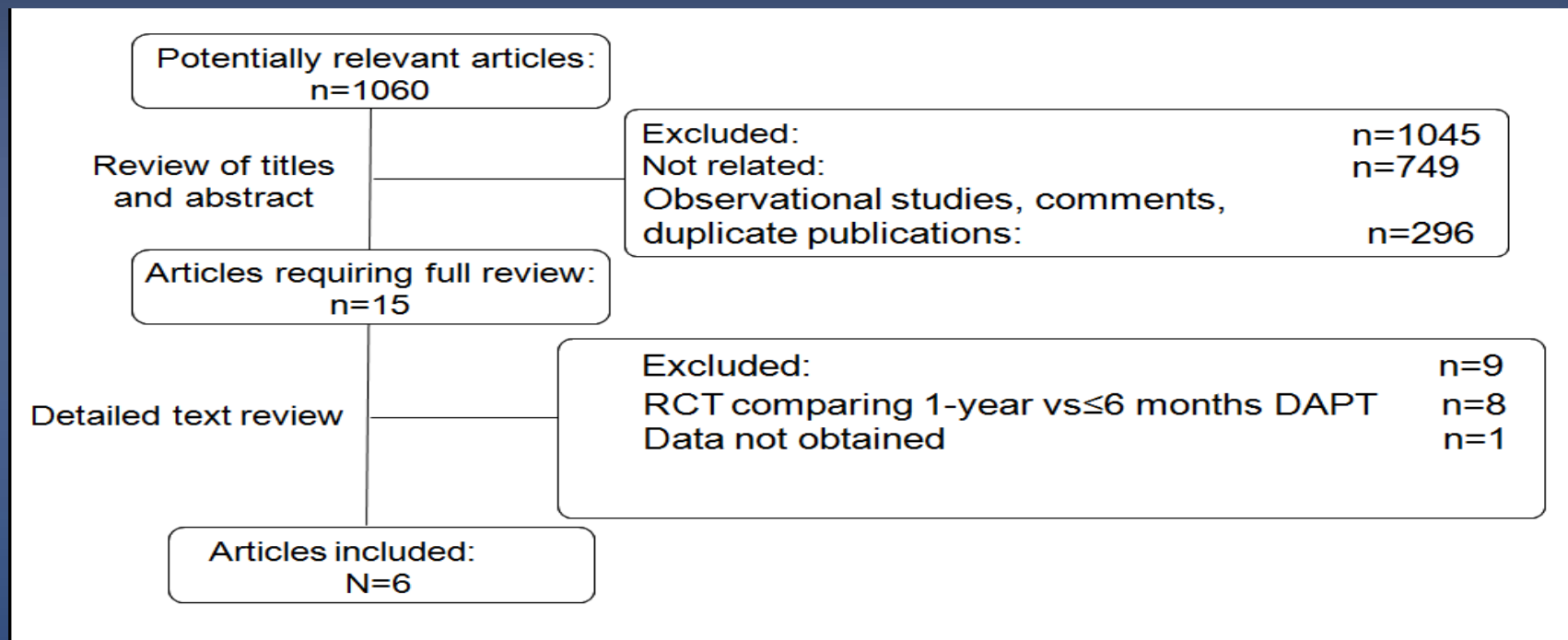
- In patients with ACS at least 1 year DAPT should be recommended, unless the patient is at high risk of bleeding
- In patients with SIHD 3 or 6 month DAPT are enough, unless the ischemic risk is very high

DAPT trial: ACS vs non ACS



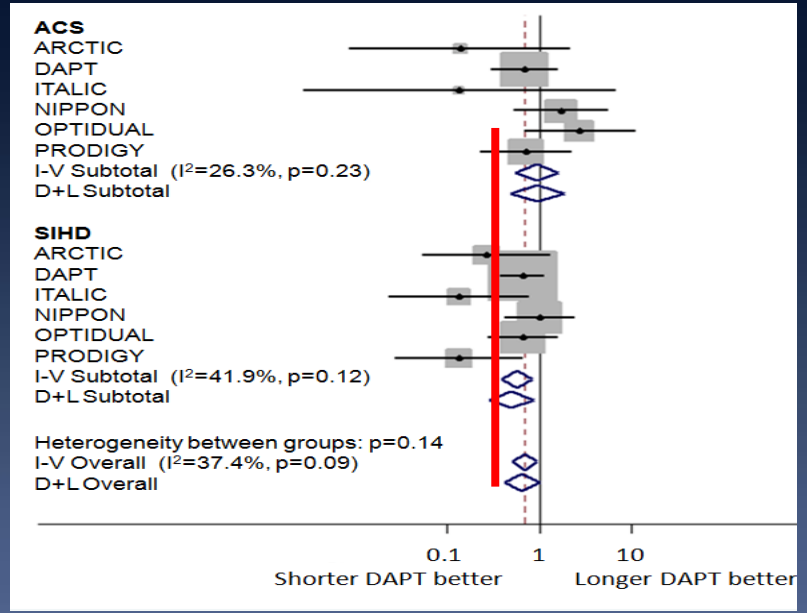
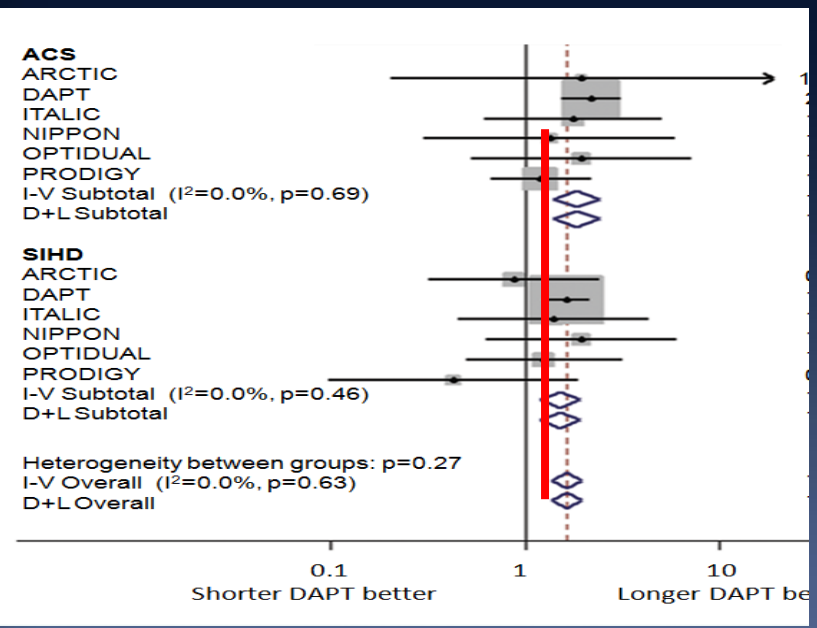
1-year or less versus longer than 1-year DAPT in patients stratified by clinical presentation

Aggregate data based meta-analysis including 6 RCTs and 21,457 patients
14,132 patients with SIHD and 7,325 patients with ACS
Median follow up of 19.5 months

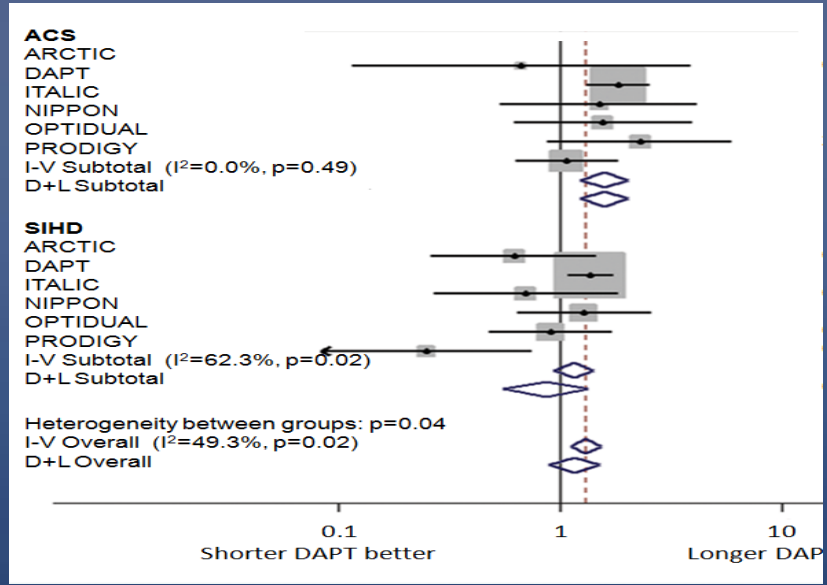


Myocardial infarction

Major bleeding



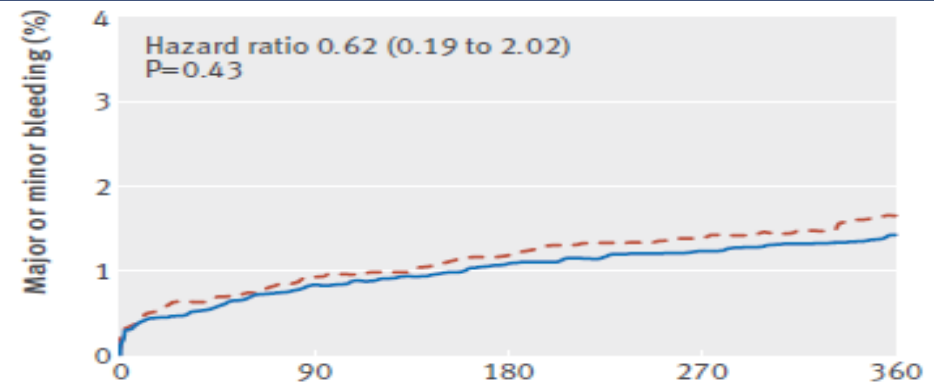
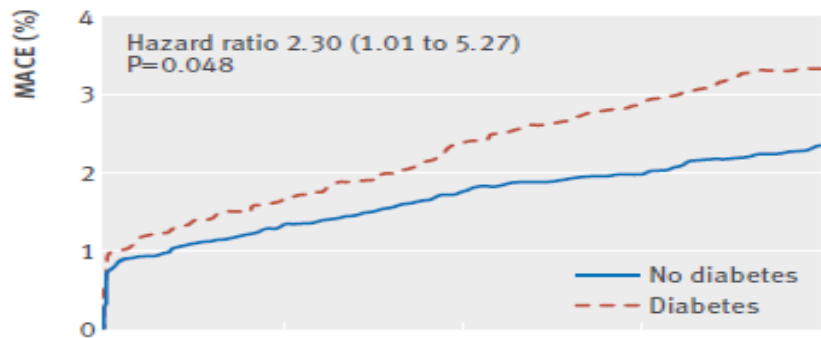
MI and bleeding



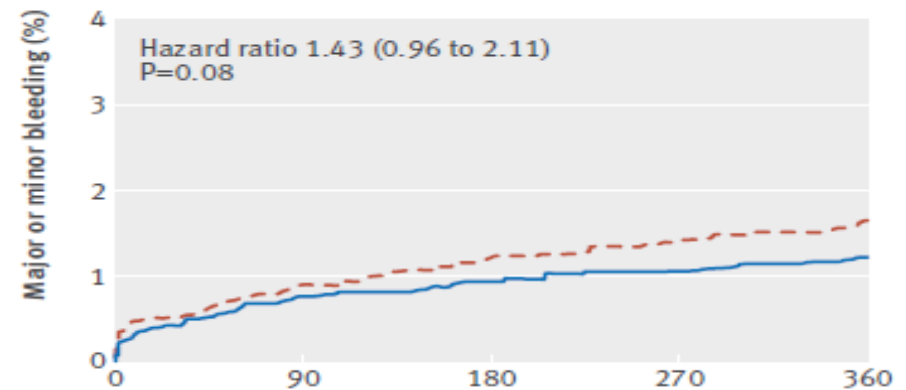
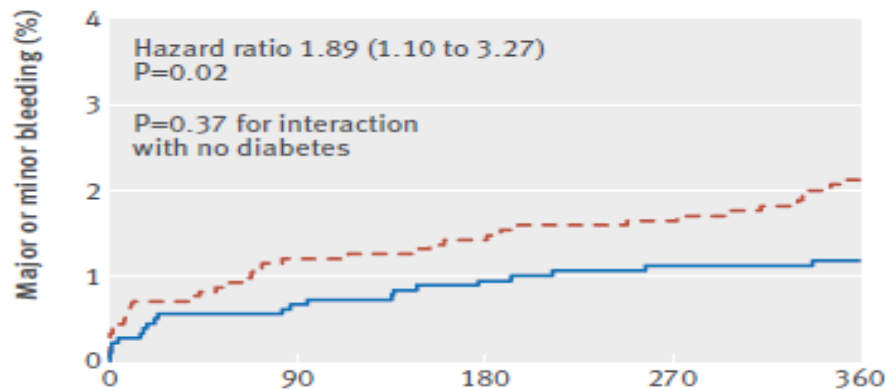
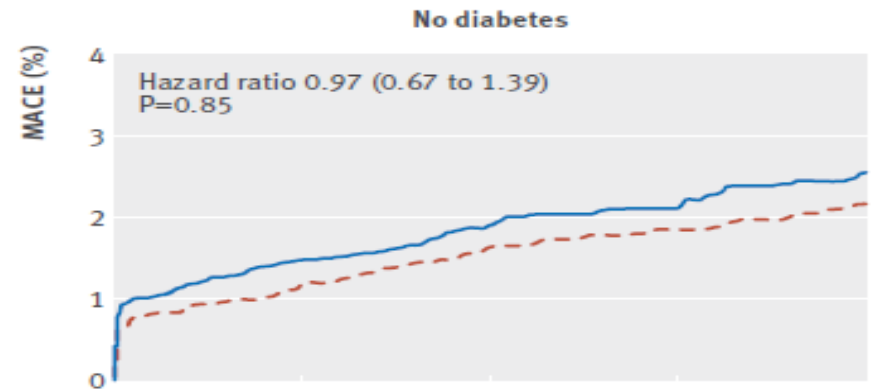
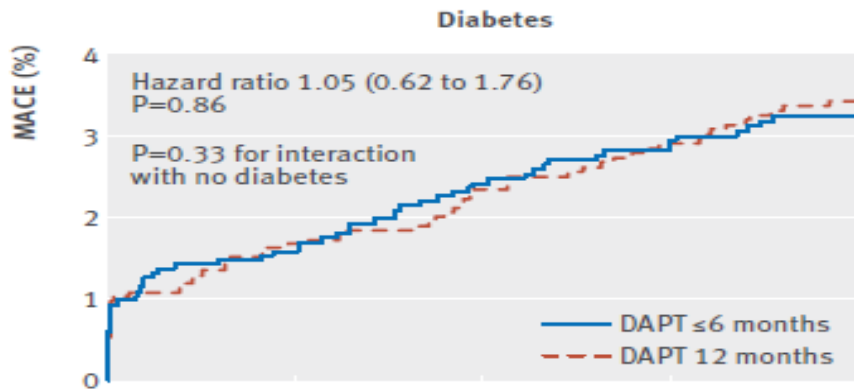
Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials

Giuseppe Gargiulo,^{1,2} Stephan Windecker,¹ Bruno R da Costa,^{1,3} Fausto Feres,⁴ Myeong-Ki Hong,⁵ Martine Gilard,⁶ Hyo-Soo Kim,⁷ Antonio Colombo,⁸ Deepak L Bhatt,⁹ Byeong-Keuk Kim,⁵ Marie-Claude Morice,⁶ Kyung Woo Park,⁷ Alaide Chieffo,⁸ Tullio Palmerini,¹⁰ Gregg W Stone,¹¹ Marco Valgimigli¹

BMJ 2016

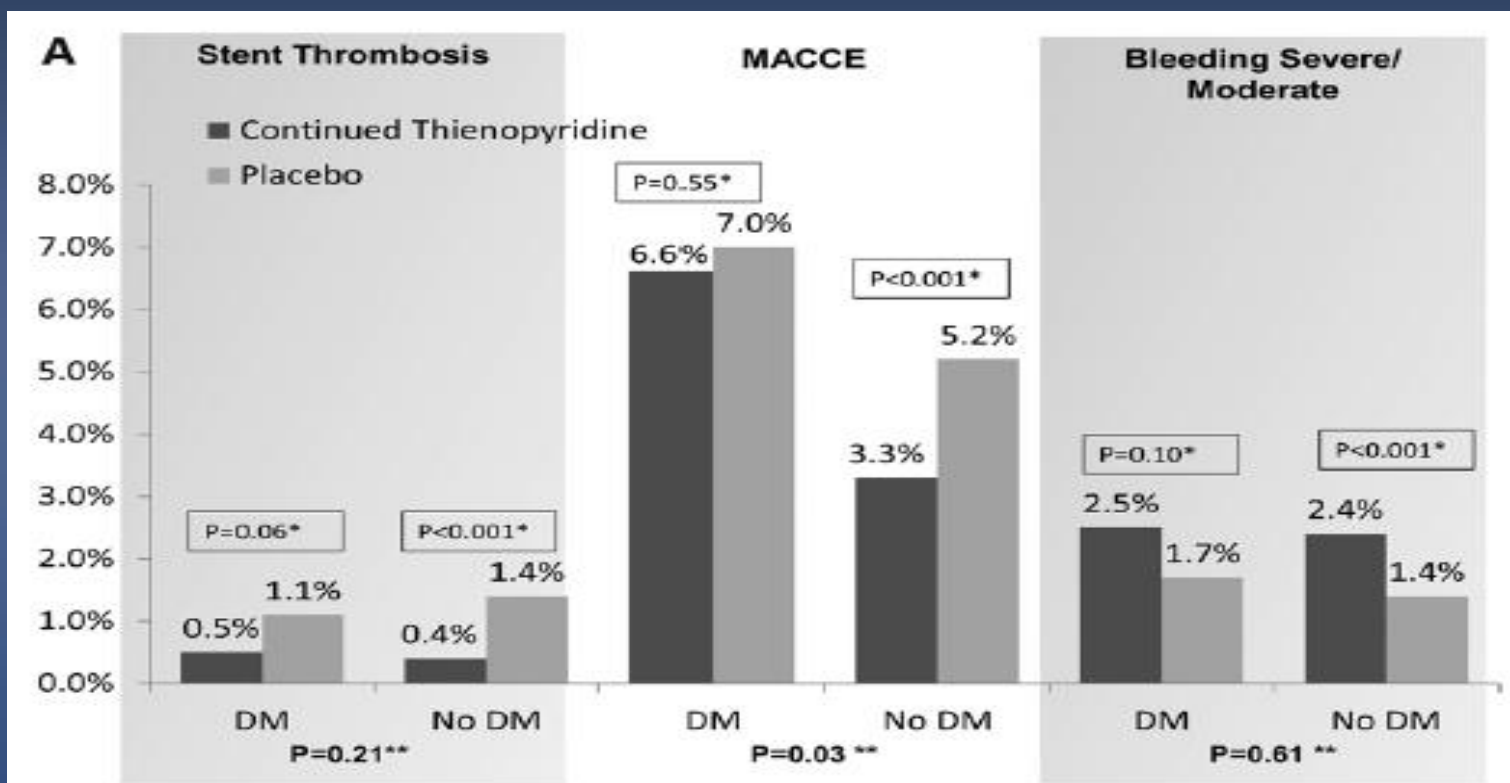


Prolonged DAPT and diabetes



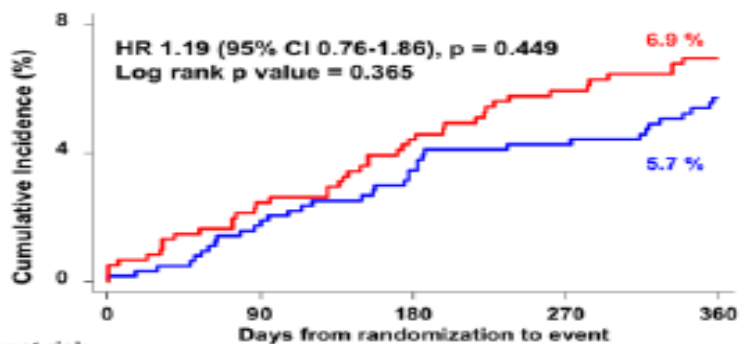
Diabetes Mellitus and Prevention of Late Myocardial Infarction After Coronary Stenting in the Randomized Dual Antiplatelet Therapy Study

Ian T. Meredith, MBBS, PhD; Jean-François Tanguay, MD; Dean J. Kereiakes, MD; Donald E. Cutlip, MD; Robert W. Yeh, MD, MSc; Kirk N. Garratt, MD; David P. Lee, MD; P. Gabriel Steg, MD; W. Douglas Weaver, MD; David R. Holmes, Jr., MD; Ralph G. Brindis, MD, MPH; Jaroslaw Trebacz, MD; Joseph M. Massaro, PhD; Wen-Hua Hsieh, PhD; Laura Mauri, MD, MSc; on behalf of the DAPT Study Investigators



DAPT duration and CKD

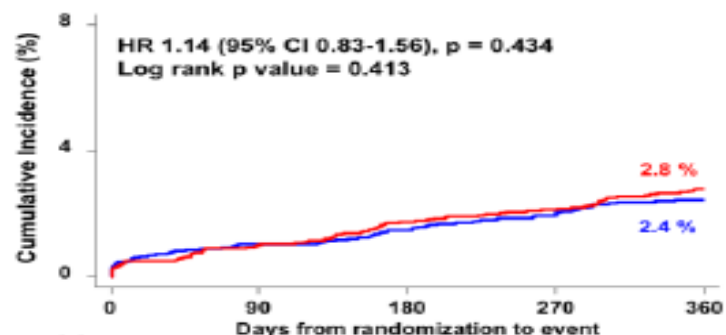
A. CKD Patients



Number at risk

| | 0 | 90 | 180 | 270 | 360 |
|-----------------------|-----|-----|-----|-----|-----|
| DAPT 3 or 6 months | 644 | 627 | 606 | 595 | 570 |
| DAPT ≥ 12 months | 617 | 600 | 576 | 556 | 532 |

C. Non-CKD Patients



Number at risk

| | 0 | 90 | 180 | 270 | 360 |
|-----------------------|------|------|------|------|------|
| DAPT 3 or 6 months | 2929 | 2891 | 2841 | 2788 | 2615 |
| DAPT ≥ 12 months | 3012 | 2972 | 2906 | 2844 | 2647 |

DAPT duration and age

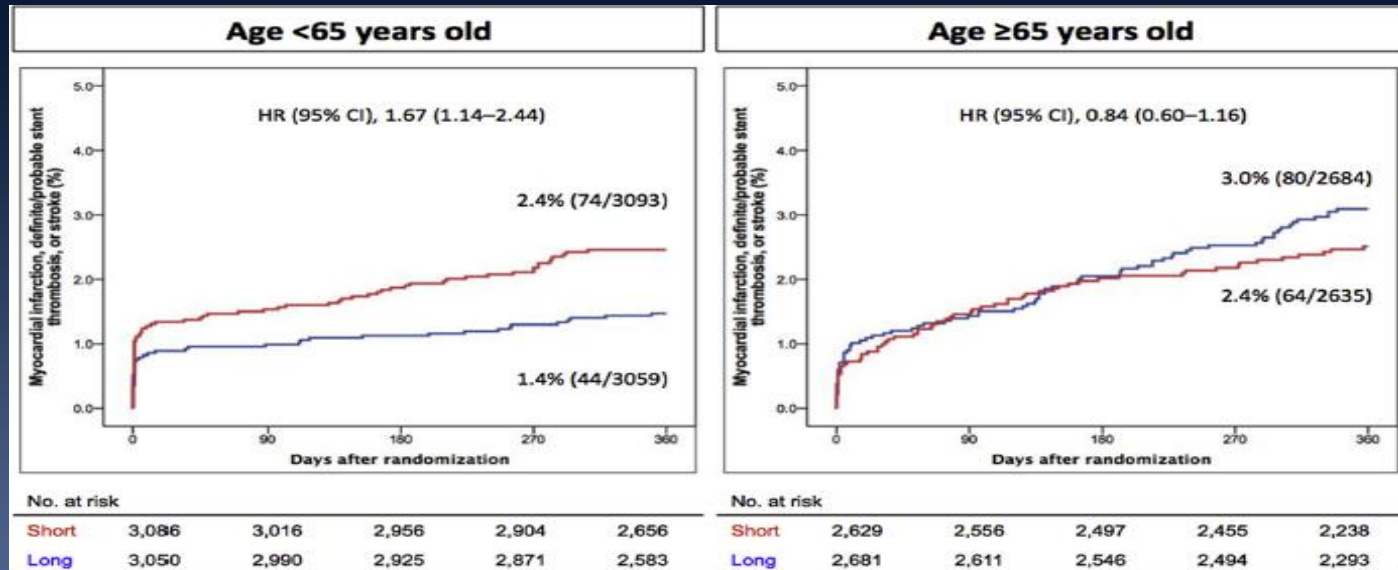


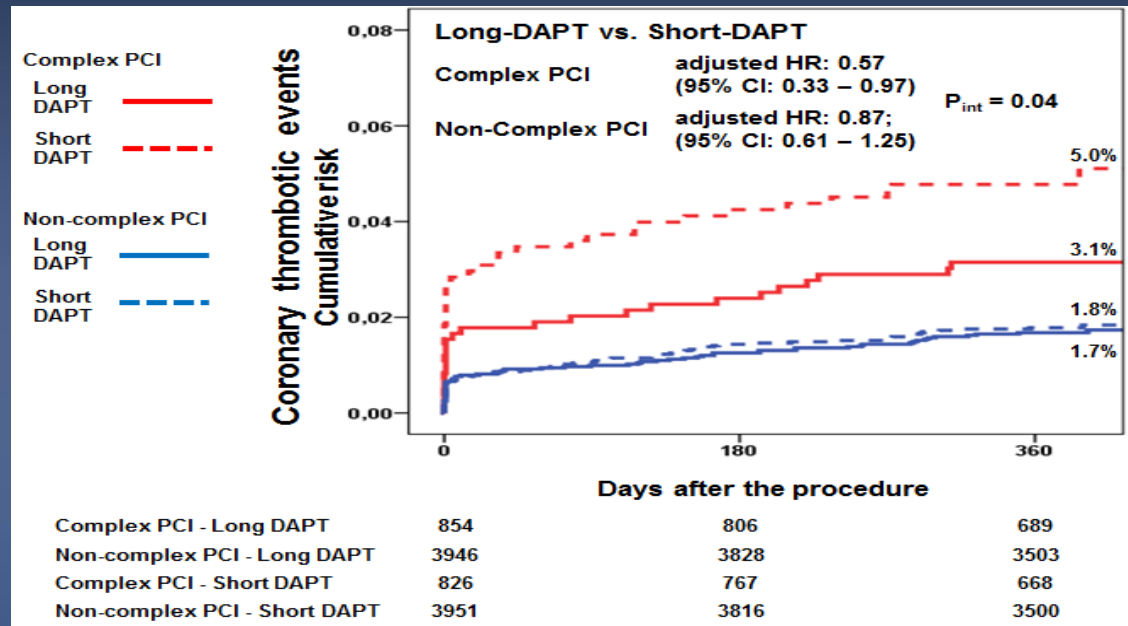
TABLE 2 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients' Age <65 Years of Age

| | ≤6-Month DAPT (n = 3,093) | 12-Month DAPT (n = 3,059) | Unadjusted HR (95% CI) | p Value |
|--|------------------------------|------------------------------|---------------------------|---------|
| All-cause death | 21 (0.7) | 41 (1.3) | 0.50 (0.30–0.85) | 0.0097 |
| Cardiac | 13 (0.4) | 25 (0.8) | 0.51 (0.26–1.00) | 0.0500 |
| Noncardiac | 8 (0.3) | 16 (0.5) | 0.49 (0.21–1.14) | 0.0989 |
| Myocardial infarction | 60 (1.9) | 37 (1.2) | 1.59 (1.05–2.39) | 0.0275 |
| Definite or probable stent thrombosis | 14 (0.5) | 10 (0.3) | 1.37 (0.61–3.09) | 0.4447 |
| Stroke* | 9 (0.3) | 6 (0.2) | – | – |
| Bleeding | 29 (0.9) | 37 (1.2) | 0.76 (0.47–1.24) | 0.2724 |
| Major | 9 (0.3) | 15 (0.5) | 0.59 (0.26–1.34) | 0.2073 |
| Minor | 21 (0.7) | 22 (0.7) | 0.93 (0.51–1.69) | 0.8029 |
| Myocardial infarction or definite/probable stent thrombosis | 65 (2.1) | 40 (1.3) | 1.59 (1.07–2.35) | 0.0214 |
| Myocardial infarction, definite/probable stent thrombosis, or stroke | 74 (2.4) | 44 (1.4) | 1.65 (1.13–2.39) | 0.0089 |

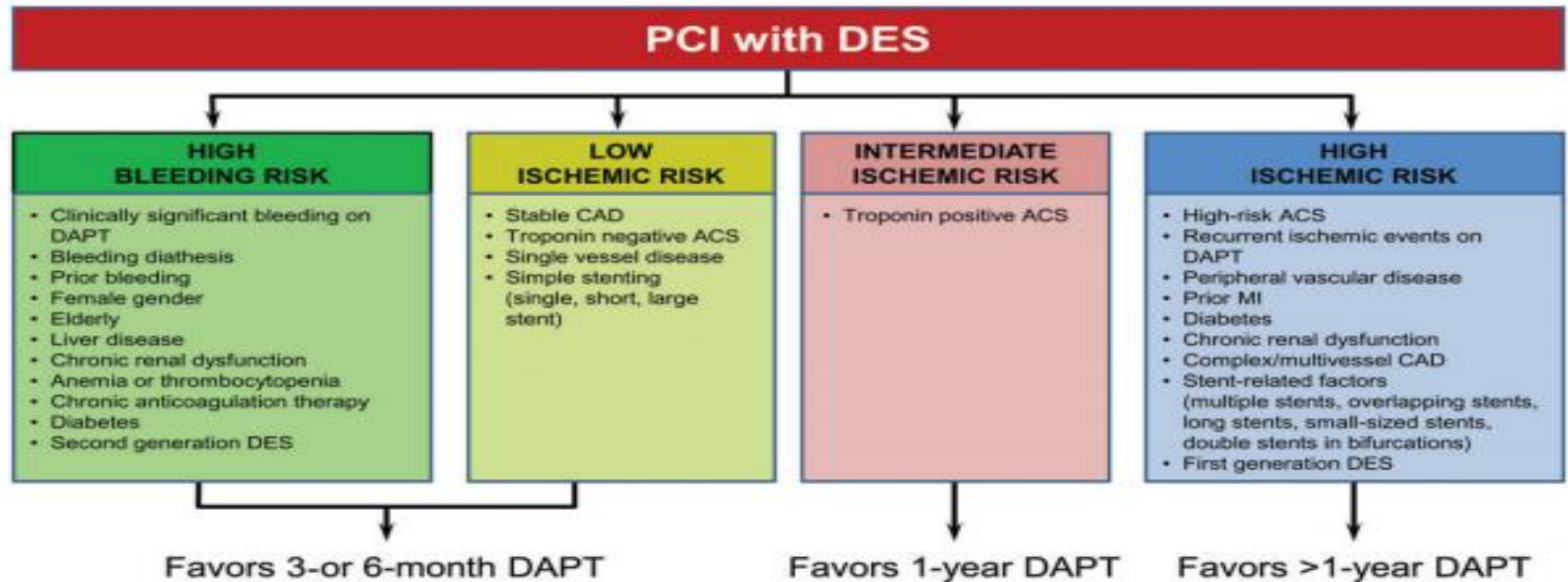
TABLE 3 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients ≥65 Years of Age

| | ≤6-Month DAPT (n = 2,635) | 12-Month DAPT (n = 2,684) | Unadjusted HR (95% CI) | p Value |
|--|------------------------------|------------------------------|---------------------------|---------|
| All-cause death | 76 (2.9) | 66 (2.5) | 1.18 (0.85–1.64) | 0.3231 |
| Cardiac | 45 (1.7) | 42 (1.6) | 1.11 (0.73–1.68) | 0.6417 |
| Noncardiac | 31 (1.2) | 24 (0.9) | 1.31 (0.77–2.24) | 0.3147 |
| Myocardial infarction | 41 (1.6) | 55 (2.1) | 0.77 (0.52–1.16) | 0.2085 |
| Definite or probable stent thrombosis | 14 (0.5) | 14 (0.5) | 1.04 (0.49–2.17) | 0.9271 |
| Stroke | 17 (0.7) | 22 (0.8) | 0.79 (0.42–1.48) | 0.4607 |
| Bleeding | 39 (1.5) | 63 (2.4) | 0.63 (0.42–0.94) | 0.0248 |
| Major | 13 (0.5) | 29 (1.1) | 0.46 (0.24–0.88) | 0.0196 |
| Minor | 27 (1.0) | 35 (1.3) | 0.79 (0.48–1.31) | 0.3585 |
| Myocardial infarction or definite/probable stent thrombosis | 47 (1.8) | 58 (2.2) | 0.84 (0.57–1.23) | 0.3703 |
| Myocardial infarction, definite/probable stent thrombosis, or stroke | 64 (2.4) | 80 (3.0) | 0.82 (0.59–1.15) | 0.2487 |

Pooled analysis of EXCELLENT, ITALIC, OPTIMIZE, PRODIGY, RESET, SECURITY



One size does not fit all



Conclusions

- Compared to shorter DAPT longer DAPT is associated with reduced rates of MI and stent thrombosis, but increased rates of bleeding.
- A tailored approach is advisable when deciding the optimal DAPT wherein ischemic and bleeding risk are balanced in individual patients.
- Patients with ACS, young age, and complex multivessel CAD benefit from prolonged DAPT.