# DAPT AND BEYOND 12 MONTHS: WHICH ONE AND HOW LONG?

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# DISCLOSURE STATEMENT OF FINANCIAL INTEREST

I, SORIN BRENER MD, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

# THE DAPT DILEMMA

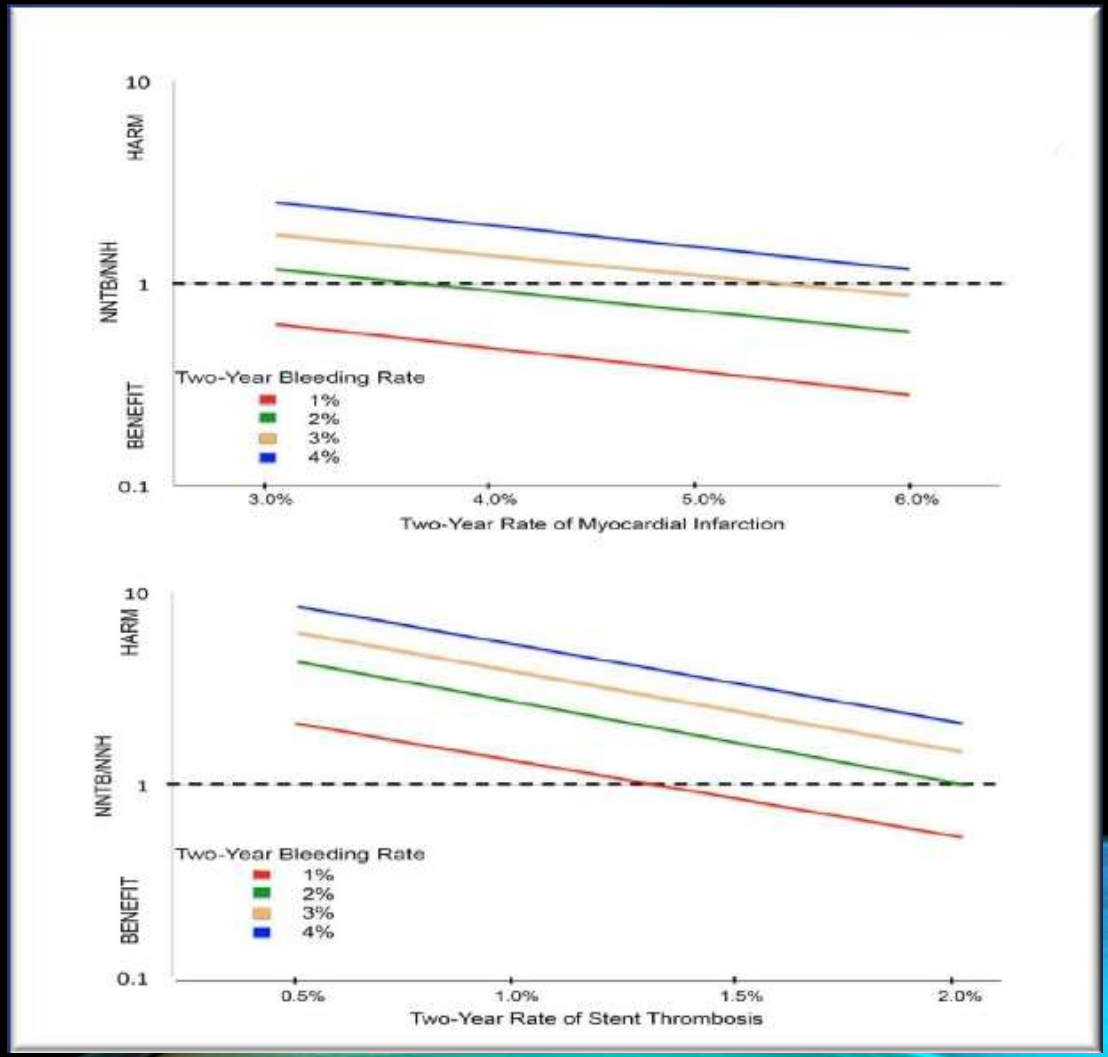
- Balance long-term risks of recurrent ischemic events and hemorrhagic complications
- Ischemic events present as:
  - Device-oriented complications: stent thrombosis, restenosis, TV MI and TLR
  - Patient-oriented complications: (cardiac) death, MI, stroke, revascularization

# RISK FOR ISCHEMIC OR BLEEDING EVENTS

| Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT) | Increased Bleeding Risk (may favor shorter-duration DAPT) |
|---|---|
| Increased ischemic risk<br>• Advanced age<br>• ACS presentation<br>• Multiple prior MIs<br>• Extensive CAD<br>• Diabetes mellitus<br>• CKD<br>Increased risk of stent thrombosis<br>• ACS presentation<br>• Diabetes mellitus<br>• Left ventricular ejection fraction <40%<br>• First-generation drug-eluting stent<br>• Stent undersizing<br>• Stent underdeployment<br>• Small stent diameter<br>• Greater stent length<br>• Bifurcation stents<br>• In-stent restenosis | • History of prior bleeding<br>• Oral anticoagulant therapy<br>• Female sex<br>• Advanced age<br>• Low body weight<br>• CKD<br>• Diabetes mellitus<br>• Anemia<br>• Chronic steroid or NSAID therapy |

# Risk / Benefit Trade Off

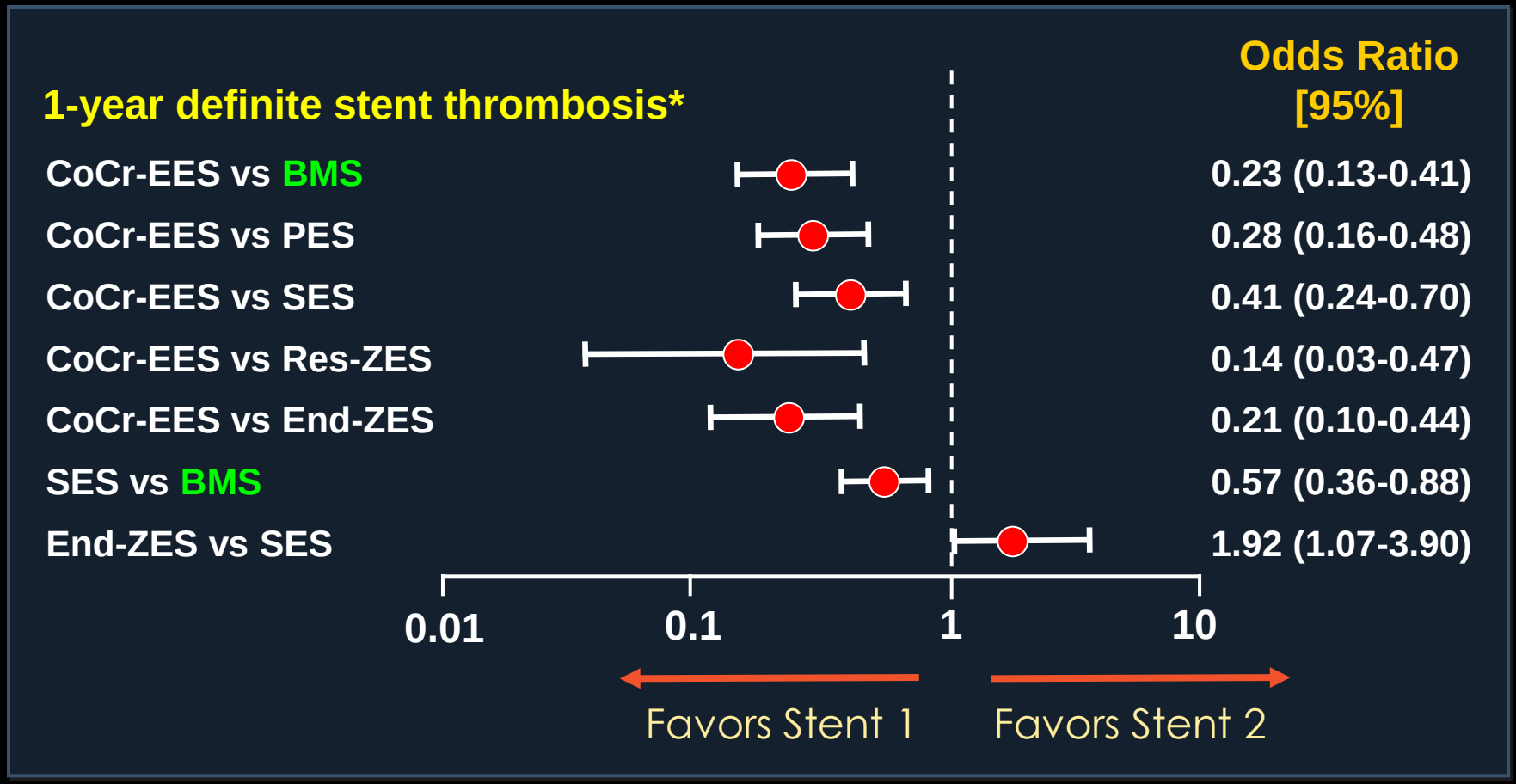
**Risk of MI or ST presented as function of bleeding risk status across 5 RCTs comparing 18-48 month DAPT to 6-12 month Tx duration**




DOI: 10.1016/j.jacc.2016.03.512

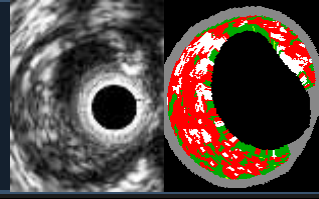
# STENT THROMBOSIS NETWORK META-ANALYSIS

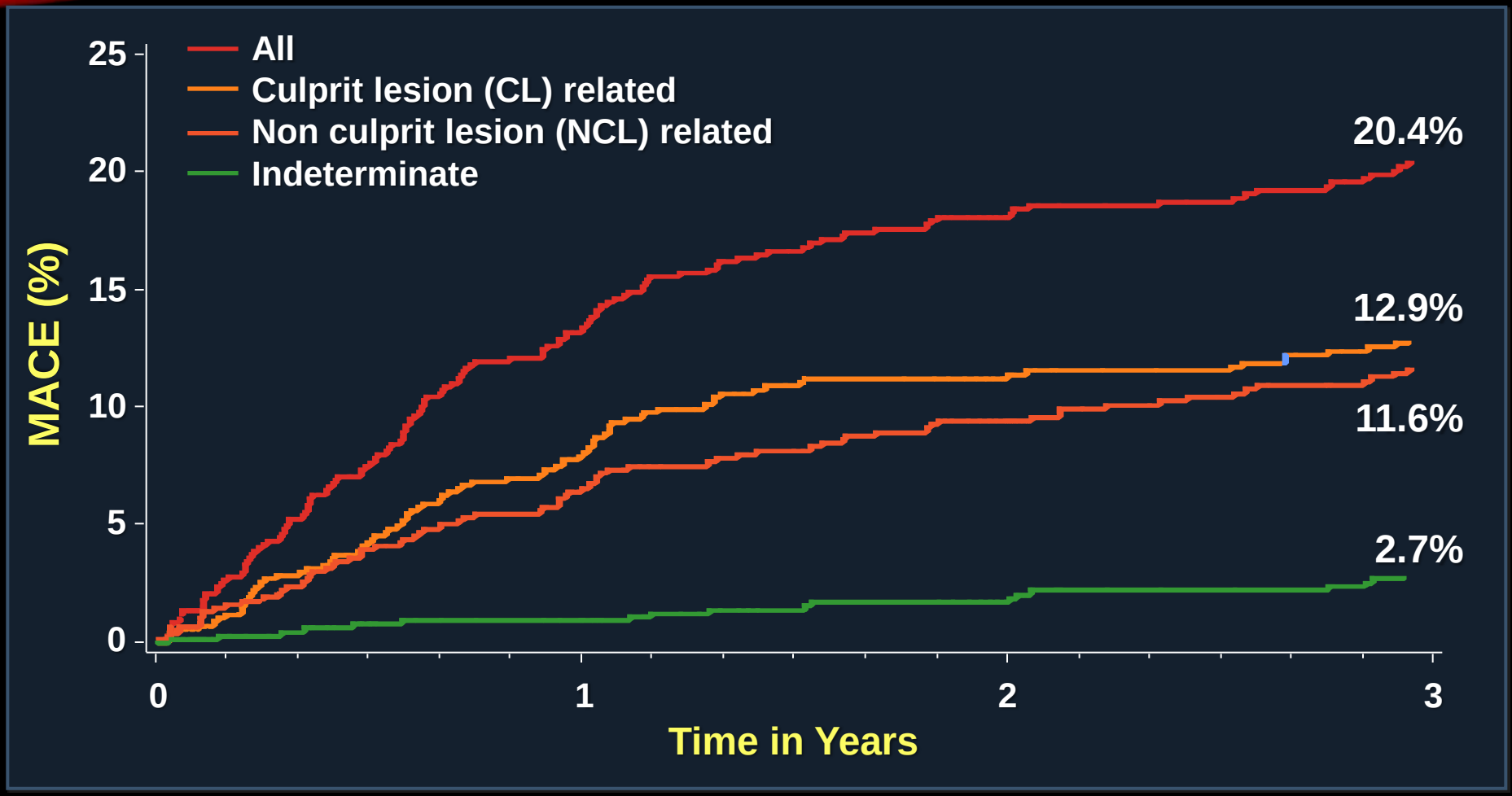
## 49 RCTs, 50,844 pts




Palmerini T et al. *Lancet* 2012; 379:1393-402

# PROSPECT: MACE (N=697)






**Number at risk**

| | | | | |
|---|---|---|---|---|
| ALL | 697 | 557 | 506 | 480 |
| CL related | 697 | 590 | 543 | 518 |
| NCL related | 697 | 595 | 553 | 521 |
| Indeterminate | 697 | 634 | 604 | 583 |

Stone et al. NEJM 2011; 364:226-35

# THE EVIDENCE (SO FAR)

| | |
|---|---|
| DES-LATE 12 vs 36 mos | *N = 5045* |
| PRODIGY 6 vs 24 mos | *N = 1501* |
| EXCELLENT 6 vs 12 mos | *N = 1443* |
| RESET 3 vs 12 mos | *N = 2117* |
| OPTIMIZE 3 vs 12 mos | *N = 3119* |
| ARCTIC 12 vs 18 mos | *N = 1259* |
| SECURITY 6 vs 12 mos | *N = 1399* |
| ITALIC 6 vs 24 mos | *N = 1822* |
| ISAR-SAFE 6 vs 12 mos | *N = 4000* |
| DAPT 12 vs 30 mos | *N = 9961* |
| OPTIDUAL 12 vs 48 mos | *N = 1385* |

# TRIAL DESIGN

| | |
|---|---|
| DES-LATE 12 vs 36 mos | *Superiority* |
| PRODIGY 6 vs 24 mos | *Superiority* |
| EXCELLENT 6 vs 12 mos | *Noninferiority* |
| RESET 3 vs 12 mos | *Noninferiority* |
| OPTIMIZE 3 vs 12 mos | *Noninferiority* |
| ARCTIC 12 vs 17 mos | *Superiority* |
| SECURITY 6 vs 12 mos | *Noninferiority* |
| ITALIC 6 vs 24 mos | *Noninferiority* |
| ISAR-SAFE 6 vs 12 mos | *Noninferiority* |
| DAPT 12 vs 30 mos | *Superiority* |
| OPTIDUAL 12 vs 48 mos | *Superiority* |

# WERE THE STUDIES POWERED FOR 1RY ENDPOINT?

| | |
|---|---|
| DES-LATE 12 vs 36 mos | *Expected 5%, observed 2%* |
| PRODIGY 6 vs 24 mos | Expected 8%, observed 10.1 |
| EXCELLENT 6 vs 12 mos | *Expected 10%, observed 4.5%* |
| RESET 3 vs 12 mos | *Expected 10-11%, observed 4.7%* |
| OPTIMIZE 3 vs 12 mos | *Expected 9%, observed 6%* |
| ARCTIC 12 vs 17 mos | *(Extension study)* |
| SECURITY 6 vs 12 mos | Expected 4.5%, observed 4.5% |
| ITALIC 6 vs 24 mos | *Expected 3%, observed 1.5%* |
| ISAR-SAFE 6 vs 12 mos | *Expected 10%, observed 1.5%* |
| DAPT 12 vs 30 mos | Expected 4.4%, observed 5.9% |
| OPTIDUAL 12 vs 48 mos | Expected 7.0%, observed 7.5% |

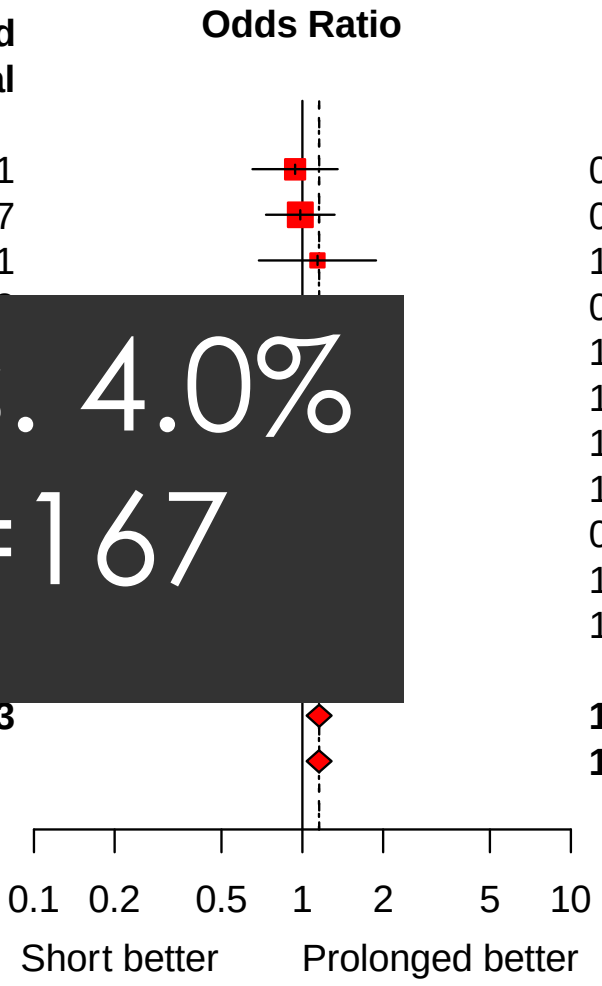
# PRIMARY ENDPOINT

| Study | Short Events | Short Total | Prolonged Events | Prolonged Total | OR | 95%−CI |
|---|---|---|---|---|---|---|
| DES−LATE (12 vs. 36 mos) | 57 | 2514 | 61 | 2531 | 0.94 | [0.65; 1.35] |
| PRODIGY (6 vs. 24 mos) | 98 | 983 | 100 | 987 | 0.98 | [0.73; 1.32] |
| EXCELLENT (6 vs. 12 mos) | 34 | 722 | 30 | 721 | 1.14 | [0.69; 1.88] |
| RESET (3 vs. 12 mos) | | | | | 0.97 | [0.62; 1.52] |
| OPTIMIZE (3 vs. 12 mos) | | | | | 1.03 | [0.76; 1.39] |
| ARCTIC (12 vs. 18 mos) | | | | | 1.15 | [0.66; 2.02] |
| SECURITY (6 vs. 12 mos) | | | | | 1.22 | [0.72; 2.06] |
| ITALIC (6 vs. 24 mos) | | | | | 1.07 | [0.51; 2.23] |
| ISAR−SAFE (6 vs. 12 mos) | | | | | 0.91 | [0.55; 1.51] |
| DAPT (12 vs. 30 mos) | | | | | 1.40 | [1.16; 1.67] |
| OPTIDUAL (12 vs. 48 mos) | | | | | 1.33 | [0.87; 2.04] |
| **Fixed effect model** | **761** | **16687** | **670** | **16833** | **1.15** | **[1.04; 1.28]** |
| **Random effects model** | | | | | **1.15** | **[1.04; 1.28]** |

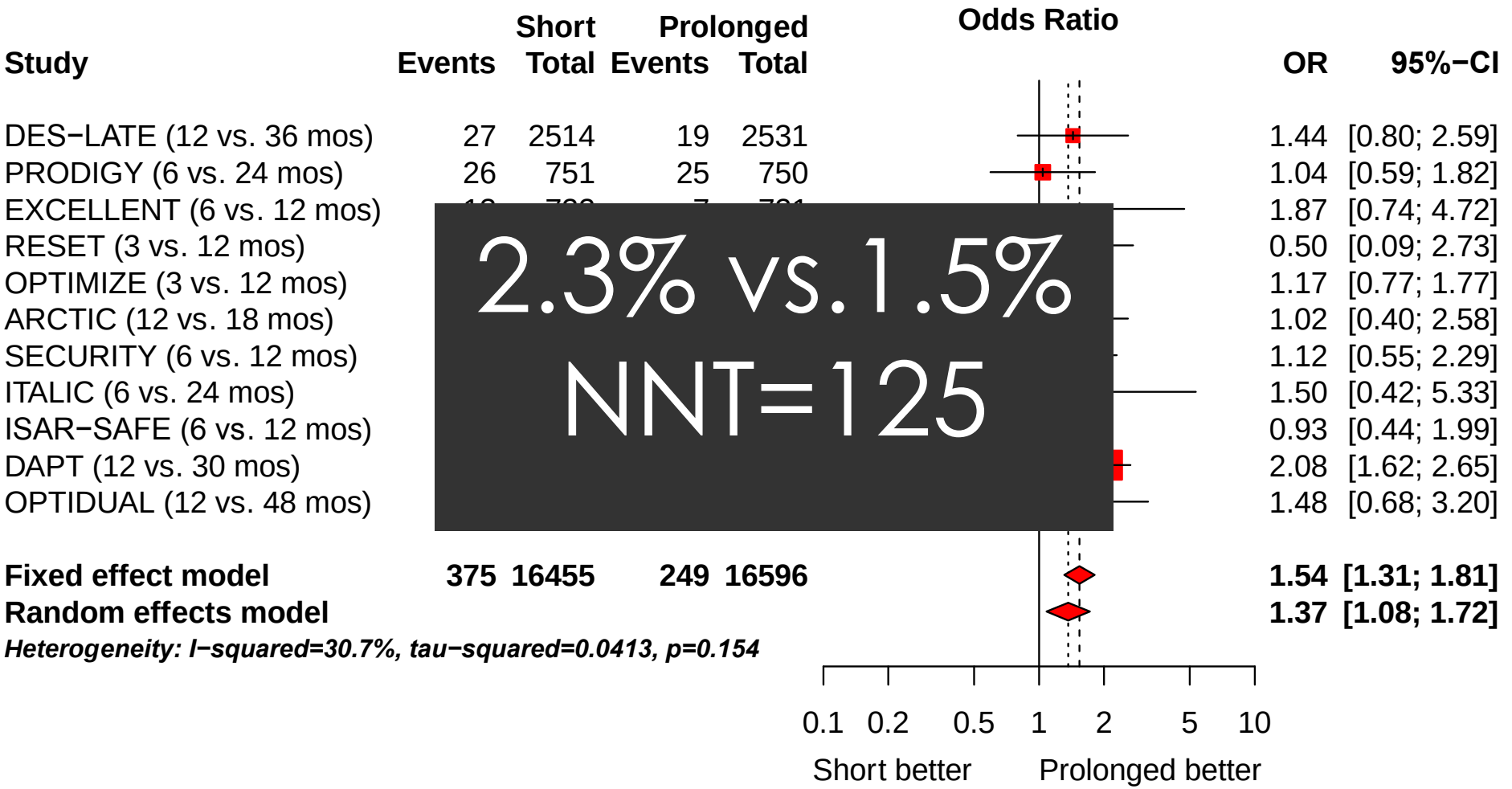
***Heterogeneity: I−squared=0%, tau−squared=0, p=0.5289***

4.6% vs. 4.0%

NNT=167



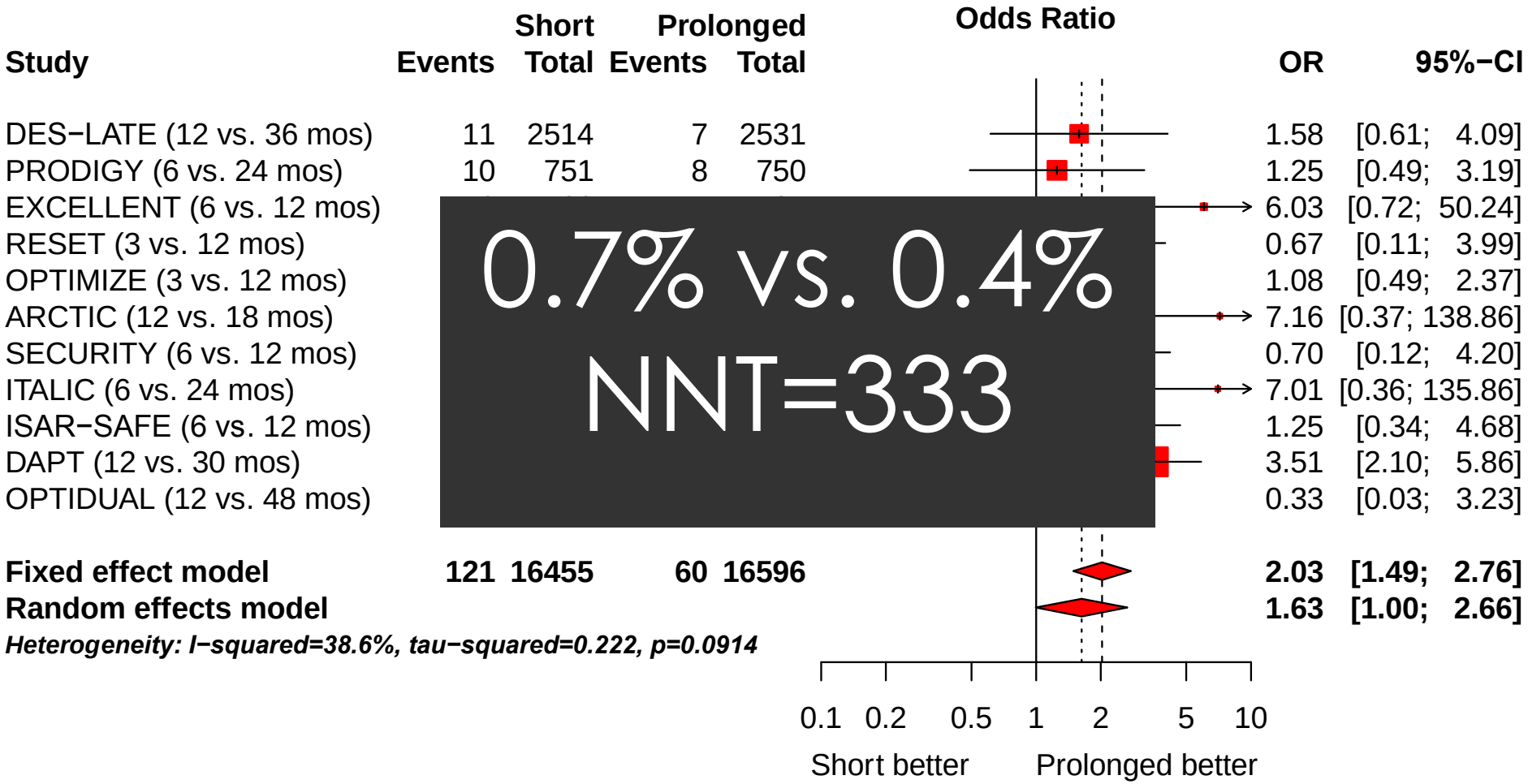
# MYOCARDIAL INFARCTION




2.3% vs.1.5%

NNT=125

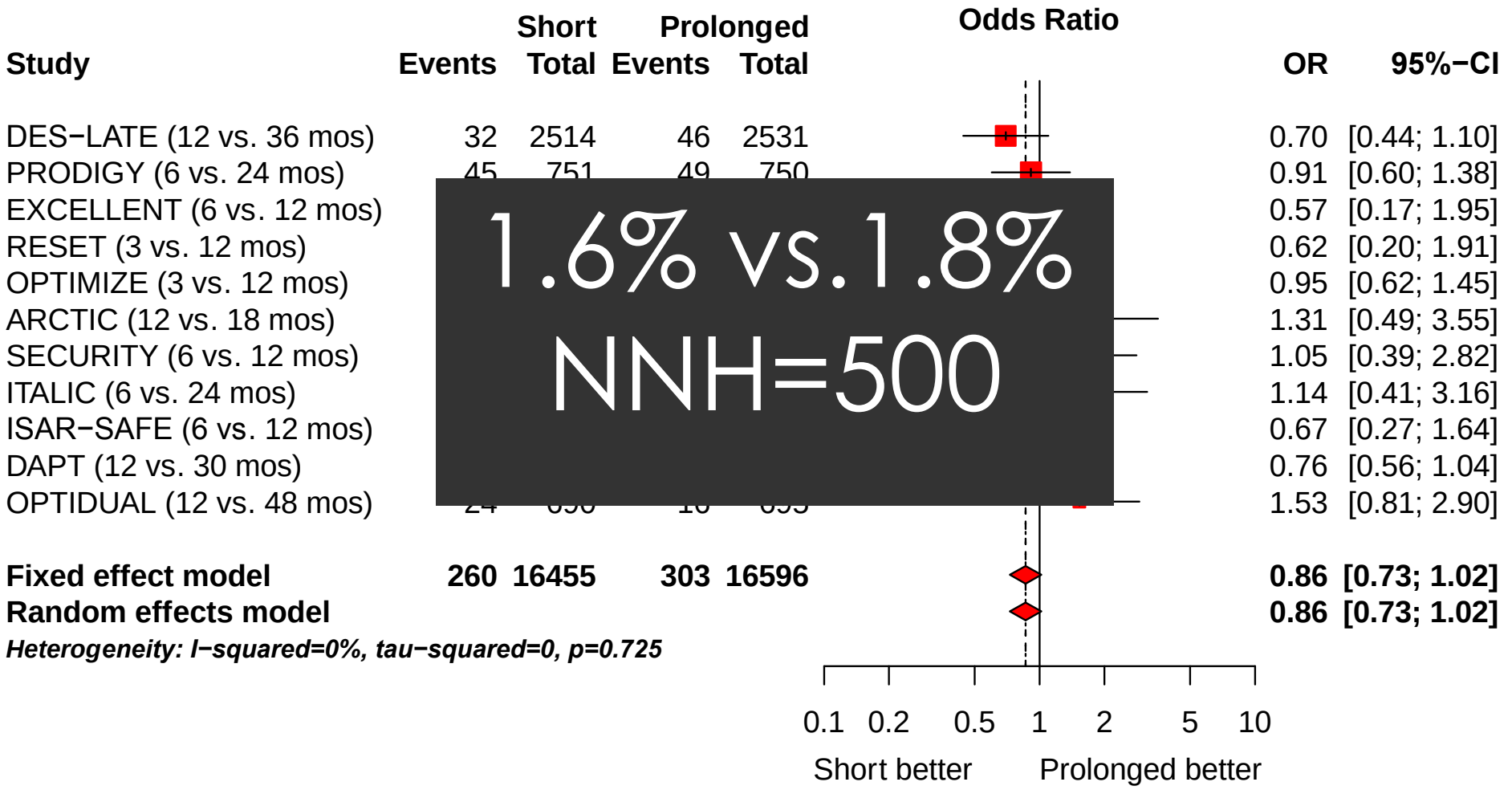
# STENT THROMBOSIS




0.7% vs. 0.4%

NNT=333

# ALL-CAUSE MORTALITY




1.6% vs.1.8%

NNH=500

# DOES DAPT INCREASE NON-CV DEATH?

[ 11-06-2015 ] A U.S. Food and Drug Administration (FDA) review has determined that long-term use of the blood-thinning drug Plavix (clopidogrel) does not increase or decrease overall risk of death in patients with, or at risk for, heart disease. Our evaluation of the Dual Antiplatelet Therapy (DAPT)[1] trial and several other clinical trials also does not suggest that clopidogrel increases the risk of cancer or death from cancer.

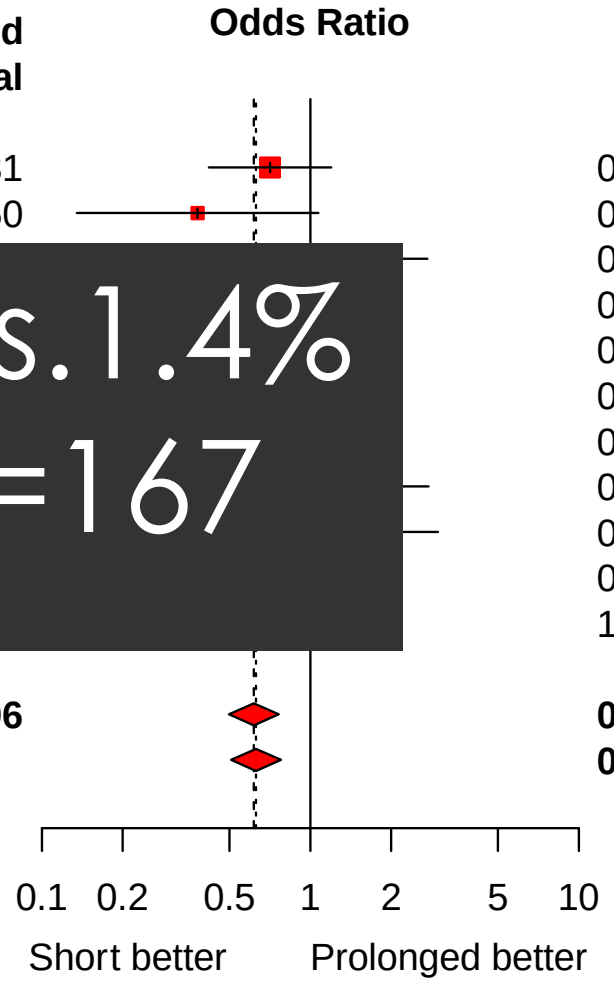
| | Number of patients included | Long-term clopidogrel plus aspirin | Short term clopidogrel plus aspirin or aspirin alone |
|---|---|---|---|
| Overall incidence of death | 56,799 | 6.7% | 6.6% |
| Incidence of cancer adverse events | 37,835 | 4.2% | 4.0% |
| Incidence of cancer death | 40,855 | 0.9% | 1.1% |

# MAJOR HEMORRHAGE

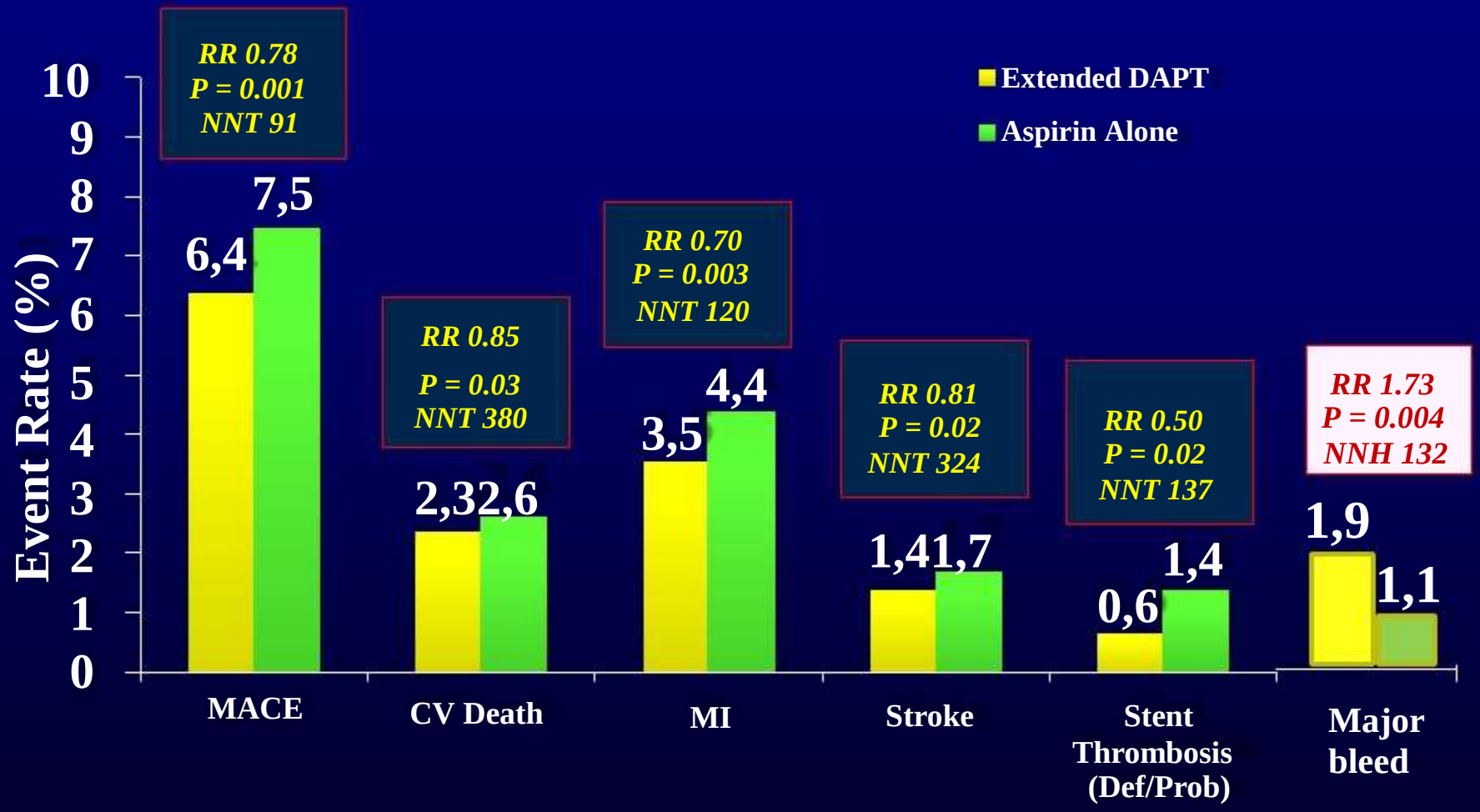
| Study | Short Events | Short Total | Prolonged Events | Prolonged Total | OR | 95%−CI |
|---|---|---|---|---|---|---|
| DES−LATE (12 vs. 36 mos) | 24 | 2514 | 34 | 2531 | 0.71 | [0.42; 1.20] |
| PRODIGY (6 vs. 24 mos) | 5 | 751 | 13 | 750 | 0.38 | [0.13; 1.07] |
| EXCELLENT (6 vs. 12 mos) | | | | | 0.50 | [0.09; 2.73] |
| RESET (3 vs. 12 mos) | | | | | 0.33 | [0.07; 1.65] |
| OPTIMIZE (3 vs. 12 mos) | | | | | 0.71 | [0.31; 1.60] |
| ARCTIC (12 vs. 18 mos) | | | | | 0.14 | [0.02; 1.17] |
| SECURITY (6 vs. 12 mos) | | | | | 0.52 | [0.16; 1.74] |
| ITALIC (6 vs. 24 mos) | | | | | 0.14 | [0.01; 2.75] |
| ISAR−SAFE (6 vs. 12 mos) | | | | | 0.80 | [0.22; 2.99] |
| DAPT (12 vs. 30 mos) | | | | | 0.62 | [0.46; 0.83] |
| OPTIDUAL (12 vs. 48 mos) | | | | | 1.01 | [0.48; 2.13] |
| **Fixed effect model** | **139** | **16455** | **227** | **16596** | **0.62** | **[0.50; 0.76]** |
| **Random effects model** | | | | | **0.63** | **[0.51; 0.78]** |

***Heterogeneity: I−squared=0%, tau−squared=0, p=0.7697***

0.8% vs.1.4%
NNH=167

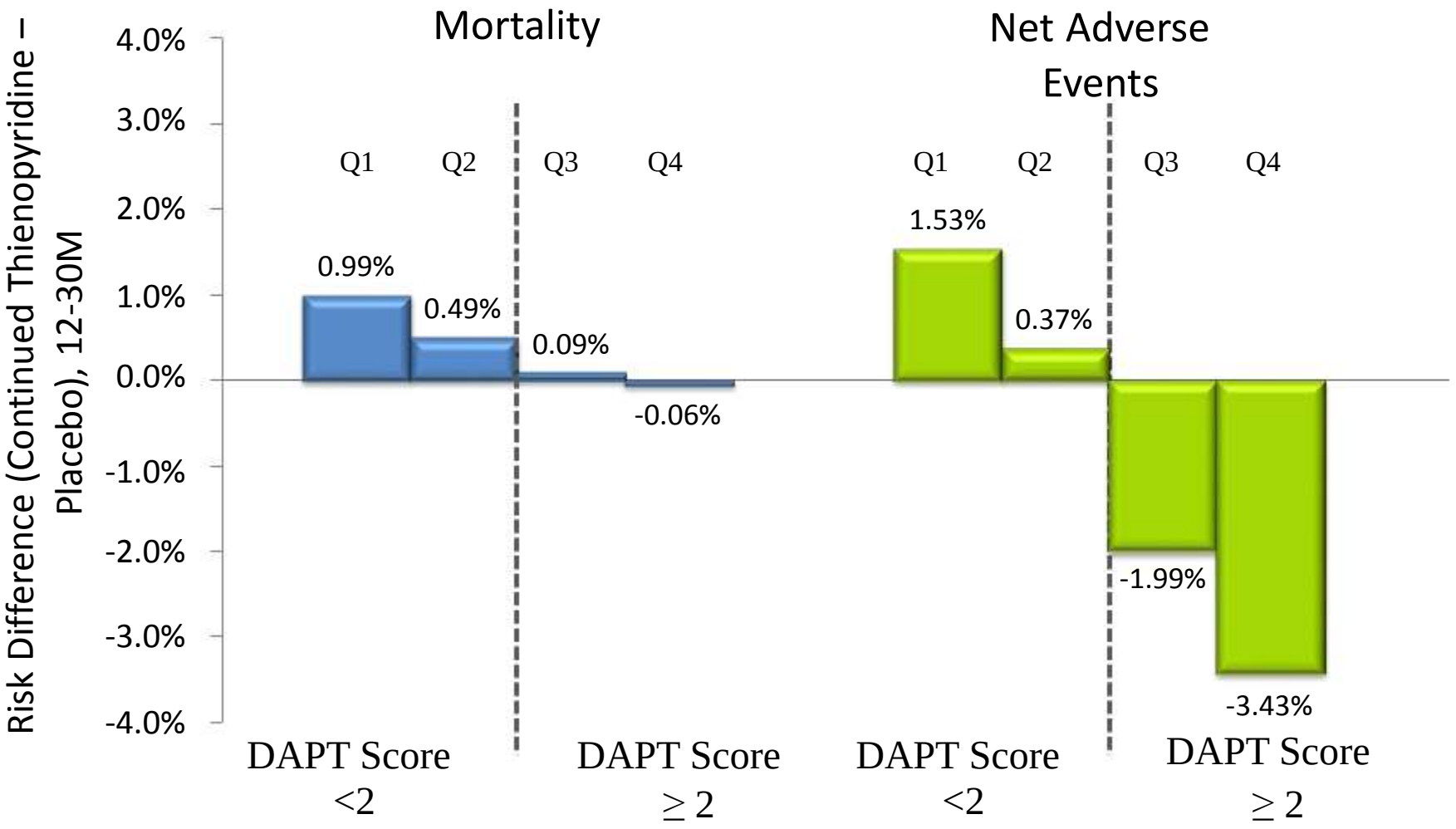


# Metaanalysis in patients with prior MI




J Udell et al - EHJ 2015

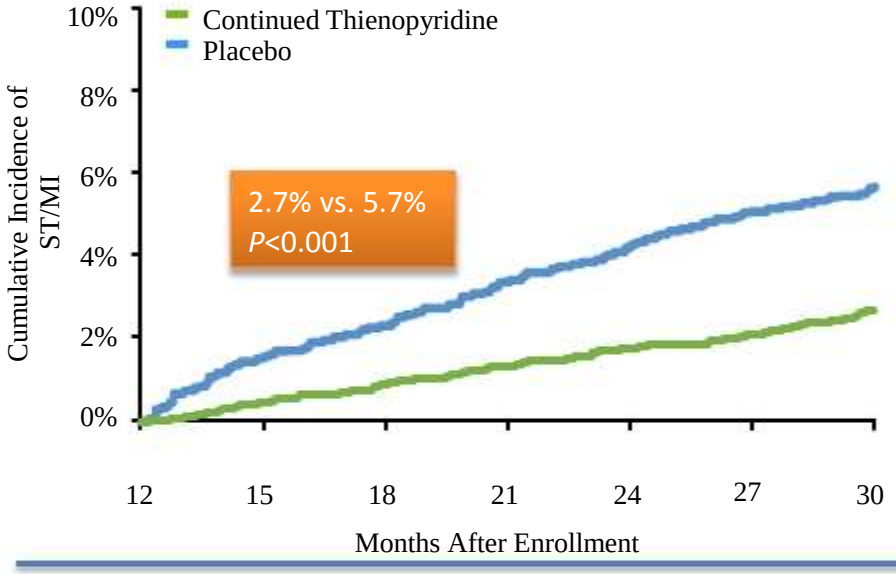
# Continued Thienopyridine vs. Placebo Treatment Effect by DAPT Score Quartile (N = 11,648)



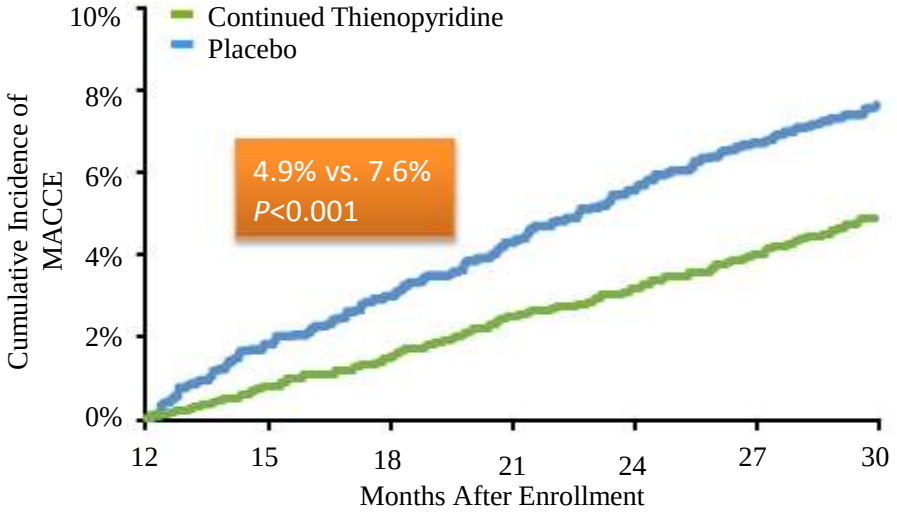
# Continued Thienopyridine vs. Placebo
# DAPT Score ≥ 2 (High); N=5917

DAPT STUDY

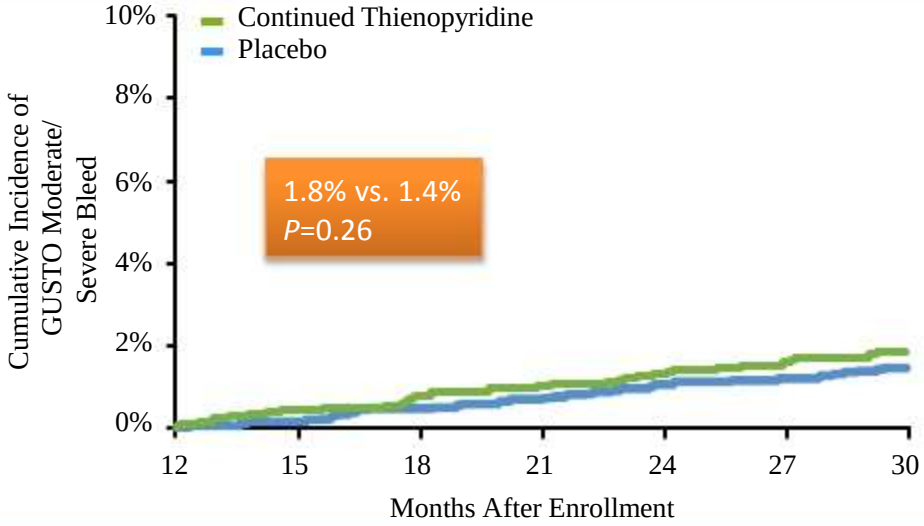
## Myocardial Infarction or Stent Thrombosis




## Death, MI or Stroke (MACCE)

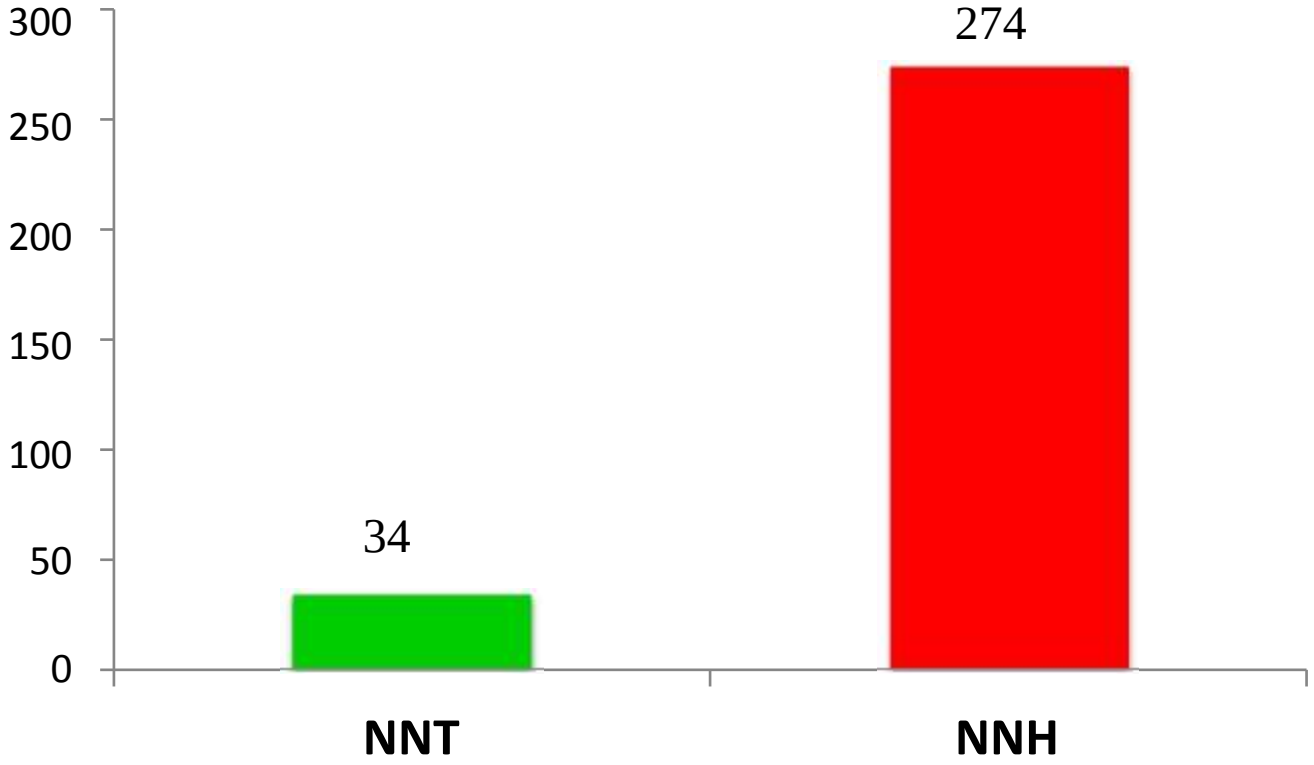



## GUSTO Moderate/ Severe Bleeding



# NNT/NNH for High DAPT Score Patients

For every 1000 patients treated, prevent 30 MIs and cause < 4 bleeds

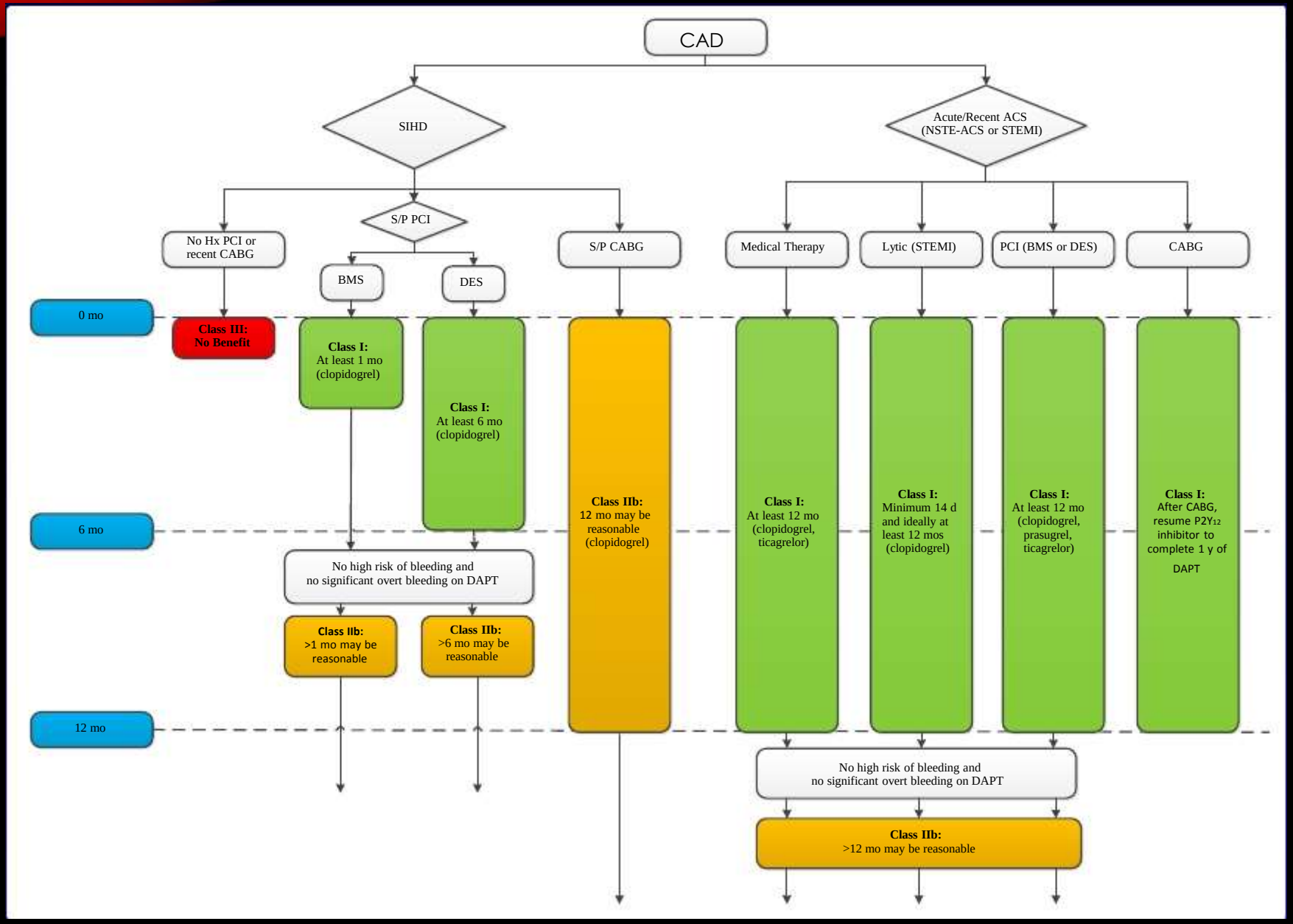


# ESC GUIDELINES 2015

| Long-term $P2Y_{12}$ inhibition | | |
|---|---|---|
| $P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient. | IIb | A |

Roffi M et al. *European Heart Journal* 2015.

# Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT



# P2Y12 inhibitor administration and Dual Anti-Platelet Therapy

| | | |
|---|---|---|
| A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. | I | A |

2015

| | | |
|---|---|---|
| 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 |
| $P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk. | IIb | A |
| **Long-term $P2Y_{12}$ inhibition** | | |
| $P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient. | IIb | A |

**UPDATE:**
Further guidance on P2Y12 inhibitor administration and DAPT

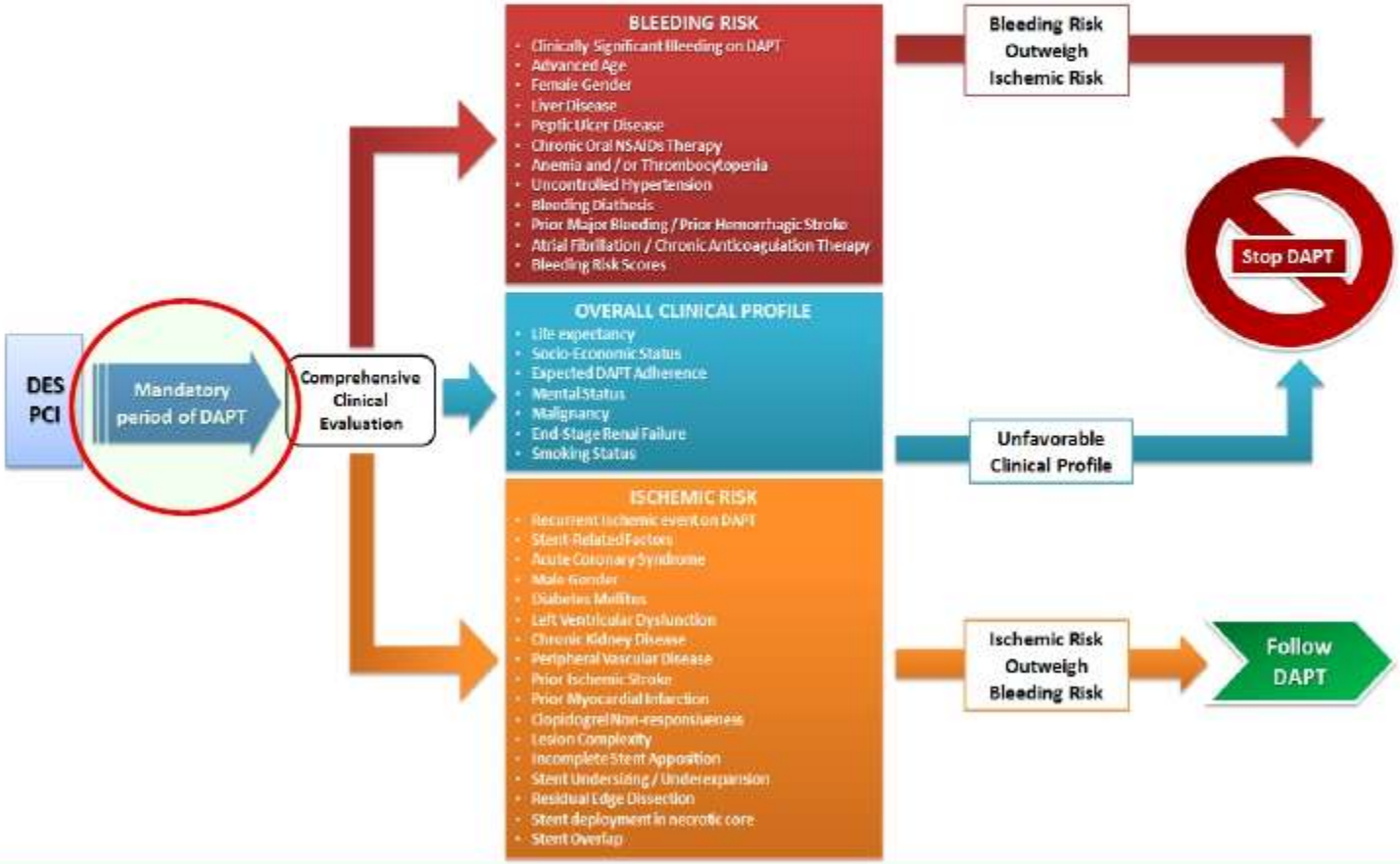
THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Duration of Dual Antiplatelet Therapy After Coronary Stenting

## A Review of the Evidence

Gilles Montalescot, MD, PhD,* David Brieger, MBBS,† Anthony J. Dalby, MB, ChB,‡ Seung-Jung Park, MD, PhD,§ Roxana Mehran, MD‖



# CONCLUSION

## LONG DAPT IS GOOD FOR THE MOST .....

It is not the stent!
It is atherosclerosis!