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Demystifying the myth of 12-month dual antiplatelet therapy after acute coronary syndrome

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ABSTRACT

Twelve-month dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor has been, for almost two decades, a class I recommendation in American and European guidelines for acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI). Twelve-month DAPT was initially established after the results of the *Clopidogrel in Unstable Angina to Prevent Recurrent Events* (CURE) trial, which, by design, studied DAPT versus no DAPT rather than the optimal DAPT duration. Notably, the mean DAPT duration in this study was 9 months, not 12 months. Subsequent ACS studies evaluating prasugrel or ticagrelor compared with clopidogrel were further interpreted as supportive evidence for 12-month DAPT duration. In these studies, the median DAPT duration was 9 or 15 months for ticagrelor and prasugrel, respectively. Subsequent DAPT studies of DAPT duration questioned the dogmatic 12-month DAPT duration and suggested that DAPT should either be shorter than 12 months in patients at high bleeding risk (HBR) or longer than 12 months in patients at high ischemic risk who can safely tolerate the treatment. Assessing bleeding risk first, rather than ischemic risk, has emerged as a treatment modifier for maximizing the net clinical benefit of DAPT, due to excessive bleeding and no benefit of prolonged treatment regimens in HBR patients. Multiple DAPT de-escalation treatment strategies, including switching from prasugrel or ticagrelor to clopidogrel, reduction in dose of prasugrel or ticagrelor, and shortening DAPT duration and maintaining monotherapy with ticagrelor have consistently shown to reduce bleeding without increasing fatal or non-fatal cardiovascular or cerebral ischemic risks compared with 12-month DAPT. However, 12-month DAPT duration remains the only class I DAPT recommendation for patients with ACS despite the lack of prospectively established evidence, leading to unnecessary and potentially harmful overtreatment in many patients. It is time for clinical practice and guideline recommendations to be updated to reflect the totality of the evidence regarding the optimal DAPT duration in ACS.

Myths are stories that are based on tradition. Some may have factual origins, while others are completely fictional. The way in which the recommendation to use dual antiplatelet therapy (DAPT), consisting of aspirin plus a $P2Y_{12}$ inhibitor for 12 months, has become entrenched within the cardiology culture resembles a myth. Twelve months of DAPT has been for 17 years the strongest recommendation of all DAPT durations in American and European guidelines (1–7). A myriad of population registries shows that 12 months is the most frequently prescribed DAPT duration in patients with, and frequently also without, acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI) (8–13). The 12-month DAPT duration was initially derived from a weak evidence-base and has progressively become less and less supported by the data. Nonetheless, it remains largely unchallenged, like a myth. A myth can only be passed on, until it is demystified.

The inception of 12-month duration of dual antiplatelet therapy

The evidence base for recommending12-month duration of DAPT was limited to a single trial which was not meant to assess optimal DAPT duration.

The 2007 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of non-ST-segment elevation (NSTE)-ACS recommended the use of clopidogrel in addition to aspirin for 12 months, unless there is an excessive risk of bleeding with a class of recommendation I, level of evidence (LOE) A (**Figure 1**) (14). In spite of the assigned LOE A, which implies the presence of multiple supportive studies, the single trial which supported this recommendation was the *Clopidogrel in Unstable Angina to Prevent Recurrent Events* (CURE) trial (15). The existence of a single study investigating clopidogrel in association with aspirin in NSTE-ACS patients was acknowledged by the American Heart Association (AHA)/American College of Cardiology (ACC) 2007 Guidelines for the management of patients with unstable angina/Non–ST-Elevation myocardial infarction (5), which assigned a class I, LOE B to "*at least 1 month and ideally up to 1-year DAPT in patients treated with bare metal stents or at least 1-year DAPT in patients treated with drug-eluting stent*".

In the CURE trial, clopidogrel was administered for 3–12 months (the mean duration of treatment was 9 months) in addition to aspirin (75–325 mg) vs. aspirin alone in 12,562 patients with NSTE-ACS (15). Patients received placebo or a loading dose of 300 mg clopidogrel followed by 75 mg daily, in

addition to conventional therapy. A significant risk reduction for death from cardiovascular causes, non-fatal myocardial infarction (MI), or stroke was observed in the treatment arm (9.3% vs. 11.4%; relative risk [RR], 0.80; 95% confidence interval [CI], 0.72 to 0.90), driven by a 1.5% absolute reduction in the rate of subsequent nonfatal MI (5.2% vs. 6.7%; RR, 0.77; 95% CI, 0.67 to 0.89) (15). The rate of major bleeding increased by an absolute rate of 1%, nearly half of which was defined as "life-threatening". The risk of transfusion of ≥ 2 U of blood increased by an absolute rate of 0.6%, and the risk of minor bleeding increased by an absolute rate of 6.7%.

Beyond the complex interpretation of the benefits versus risks of aspirin and clopidogrel compared with aspirin alone, the CURE trial does not support DAPT for 12 months for the following reasons. Firstly, the CURE study was not designed to assess the optimal DAPT duration but rather DAPT versus no DAPT (**Figure 2**). This is acknowledged by the investigators who wrote that "*the exact duration of therapy cannot be deduced reliably from a trial with the design of CURE"* and that *"the only way to reliably estimate the exact length of time that various treatments in any condition should be given is by prospectively randomizing patients to various durations of therapy*" (16). Secondly, the CURE trial allowed patients to discontinue the study treatment (i.e., clopidogrel) as early as 3 months after randomization. The mean treatment duration was 9 months and only 37.9% of the patients allocated to clopidogrel continued treatment for 12 months (**Figure 2**). Finally, analysis of the events that were prevented over time by DAPT disclosed an incremental reduction of the primary endpoint until 3 months after randomization, but not thereafter (16).

Since specific DAPT duration studies were unavailable in 2007, a more evidence-based approach would have been to recommend aspirin and clopidogrel for a minimum of 3 and up to 12 months in NSTE-ACS patients. However, since CURE, international guidelines have arbitrarily recommended the longest DAPT duration tested in the study (i.e., 12 months) as default approach, which was actually administered to a minority of patients. Since then, this 12-month DAPT recommendation has been passed on from guidelines to guidelines, without critical analysis or acknowledgment of its weak scientific foundation.

The 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation MI stated that long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per

day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy *(*class IIa, LOE C*)* (**Figure 1**) (5).

The 2008 ESC Task Force on the management of STEMI subsequently stated that "*the optimal duration of clopidogrel treatment after STEMI has not been determined (17). Considering the long-term effect of clopidogrel in patients after a NSTE-ACS in the CURE trial and taking into account the current recommendation for non-STEMI patients, a treatment duration of 12 months is recommended whether or not a stent has been placed (Class I, LOE C)*" (**Figure 1**) (17). Therefore, in 2007 and 2008 the 12-month duration of DAPT became the default approach for the entire spectrum of ACS patients, grounded on a single study, which exclusively investigated DAPT for between 3 and 12 months compared with no DAPT (or compared with 1-month DAPT in the few patients with PCI) among NSTE-ACS patients. This recommendation has not been challenged ever since, despite 12-month DAPT never being shown to provide convincing net benefit compared with other DAPT durations in any population.

The propagation of the 12-month duration dual antiplatelet therapy dogma

Two pivotal ACS studies after CURE, evaluating prasugrel or ticagrelor compared with clopidogrel, were further interpreted as supportive evidence for 12-month DAPT duration. However, these two studies, by design, cannot inform on the optimal DAPT duration in ACS patients.

The *Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction* (TRITON–TIMI) 38 trial assessed DAPT with prasugrel in comparison with DAPT with clopidogrel for patients undergoing PCI in the setting of STEMI or NSTEMI (18). The median treatment duration was 14.5 months and efficacy and safety endpoints (including the primary study outcome) were assessed at 15 months (**Figure 2**). In the *Platelet Inhibition and Patient Outcomes* (PLATO) trial (19), DAPT, consisting of aspirin and ticagrelor, was tested against clopidogrel-based DAPT. The randomized treatment was scheduled to continue for up to 12 months, with a median duration of therapy in the study of 9 months (**Figure 2**). Although neither of these studies specified 12 months of DAPT nor were they designed to study the duration of DAPT, guidelines continued to recommend 12 months of DAPT duration in ACS patients, which was deemed

supported by CURE (15,20), TRITON–TIMI 38 (18) and PLATO (19) trials. This recommendation was further entrenched by the recognition in late 2006 of the phenomenon of very late stent thrombosis (ST) with first-generation drug-eluting stents (DES) (21), which led to the "DES firestorm" and a blanket recommendation of 12 months of DAPT for all patients undergoing DES implantation, based on expert opinions. Interestingly, this recommendation left the issue of very late ST (i.e. > 12 months after PCI) unaddressed.

The ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) acknowledged the uncertainty around DAPT duration particularly after DES, by stating that "*It is not entirely clear how long therapy (e.g. DAPT) should be maintained (5). Whereas increased hazard is clearly associated with premature discontinuation of dual antiplatelet therapy after DES, the benefit of extended therapy beyond 1 year is uncertain. Hence, the minimum requirements for DAPT duration should be vigorously applied for each DES type. However, 1 year of DAPT may be ideal for all UA/NSTEMI patients who are not at HBR given the secondary preventive effects of DAPT, perhaps especially after DES. On the other hand, the limited database at this point in time does not support a recommendation for DAPT beyond 1 year for all DES-treated patients*" (**Figure 1**) (5).

DAPT duration studies

DAPT duration studies, comparing different DAPT durations, followed by aspirin monotherapy, showed that there is a linear and time-dependent increase of bleeding when DAPT is prolonged in excess of 1-month. While many studies and meta-analyses assessing shorter than 12-month compared with 12-month DAPT did not show evidence of a trade-off of ischemic events with abbreviated DAPT in mixed or largely CCS and/or low ischemic risk patients, ACS studies identified the existence of an inferior ischemic protection with abbreviated compared with prolonged DAPT, both within and beyond one year, when DAPT is followed by aspirin monotherapy in patients at higher ischemic risk (e.g. ACS).

In the *Dual Antiplatelet Therapy* (DAPT) trial, prolonged DAPT was superior to 12-month DAPT for the prevention of ischemic events (22). Continued treatment with aspirin and thienopyridine for 30 months, as compared with aspirin monotherapy after 12-month DAPT, reduced the rates of stent thrombosis (0.4% vs. 1.4%; HR, 0.29, 0.17 to 0.48]; P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; P<0.001). The rate of myocardial infarction was lower with thienopyridine treatment than with placebo (2.1% vs. 4.1%; hazard ratio, 0.47; P<0.001). The use of first-generation DES in the DAPT trial makes this trial difficult to interpret in current practice.

A meta-analysis of 10 randomized duration studies, including 32,287 unselected patients with ACS or CCS with DES implantation, assessed outcomes with either short-term (3 to 6 months) or extended (beyond 12 months) DAPT duration compared with 12-month therapy (23). Short-term DAPT compared with 12-month therapy was similarly effective in reducing the incidence of ST or MI and was associated with lower risk of major bleeding (0.35% vs 0.61%; odds ratio [OR], 0.58; 95% CI, 0.36 to 0.92) (23). Extended DAPT, compared with a 12-month regimen, was associated with reduced odds of very late ST (0.32% *vs* 0.98%; OR, 0.33; 95% CI, 0.21 to 0.51) and MI (1.55% *vs* 2.89%; OR, 0.53; 95% CI, 0.42 to 0.66), but increased odds of major bleeding (1.95% *vs* 1.21%; OR, 1.62; 95% CI, 1.26 to 2.09) (23). **Figure 2** shows the history of DAPT duration studies and the main findings of this meta-analysis. This pooled analysis showed that DAPT carries a time-dependent incremental bleeding risk; however, it remained difficult to reconcile why prolonged DAPT beyond 12 months was associated with lower risk of MI and ST whereas a shorter than 12-month DAPT was not associated with an excess of MI or ST compared with standard 12-month treatment.

The subsequent SMART DATE trial results provided a framework for reconciling the apparent discrepant findings (24). In this trial, unlike previous short-term DAPT trials which included low-risk or all-comer PCI populations, 2,712 ACS patients with PCI were allocated to 6-month DAPT or 18-month DAPT (24). Mortality and stroke risks did not differ between groups, but MI was more frequent with 6-month DAPT (1.8% *vs* 0.8%; hazard ratio [HR], 2.41; 95% CI, 1.15 to 5.05; p=0.02). ST did not differ significantly with 6- versus 18-month DAPT (1.1% *vs* 0.7%; HR, 1.50; 95% CI, 0.68 to 3.35; p=0.32). The excess of MI with 6-month DAPT was driven by a two-fold higher rate of target

vessel MI (1.1% *vs* 0.5%), presumably driven by a nonsignificant increase of ST, and a 3-fold higher rate of non-target vessel MI (0.8% *vs* 0.2%). The rates of major bleeding were 0.5% with 6-month DAPT and 0.8% with 18-month DAPT (HR, 0.60; 95% CI, 0.22 to 1.65; p=0.33), whereas the rates of Bleeding Academic Research Consortium (BARC) type 2-5 bleeding were 2.7% with 6-month DAPT and 3.9% with 18-month DAPT (HR, 0.69; 95% CI, 0.45 to 1.05; p=0.09). The SMART DATE trial demonstrated that in ACS patients the benefits of greater than 12-month DAPT might outweigh the risks compared with 6-month DAPT.

The *Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54* (PEGASUS-TIMI 54) trial leveraged prior evidence from DAPT duration studies and investigated a prolonged DAPT regimen with ticagrelor 90 mg or 60 mg twice-daily compared with aspirin alone in stable patients with prior MI (25). Patients were further selected for having additional ischemic risk enhancers, including age ≥65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction. In this trial, ticagrelor 60 mg twice daily in combination with aspirin reduced MI (4.53% *vs* 5.25%; HR, 0.84; 95% CI, 0.72 to 0.98; P=0.03), stroke (1.47% *vs* 1.94%; HR, 0.75; 95% CI, 0.72 to 0.98; P=0.03), and a borderline significant cardiovascular mortality benefit (2.86% *vs* 3.39%; HR, 0.83; 95% CI, 0.68 to 1.01; P=0.07) compared with aspirin alone after standard 12-month DAPT duration.

The Kaplan–Meier rates at 3 years for the primary endpoint of cardiovascular death, MI, or stroke were 7.77% in the ticagrelor 60 mg and 9.04% in the placebo group (HR, 0.84; 95% CI, 0.74 to 0.95; P=0.004), with a number needed to treat for benefit (NNTB) of 79 for 3 year-treatment. The Kaplan–Meier rates for 3-year Thrombolysis in Myocardial Infarction (TIMI) major bleeding were 2.30% in the ticagrelor 60 mg and 1.06% in the placebo group (HR, 2.32; 95% CI, 1.68 to 3.21; P<0.001), yielding a number needed to treat for harm (NNTH) of 81 for 3 year-treatment. Unlike for high ischemic risk features, patients in PEGASUS-TIMI 54 were not selected for bleeding risk characteristics. Bleeding risk assessment was limited to a known bleeding disorder, history of an ischemic stroke or intracranial bleeding, a central nervous system tumor, an intracranial vascular

abnormality; or gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days.

Taken together, these findings challenge the dogma of 12-month DAPT duration and suggest that DAPT duration should be tailored according to the individual ischemic and bleeding risks, either in terms of shorter than 12-month treatment duration among HBR patients or longer than 12 months in those at high ischemic risks who can safely tolerate the treatment.

Optimizing benefits over risks across DAPT duration studies

The recognition of a trade-off between bleeding risk and ischemic benefit with DAPT when followed by aspirin has fostered an unprecedented amount of research for the identification of patient selection algorithms for optimal treatment duration. Current evidence supports the concept that bleeding risk assessment should be prioritized and high bleeding risk patients should not be offered a prolonged treatment duration even if concomitant ischemic risk exists. On the other hand, among the non-HBR patients, ischemic risk should be assessed as second-step driver for the decision making on treatment duration and prolonged more than abbreviated DAPT is preferable.

A large number of studies have investigated the balance between ischemic and bleeding risks to further optimize DAPT duration, when DAPT was followed by aspirin monotherapy (26,27). However, only a few studies addressed how much of each (i.e., ischemic vs bleeding) risk is truly modifiable by DAPT duration. The absolute risk of fatal or non-fatal ischemic events, considered in isolation, might not necessarily identify the good candidates for a prolonged over an abbreviated DAPT duration. Patients at high or even very high ischemic risk should be offered prolonged DAPT, given its trade-off for bleeding, only if evidence exists that prolonged compared with abbreviated DAPT significantly mitigates that risk (i.e., DAPT modifiable ischemic risk) to a sufficient extent as to outweigh the harm associated with bleeding. This assessment can only be performed in the setting of randomized controlled trials for DAPT duration. The use of patient selection frameworks in randomized trials of DAPT duration suggests that bleeding risk is a major treatment modifier for DAPT duration: prolonged DAPT mitigates the ischemic risk in non-HBR but not in HBR patients.

The DAPT trial investigators developed the DAPT score in an effort to maximize the benefits and minimize the risks of 30-month DAPT, compared with 12-month DAPT (28). The DAPT score was generated by identifying independent predictors of fatal or non-fatal ischemic (i.e. MI and ST) events and bleeding (GUSTO severe or moderate) events in the randomized DAPT trial population (n=11,648 patients). When separated into groups (high score group [score, ≥2] vs low score group [score, <2]), among patients in the high score group (n = 5,917), randomization to continued thienopyridine was associated with large reductions in MI or ST (2.7% for continued thienopyridine vs 5.7% for placebo; risk difference [RD] −3.0%; 95% CI −4.1% to −2.0%; $P < .001$) compared with those in the low score group (n = 5731; 1.7% for continued thienopyridine vs 2.3% for placebo; RD −0.7%; 95% CI, −1.4% to 0.09%; P=0.07; P value for interaction <0.001). Conversely, randomization to continued thienopyridine was associated with relatively small increases in bleeding among the high score group (1.8% for continued thienopyridine vs 1.4% for placebo; RD 0.4%; 95% CI, −0.3% to 1.0%; $P = 0.26$) compared with the low score group (3.0% for continued thienopyridine vs 1.4% for placebo; RD 1.5%, 95% CI 0.8% to 2.3%; P < 0.001; P for interaction =0.02). However, in the derivation cohort, the interaction testing between score and randomized treatment was no longer significant for the rates of MI or ST when tested in patients who were treated with newer generation everolimus-eluting stents. An independent validation of the DAPT score in the PRODIGY trial, which randomized patients to 6- or 24-month DAPT duration (29), showed that the DAPT score could identify patients with excessive bleeding risk with prolonged DAPT, whereas the score failed to identify the patients with benefits from prolonged DAPT if patients with first-generation DES were excluded (30).

The PRECISE-DAPT (age, creatinine clearance, haemoglobin, white-blood cell count, prior spontaneous bleeding) score was generated for prediction of out-of-hospital bleeding in patients treated with DAPT (31). The score has been so far externally validated in a total of twenty-one studies and 67,283 patients, with consistent moderate discriminative ability for 1-year major bleeding events (pooled c-stat: 0.71; 95% CI 0.64 to 0.77) (32). In a pooled dataset from 5 DAPT duration randomized trials, a longer DAPT duration (12 months or longer) significantly increased bleeding in high-risk patients (score ≥25), but not in those at lower risk profiles (P for interaction: 0.007) and

provided a significant ischemic benefit only in this latter group (31). These findings suggest that a prolonged DAPT regimen in patients selected exclusively for low out-of-hospital bleeding risk might minimize risks and maximize benefits. Prolonged DAPT should therefore not be offered to high ischemic risk patients regardless of concomitant bleeding features, rather to low bleeding risk patients if ischemic risk is high.

In a subsequent pooled analysis of individual patient data (IPD) from 8 randomized controlled trials of alternative durations (n=14,963), patients not fulfilling HBR criteria (PRECISE-DAPT score less than 25) had a consistent benefit from long compared with short DAPT duration, with no apparent trade-off in bleeding (33). The absolute magnitude of the ischemic risk benefit offered by a long DAPT regimen was greater in patients who underwent complex PCI and/or underwent treatment for an ACS as compared with non-complex PCI and CCS patients (P value for interaction< 0.001) (33). Conversely, HBR patients did not derive ischemic or mortality benefit from prolonged DAPT, regardless of PCI complexity and/or ACS as clinical presentation, and experienced an excess of bleeding events compared with a shorter treatment duration (**Figure 4**).

The "bleeding risk first assessment" paradigm to model DAPT duration and maximize benefits over risks has been reproduced in two important DAPT duration studies.

In a post-hoc analysis of PEGASUS-TIMI 54, HBR was defined as either a history of spontaneous bleeding requiring hospitalization, anemia at baseline, or both (N=2,714; 19% of the population), whereas low bleeding risk was defined as the absence of either characteristic (N=11,240; 81% of the population) (34). When comparing the safety of ticagrelor 60 mg twice daily versus placebo, the HR for TIMI major or minor bleeding was 2.93 (95% CI, 1.80 to 4.78) in HBR patients, and 2.37 (95% CI, 1.70 to 3.32) in patients at low bleeding risk (34). There was a greater absolute increase in the rate of TIMI major or minor bleeding with ticagrelor in the HBR group (increase of 4.4% at 3 years; 95% CI, 2.3% to 6.4%) compared with the increase with ticagrelor in the low bleeding risk group (increase of 1.5% at 3 years; 95% CI, 0.8% to 2.1%) with a significant interaction based on absolute differences (P value for absolute risk difference [ARD]= 0.01) (34). Ticagrelor 60 mg reduced the risk of cardiovascular death, MI, or stroke by 20% in patients with low bleeding risk (HR, 0.80; 95% CI, 0.70 to 0.92; P = 0.0015). However, there was no apparent benefit of ticagrelor in HBR patients (HR,

0.98; 95% CI, 0.77 to 1.26; P=0.88; P for interaction=0.15). Risk differences for ischemic, bleeding and net adverse events stratified by bleeding risk in the PEGASUS-TIMI 54 are shown in **Figure 4**. There was significant heterogeneity for all-cause mortality with ticagrelor based on low versus high bleeding risk with a reduction in low bleeding risk (HR, 0.79; 95% CI, 0.65 to 0.96) and no benefit in the HBR group (HR, 1.14; 95% CI, 0.86 to 1.50; P for interaction=0.03) (34).

The SMART DATE trial also retrospectively assessed the relationship between bleeding risk and the net clinical benefit of prolonged DAPT (24).-In patients with non-high PRECISE-DAPT score (<25, n=1967 [72.5%]), 6-month DAPT was associated with higher ischemic risk (2.7% *versus* 1.3%; HR, 2.01; 95% CI, 1.03 to 3.91; P=0.040; ARD, +1.3%; P=0.035) with similar bleeding risk (0.4% *versus* 0.3%; HR, 2.00; 95% CI, 0.37 to 10.94; P=0.422; ARD, +0.2%; P=0.498), compared with 12-month or longer DAPT (35). Among patients with high PRECISE-DAPT score (≥25, n=745 [27.5%]), 6-month DAPT presented a similar ischemic risk (4.8% *versus* 3.4%; HR, 1.43; 95% CI, 0.68 to 2.98; P=0.348; ARD, +1.5%; P=0.327) but significantly reduced major bleeding risk (0.6% *versus* 2.3%; HR, 0.25; 95% CI, 0.05 to 1.17; P=0.079; ARD, −1.7%; P=0.045) (35). Risk differences for ischemic, bleeding and net adverse events stratified by bleeding risk in the SMART DATE are shown in **Figure 4**.

The *Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen* (MASTER DAPT) trial was the first to enroll an all-comer HBR population across the entire spectrum of ischemic risk, including patients with ACS and those undergoing complex intervention. Overall, 4,579 patients with a mean of 2.1 HBR criteria, of whom 2,211 (48.3%) had recent ACS, were randomized to an abbreviated (N=2295, median DAPT duration 34 days) or a standard (N=2284, median DAPT duration 193 days) DAPT regimen (36). In the abbreviated arm, single antiplatelet therapy was implemented with clopidogrel in 53.9% of the patients, with aspirin in 28.8% of the patients, with ticagrelor in 13.6% and prasugrel in 1.2% of the patients (36).

Net adverse clinical events (NACE) occurred in 7.5% of the patients in the abbreviated-treatment group and 7.7% of the patients in the standard-treatment group (HR, 0.97; 95% CI, 0.78 to 1.20) in the per-protocol population, for a difference in risk of −0.23 percentage points (95% CI, −1.80 to

1.33; P for noninferiority <0.001). A total of 6.1% of the patients in the abbreviated-treatment group had a major adverse cardiac and cerebral event (MACCE) versus 5.9% of the patients in the standard-treatment group (HR, 1.02; 95% CI, 0.80 to 1.30), for a difference in risk of 0.11 percentage points (95% CI, −1.29 to 1.51; P for noninferiority = 0.0014). Major or clinically relevant nonmajor bleeding was less frequent in patients in the abbreviated versus the standard-treatment group (6.5% versus 9.4%; HR, 0.68; 95% CI, 0.55 to 0.84), for a difference in risk of −2.82 percentage points (95% CI, −4.40 to –1.24; P for superiority <0.001). The rates of NACE and MACCE remained consistently similar with abbreviated or standard DAPT regimen in ACS patients as well as patients with both ACS and complex PCI (37,38). A pre-specified subgroup analysis suggested that women may derive enhanced benefit from abbreviated DAPT owing to lower risks of bleeding and ischemic events (39). In a meta-analysis of 11 trials (n= 9,006 HBR patients), 1- or 3-month abbreviated DAPT resulted in lower bleeding and cardiovascular mortality, without ischemic harm, compared with a ≥6-month DAPT regimen (40) (**Figure 5**).

New $P2Y_{12}$ inhibitor-centered DAPT de-escalation studies

The trade-off of ischemic and bleeding risks with standard 12-month DAPT and the need to tailor DAPT duration according to bleeding and ischemic risks, when DAPT is followed by aspirin monotherapy, had led to new de-escalation modalities, which simplify treatment by either abbreviating aspirin rather than oral $P2Y_{12}$ that duration, or lessening $P2Y_{12}$ inhibition potency in the post-acute ACS phase (41,42). The evidence which has been generated shows consistent reductions in bleeding without an increase in fatal or non-fatal ischemic events across studies investigating reduced DAPT potency from 30 days onwards or ticagrelor monotherapy 1 to 3 months after DAPT compared with 12-month DAPT (43,44) (**Figure 6**). In fact, IPD meta-analyses of these newer de-escalation treatment strategies have shown that both bleeding and fatal or non-fatal ischemic endpoints might be reduced with these DAPT de-escalation strategies (43,44). The only exception to this “less is more” principle is in studies that have used clopidogrel monotherapy 1 month after ACS, where there is a possible increased risk of ischemic/thrombotic events with SAPT. Studies of more potent P2Y12 inhibitors after 30-days to 3 months or clopidogrel after 3 months have shown no excess of fatal or

non-fatal ischemic events, even among ACS patients who underwent complex PCI (45), whereas bleeding is consistently reduced, irrespective of HBR features (43,44). Thus, strategies that de-escalate DAPT, particularly to more potent $P2Y_{12}$ inhibitor therapy seems to offer net benefit in unselected patients, irrespective of ischemic and bleeding risks. These newer de-escalation strategies simplify the approach to DAPT de-escalation compared with older approaches of switching to ASA monotherapy, which require careful patient selection.

De-escalation by switching or dose-reduction

No single study or meta-analysis has shown an excess of ischemic events with de-escalation strategies based on switching or dose-reduction, whereas there is clear evidence that de-escalation mitigates the bleeding risk associated with standard 12-month DAPT (42,46,47).

In a pooled study-level meta-analysis of five randomized trials (N = 10,779 ACS patients) that assigned DAPT de-escalation (genetically guided to clopidogrel: N = 1,242; platelet function guided to clopidogrel: N= 1304; unguided to clopidogrel N = 1,672; unguided to lower dose N = 1,170) vs. standard 12-month DAPT (control group: N = 5,391) (48), DAPT de-escalation was associated with a reduction of BARC ≥2 bleeding (HR, 0.57; 95% CI, 0.42 to 0.78; I^2 = 77%) as well as major adverse cardiac events, defined mainly as the composite of cardiovascular mortality, MI, ST, and stroke (HR, 0.83; 95% CI 0.69 to 1.00; I^2 = 0%). A greater reduction of bleeding risk was found with unguided *versus* guided DAPT de- escalation whereas a similar reduction in risk of ischemic events with guided and unguided DAPT de-escalation was observed. Unguided de-escalation was associated with more prevalent use of clopidogrel than newer oral $P2Y_{12}$ inhibitors, which was seemingly associated with lower bleeding without ischemic risk trade-off on a background of aspirin across these trials (48). In a network meta-analysis (NMA) encompassing twenty-nine studies (n= 50,602 patients), de-escalation by switching or dose reduction ranked first for the reduction of NACE, while de-escalation by discontinuation (i.e., short DAPT) ranked first for reducing major bleeding (49). Antiplatelet therapy guided by platelet function test or genotype has been associated with lower risks of major adverse cardiovascular events (RR, 0.78; 95% CI, 0.63 to 0.95; p=0.015) as well as numerical trends suggesting less bleeding (RR, 0.88; 0.77 to 1.01, p=0.069) (50) (**Figure 7**). In a NMA including

61,898 ACS patients from 15 trials, guided antiplatelet therapy was the only strategy associated with lower risks of major adverse cardiovascular events without bleeding risk trade-off compared with potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) (51).

De-escalation by aspirin discontinuation

Across six trials, including 24,096 patients, the risks and benefits of $P2Y_{12}$ inhibitor monotherapy after 1-to-3-month DAPT was compared with 12-month DAPT in an IPD meta-analysis (44). Since aspirin was omitted in the de-escalation group, this meta-analysis pre-specified a noninferiority analysis with a margin of 1.15 on a hazard ratio scale, which preserves 50% of the treatment effect observed in aspirin versus no aspirin trials. The primary outcome of all-cause death, MI, and stroke occurred in 283 (2.95%) or 303 (2.94%) and 315 (3.27%) or 338 (3.36%) patients with $P2Y_{12}$ inhibitor monotherapy and DAPT in the per-protocol (HR, 0.93; 95% CI, 0.79 to 1.09]; P for non-inferiority = 0.005; P for superiority=0.382; Tau^2 0.00) or intention-to-treat (HR, 0.90; 95% CI, 0.77 to 1.05; P for superiority=0.188; Tau^2 0.00) populations, respectively (44). The treatment effect was consistent across all subgroups, including ACS patients (13,699 patients, of whom 5,122 patients with NSTEMI and 3,265 patients with STEMI). There was strong evidence for a reduction in the risk of BARC type 3 or 5 bleeding among patients randomly allocated to $P2Y_{12}$ inhibitor monotherapy compared with DAPT (0.89% *versus* 1.83%; HR, 0.49; 95% CI, 0.39 to 0.63; p<0.001; Tau^2 0.03). Cardiovascular death was lower with $P2Y_{12}$ inhibitor monotherapy (0.57% *versus* 0.90%; HR, 0.69; 95% CI, 0.50 to 0.95; p=0.025), with no between-trial heterogeneity (Tau^2 0.00). In the $P2Y_{12}$ monotherapy group, 8,956 (77%) patients received ticagrelor, 2,586 (22.2%) received clopidogrel and 92 (0.8%) received prasugrel. In a prespecified subgroup analysis based on the type of monotherapy, the composite of all-cause death, myocardial infarction, and stroke was similar with clopidogrel vs DAPT (HR 0.94; 95% CI, 0.66 to 1.33) or with newer $P2Y_{12}$ inhibitors vs DAPT (HR, 0.89; 95% CI, 0.75 to 1.06), with no evidence of heterogeneity by type of P2Y12 inhibitor (P value for interaction= 0.16) (44). However, this analysis cannot be considered conclusive for clopidogrel, since the 95% confidence interval for clopidogrel monotherapy did not exclude harm with monotherapy versus DAPT and a significant mortality reduction was observed with newer $P2Y_{12}$ inhibitors vs DAPT (HR, 0.71; 95% CI 0.53 to

0.95) but not with clopidogrel vs DAPT (HR, 1.09; 95% CI, 0.65 to 1.84; P value for interaction= 0.16)(44). Concerns over the use of clopidogrel monotherapy after 1-month DAPT were raised by the results of STOPDAPT-2-ACS (52), where non-inferiority for the composite of cardiovascular death, MI, definite ST and stroke of 1-month DAPT with aspirin and clopidogrel followed by clopidogrel monotherapy was not shown compared with 1-year DAPT (HR, 1.14; 95% CI, 0.80 to 1.62; P value for noninferiority=0.06) due to a significant excess of MI in the monotherapy arm (HR, 1.91; 95% CI, 1.06 to 3.44). It should be acknowledged that event rates were very low in both groups in the STOPDAPT-2 ACS and larger and more adequately powered studies on clopidogrel monotherapy remain desirable.

Evidence from a NMA including PCI and/or ACS patients, focused on 12-month treatment effects, suggests that ticagrelor monotherapy is associated with lower risks of mortality (HR, 0.68; 95% CI, 0.52 to 0.89) and MI (HR, 0.69; 95% CI, 0.50 to 0.95) compared with aspirin and with lower risk of mortality (HR, 0.70; 95% CI, 0.55 to 0.89) and similar risk of MI and bleeding compared with 12-month DAPT with aspirin and clopidogrel (53).

A recent consensus statement in patients with ACS managed with PCI states that, compared with 12-month DAPT, aspirin withdrawal after 1-to-3-month DAPT and continuation with $P2Y_{12}$ inhibitor in the form of ticagrelor monotherapy, provides net benefit with reduced bleeding complications without increased risk of non-fatal or fatal ischemic events (54). Prasugrel monotherapy has not been investigated, while clopidogrel monotherapy is associated with greater MI risk among patients who were not selected for being at HBR (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25) (54). Therefore, 1-to-3-month DAPT followed by ticagrelor monotherapy was identified as the default treatment in ACS patients managed with PCI, whereas 12-month DAPT with prasugrel of ticagrelor was identified as a second-line option (54).

Contemporary guidelines recommendations on DAPT

A summary of recommendations from the 2023 ESC Guidelines and 2021 ACC/AHA/SCAI Guidelines on antithrombotic treatment strategies in ACS patients undergoing PCI is depicted in **Figure 8**. The 2021 ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization provided a

single class I DAPT duration recommendation in ACS patients to 12-month DAPT with prasugrel or ticagrelor (7) (**Figure 8**). Discontinuation of aspirin 1-3 months after DAPT with continued $P2Y_{12}$ monotherapy was supported with a class IIa recommendation, whereas discontinuation of $P2Y_{12}$ inhibitor after 6-month DAPT received a class IIb in HBR patients or those with on DAPT overt bleeding (7).

The 2023 ESC ACS guidelines states that, in all ACS patients, a $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, given as an initial oral loading dose followed by a maintenance dose for 12 months unless there is HBR (3,55) (**Figure 8**). HBR should be assessed in a structured manner, e.g. presence of a single major or two minor characteristics as defined by ARC-HBR. However, no study has shown that ARC-HBR features are a treatment modifier for DAPT duration and the ARC-HBR single criteria require recalibration (56,57).

The de-escalation options are identified as alternatives to the default strategy of 12 months DAPT with either a class IIa or IIb recommendation, because "*the evidence on these strategies in ACS patients is derived from trials powered primarily for bleeding outcomes, many of which had a non-inferiority design and were, therefore, not powered to detect potentially relevant differences in ischaemic outcomes*" (3). They also stated that "*the patient populations enrolled in these studies were also often relatively selected, often excluding or under-representing the highest risk ACS patients*", likely referring to STEMI patients (3). Interestingly, these considerations apply even more to studies assessing DAPT duration among patients with oral anticoagulation, but were not argued by guidelines as a possible reason to disqualify their findings.

Conclusions

The scientific foundation of 12 months of DAPT, which has been for almost two decades the strongest and the only class I recommendation of all DAPT durations in American and European guidelines for non-OAC ACS patients, has been historically attributed to the results of 3 studies, none of which were designed the assess the optimal duration of DAPT duration. More recently, in studies designed

specifically assess DAPT duration, 12-month DAPT has never been associated with convincing net benefits, either because of excessive bleeding compared with more abbreviated regimens or because of inferior protection towards ischemic events compared with more prolonged regimens.

Shorter than 12-month DAPT, followed by a single antiplatelet therapy, is associated with similar ischemic and lower bleeding risks than a up to 12-month DAPT in HBR patients, irrespective of the ischemic risk profile. Compared with 12-month DAPT, newer DAPT de-escalation strategies (by switching, dose-reduction or ticagrelor monotherapy) have shown to preserve if not improve ischemic risk protection and to lower major bleeding risk, therefore yielding improved net benefit across the full spectrum of bleeding risk patients. Yet, none of these de-escalation strategies has been so far recommended by guidelines as preferable or at least comparable to 12-month DAPT. This dogmatic position embraced by international guidelines has made 12-month DAPT a myth throughout the years, and as such apparently unchallengeable. Like a myth, the 12-month DAPT myth can only be passed on, at least until it is demystified. The demystification process can only go through an in-depth and open-minded review of the weak evidence surrounding the 12-month DAPT duration after ACS and/or PCI. Twelve-month DAPT duration should no longer remain the default approach and class I recommendation after ACS and/or PCI.

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FIGURE LEGENDS

Figure 1. Evolution of American and European guidelines recommendations on dual antiplatelet therapy (DAPT) duration in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Guidelines recommendations on DAPT duration are reported with class of recommendation (first colored box) and level of evidence (blue box). *Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; NSTE-ACS, non-ST-segment elevation-ACS; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-segment elevation myocardial infarction.*

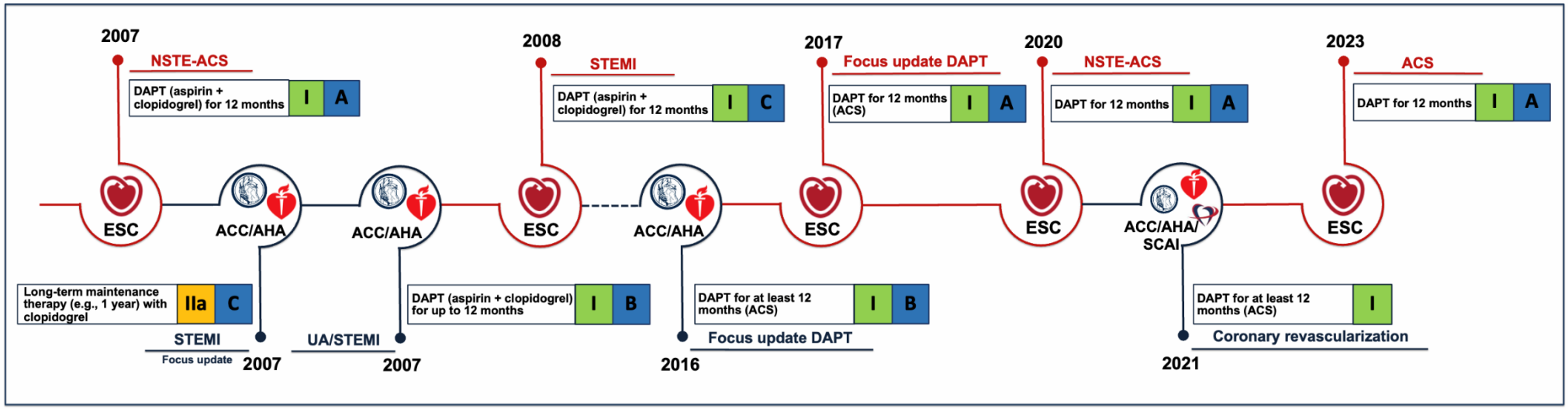

Figure 2. Key study features and main findings of the PCI-CURE, TRITON-TIMI 38 and PLATO trials. *Abbreviations: CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction; SAPT, single antiplatelet therapy.*

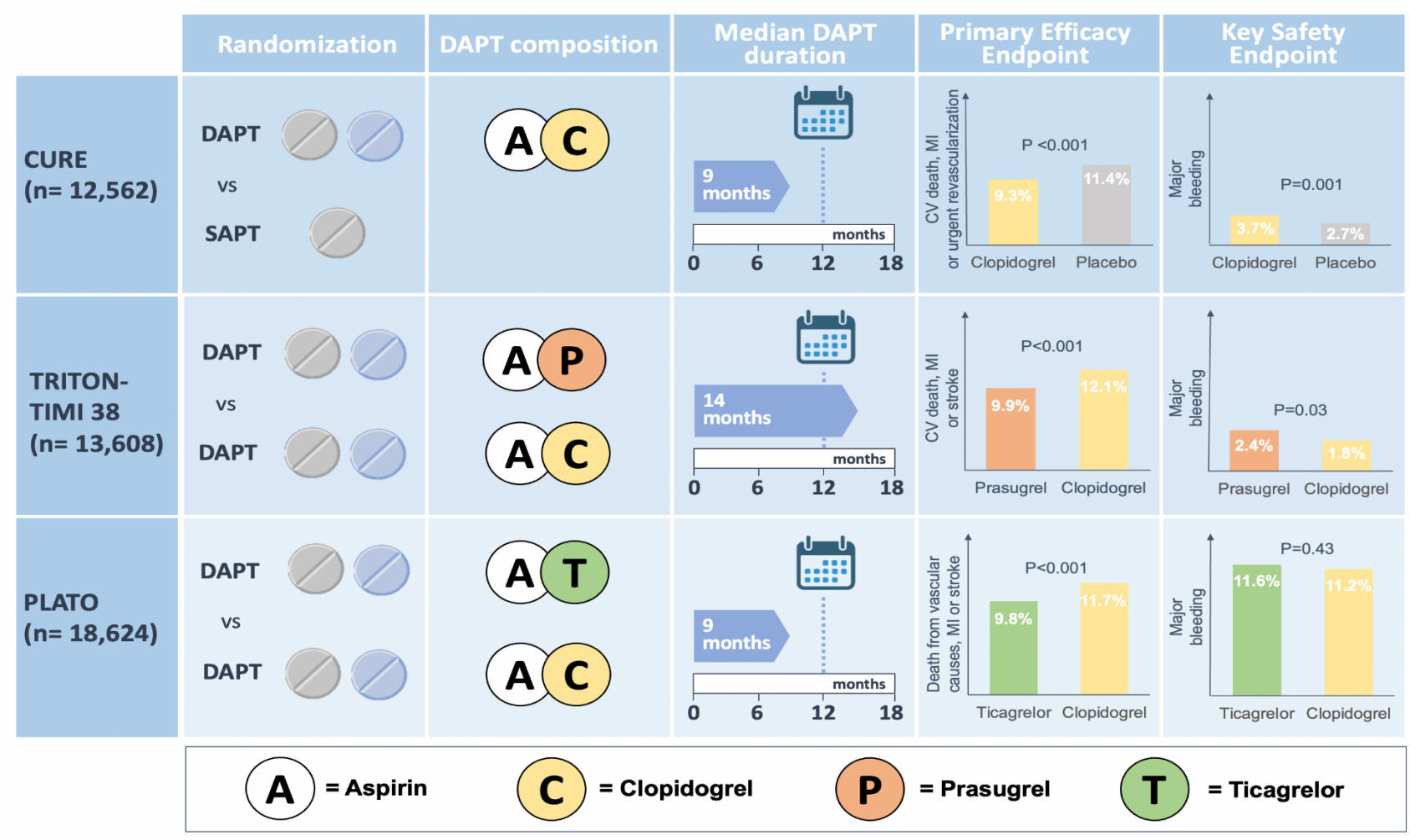

Figure 3. ~~History of~~ DAPT duration studies in patients with CAD. The colors within each circle identify the antiplatelet agent(s) investigated. Head-to-head studies comparing similar durations of two different antiplatelet strategies are shown with a vertical line, whereas those investigating different treatment durations are shown with a horizontal line. Studies investigating different treatment strategies or regimens and not treatment durations or type are represented with a single color indicating the $P2Y_{12}$ inhibitor, which was tested on top of aspirin. The forest plot shows efficacy and safety outcomes from a meta-analysis (23) with short-term (<12 months) or extended (beyond 12 months) DAPT duration compared with standard 12-month therapy. *Abbreviations: CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet therapy; pts, patients; ST, stent thrombosis.*

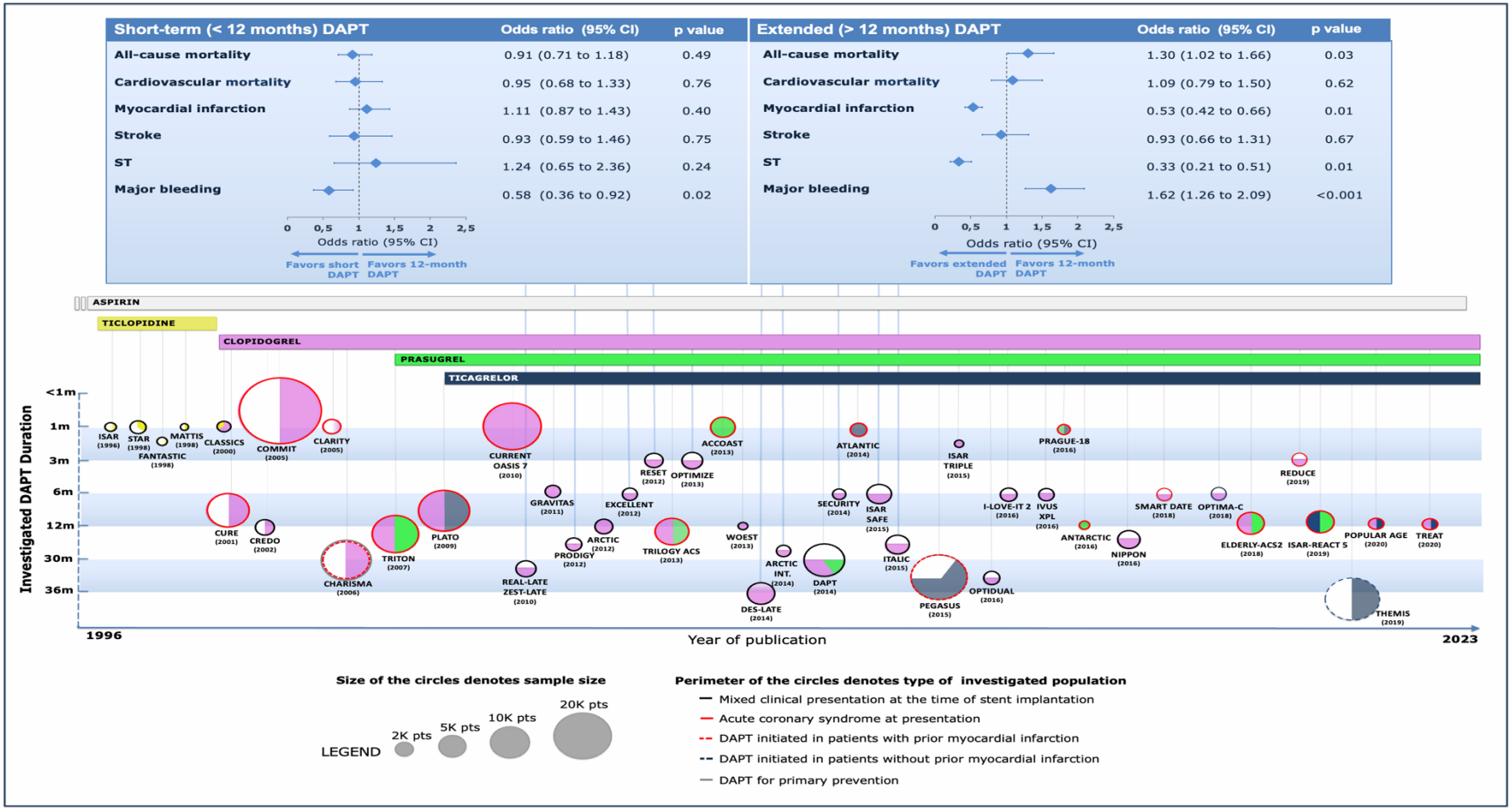

Figure 4. Long versus short DAPT stratified by high bleeding risk in the DAPT randomized studies (33)**, SMART DATE** (35) **and PEGASUS-TIMI 54** (34)**.** §§ used in the derivation cohort of the PRECISE DAPT score (ACS subgroup).
Risk difference for long-term or intensified DAPT versus short-term or less intensified DAPT for bleeding*, ischemic § and net adverse events#. *Bleeding was defined as TIMI major and minor bleeding in DAPT randomized studies, BARC 3 or 5 in the SMART-DATE and TIMI major bleeding in the PEGASUS-TIMI 54 study. § Ischemia was defined as the composite of MI, ST, stroke and TVR in the DAPT randomized studies, the composite of MI, ST and stroke in the SMART DATE study and the composite of CV death, MI and stroke in the PEGASUS- TIMI 54. The endpoint of net adverse events# was defined as the composite of ischemic and bleeding events in the DAPT randomized studies, the composite of all-cause death, MI, CVA, BARC type 2-5 bleeding in the SMART DATE and the composite of CV death, MI, stroke, fatal bleeding in the PEGASUS-TIMI 54 study. **High bleeding risk was defined as a PRECISE DAPT score ≥ 25 (DAPT randomized studies and SMART DATE), history of spontaneous bleeding requiring hospitalization or anemia (PEGASUS-TIMI 54). *Abbreviations: BARC, Bleeding Academic Research Consortium; CV, cerebrovascular; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; MI, myocardial infarction; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization.*

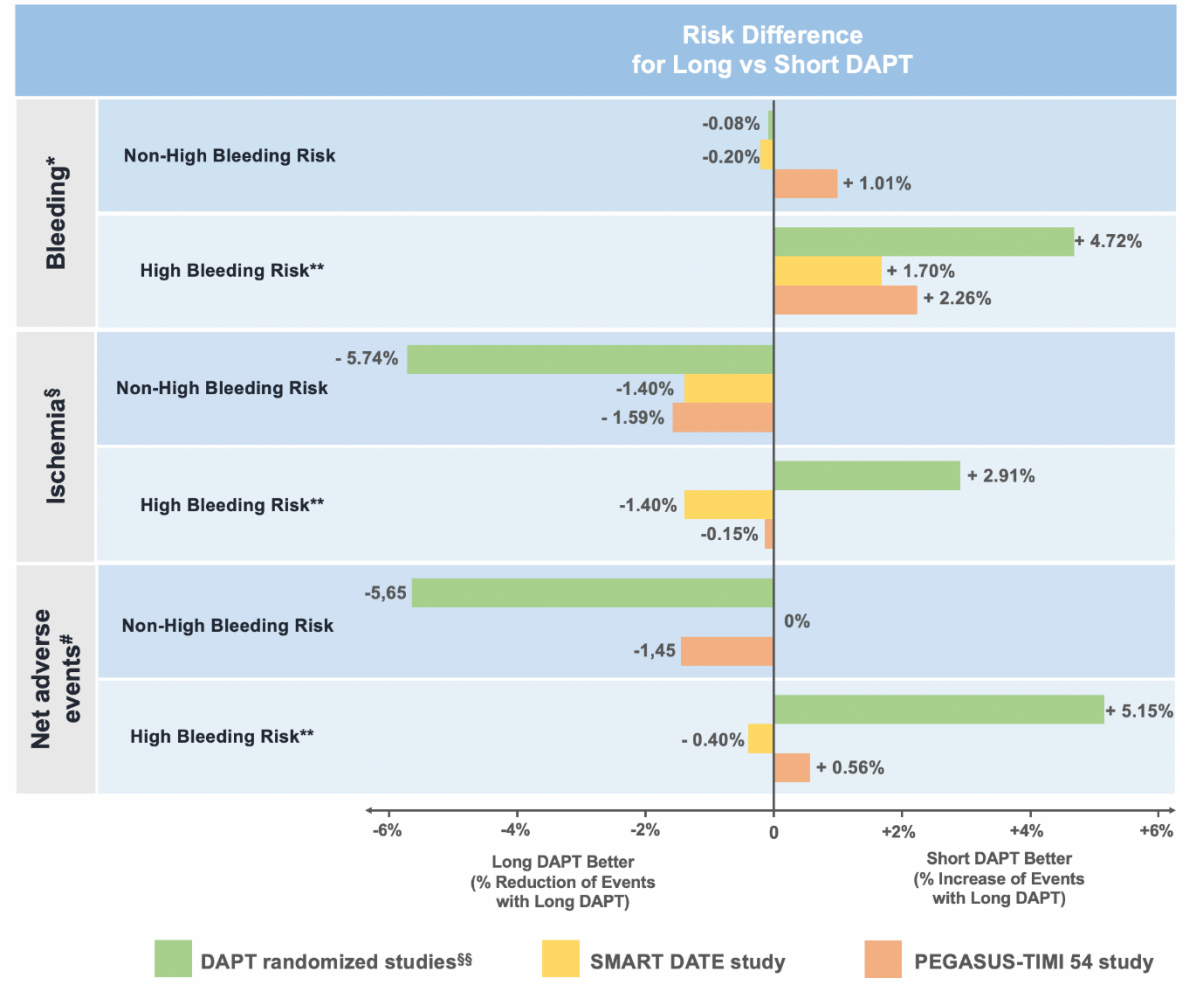

Figure 5. Risk of bleeding and ischemic complications with abbreviated vs standard antiplatelet therapy in patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI). Relative risks for the random-effects model are reported. Reproduced with permission from a meta-analysis of randomized clinical trials in HBR patients undergoing PCI (40). *Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; RR, risk ratio.*

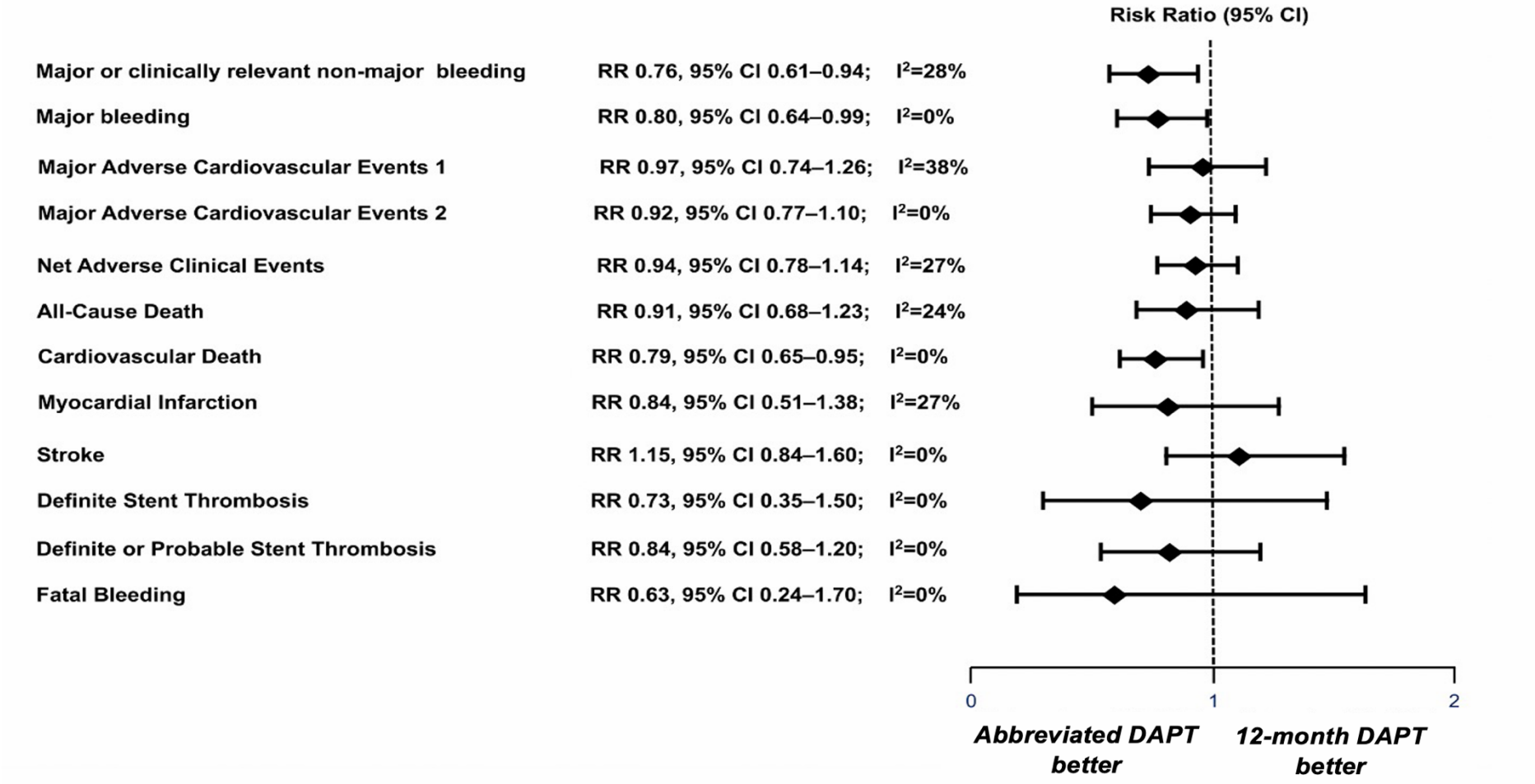

Figure 6. ~~History of~~Studies assessing $P2Y_{12}$ inhibitor ~~or aspirin~~ monotherapy or DAPT in patients with CAD. The colors within each circle identify the single antiplatelet agent(s) investigated after short course of DAPT. The forest plots show the main findings of two IPD meta-analysis (43,44) investigating the effects 1- to 3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy versus standard DAPT. *Abbreviations: BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet therapy; IPD, individual patient data; MI, myocardial infarction.*

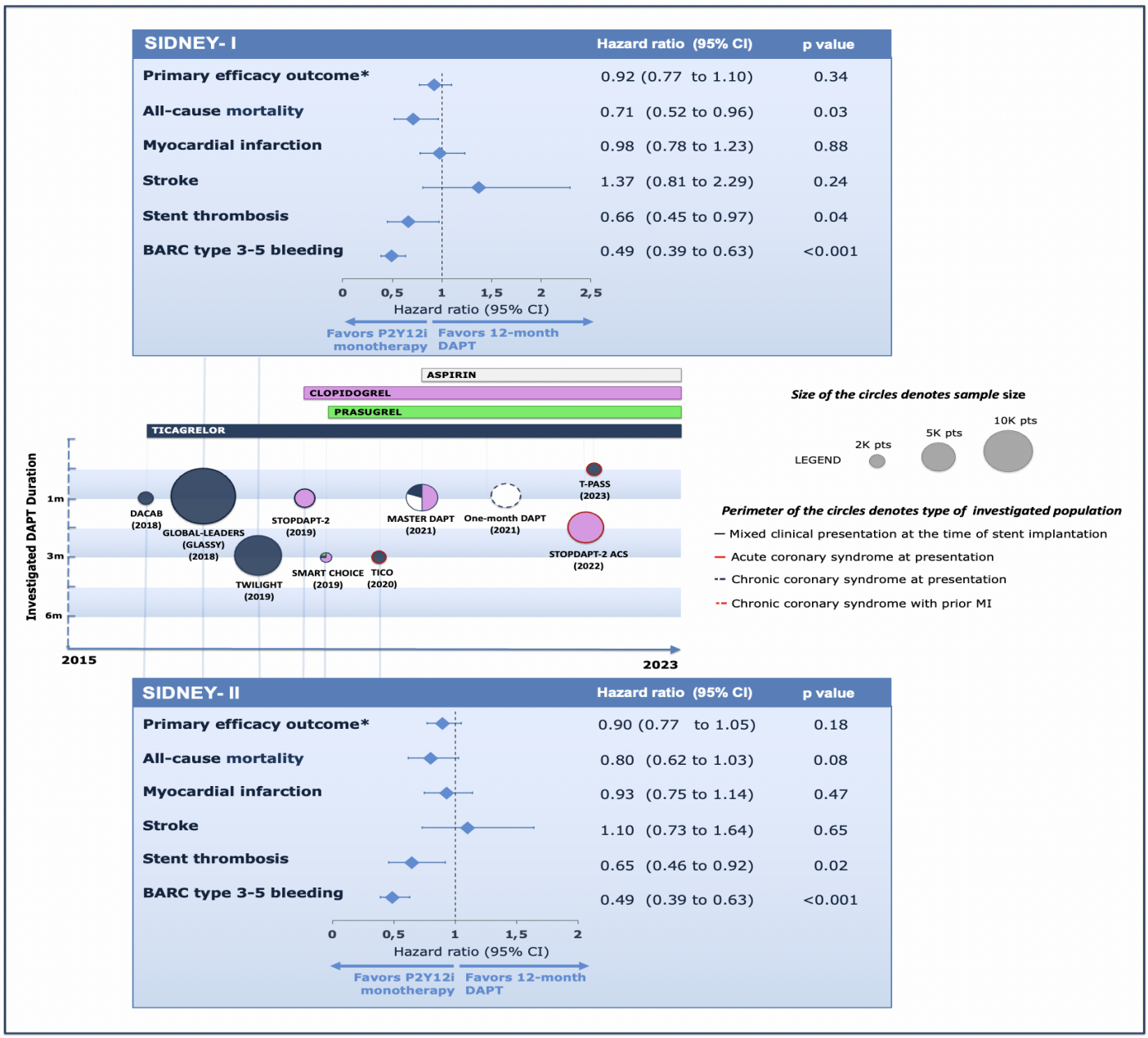

Figure 7. ~~History of~~Studies assessing antiplatelet therapy guided by platelet-function test (PFT) or genotype in patients with CAD. The circle colors identify escalation or de-escalation strategies. The forest plot (upper panel) shows the main findings of a study-level meta-analysis (49) comparing de-escalation of dual antiplatelet therapy (either guided or unguided by PFT or genotype) versus standard treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI). The lower panel shows the main results of a meta-analysis (50) investigating the effects of APT guided by PFT or genotype in patients undergoing PCI (only data from randomized studies are reported). *Abbreviations: APT, antiplatelet therapy; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet therapy; PFT, platelet-function test.*

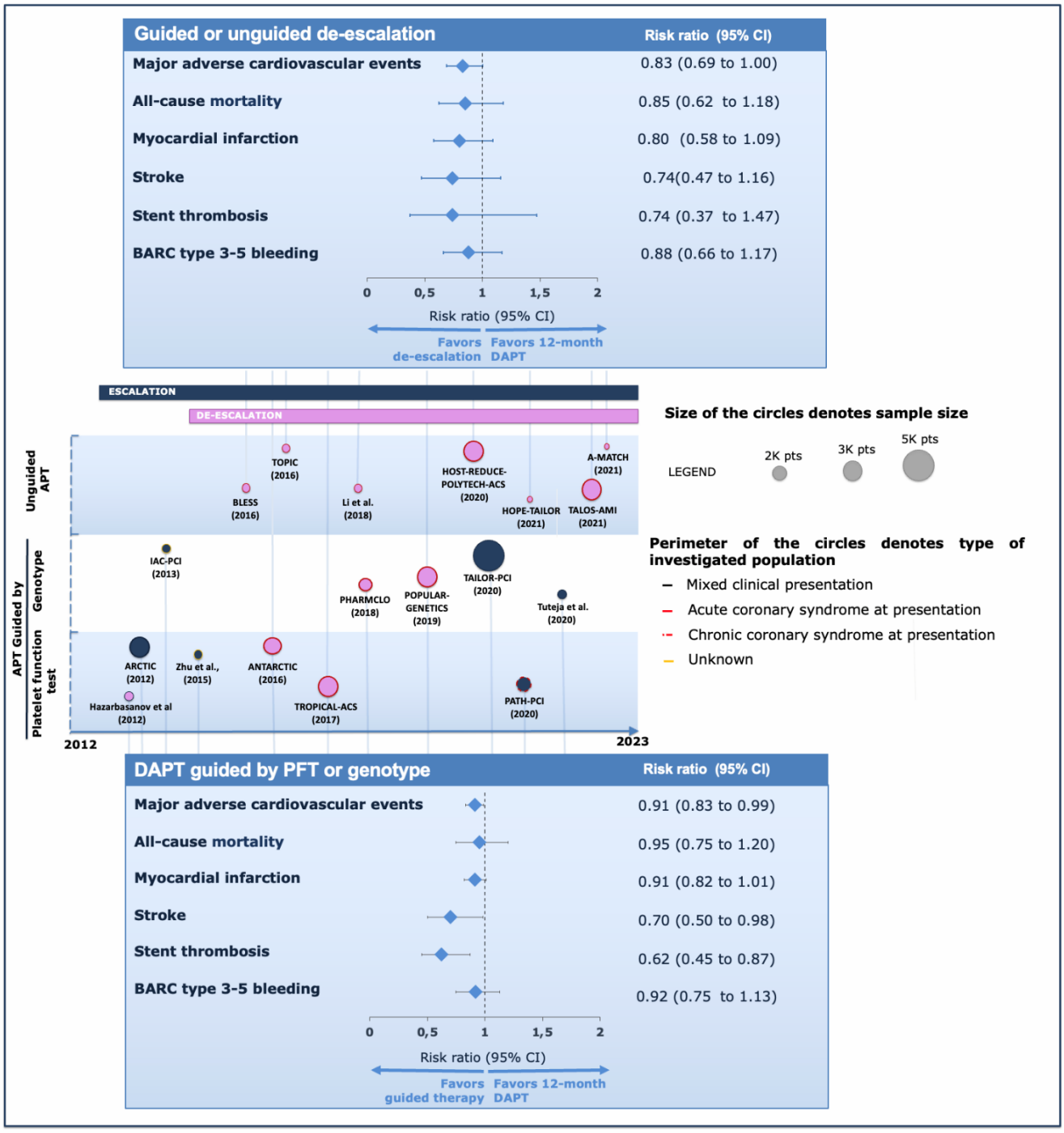

Figure 8. Summary of recommendations from the 2023 ESC Guidelines and 2021 ACC/AHA/SCAI Guidelines on antithrombotic treatment strategies in ACS patients undergoing PCI. Box colors reflects classes of recommendation. Treatment preferences within each box are presented from above to below, whereas treatments in the same line are reported in alphabetical order. § If patient is not eligible for above shown treatment options. # In patients not at high ischemic risk who are event-free after 3-6 months of DAPT. *Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ACS, acute coronary syndrome; ASA, aspirin; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; SCAI, Society for Cardiovascular Angiography and Interventions.*