Abstract The residual risk of patients surviving until 1 year after acute coronary syndromes (ACS) is still high, despite secondary prevention. The cornerstone of treatment of patients with ACS is dual antiplatelet therapy (DAPT) consisting of low-dose aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) for 12 months, or less in those patients at higher risk for bleeding. To reduce the residual risk beyond 1 year in those patients not at high bleeding risk who tolerated DAPT and did not suffer an (ischaemic or bleeding) event would intuitively mean to prolong DAPT. However, prolonged DAPT always comes at the cost of more bleeding. Therefore, assessing both ischaemic and bleeding risk in these patients at 1 year after ACS is crucial. In addition, another antithrombotic treatment consisting of low-dose rivaroxaban combined with low-dose aspirin has been shown to reduce ischaemic events. In this review, we describe residual thrombotic risk at 1 year after ACS, evaluate the evidence for antithrombotic options beyond 1 year and provide a practical guide to determine which patients would benefit the most from these therapies.

Keywords Acute coronary syndrome · Antithrombotic therapy · Ischaemic risk · Myocardial infarction

Residual risk at 1 year after acute coronary syndrome

Over the past decades, the overall mortality of patients admitted with acute coronary syndrome (ACS) has decreased [1, 2]. Simultaneously, implementation of evidence-based treatments in ACS patients has led to a lower risk of recurrent ischaemic events [1, 2]. Also, with the use of newer generation drug-eluting stents (DES) [3], the incidence of both early and especially late (>1 year after percutaneous coronary intervention (PCI)) stent thrombosis (ST), the most feared complication, has decreased. However, nationwide registries in different countries have also shown that a large proportion of patients have a recurrent cardiovascular event [i.e. myocardial infarction (MI), stroke or cardiovascular death] in the years following their initial admission [4, 5]. For example, a registry of ACS patients from the United Kingdom and Belgium has shown that one in five ACS patients have died after 5 years, 13% of them due to cardiovascular causes, implying that additional secondary prevention measures are warranted beyond the 1st year [4]. In addition, not only in registries, but even in randomised controlled trials (RCTs) where medical treatment is optimally controlled, the incidence of recurrent cardiovascular events is still high [6]. Extended antithrombotic strategies have been developed to reduce these long-term cardiovascular events, but all come at the cost of more bleeding [6–9]. However, it is important to acknowledge the different grades of severity in both bleeding and ischaemic events as, for example, not all moderate or severe bleeding events have the same impact on mortality as MI [10]. Therefore, a careful assessment should be made to select those patients who would benefit from such an intensified strategy based on both bleeding and residual ischaemic risk post-ACS [11, 12]. In this review, we discuss the evi-
dence behind the different strategies of extended anti-
thrombotic treatment and provide a practical guide
to determine which patients would benefit the most
from these therapies. As a consequence, we do not
discuss the optimal antithrombotic therapy in the 1st
year post-ACS, neither are other pathways, such as
inflammation, the topic of this review.

Extended dual antiplatelet treatment beyond
1 year

Several trials have studied the effect of longer dual
antiplatelet therapy (DAPT) duration (i.e. beyond
12 months) in patients undergoing PCI [7, 13–15]. The
DAPT study was the first placebo-controlled trial that
showed superiority of continued DAPT to 30 months
compared to standard DAPT of 12 months in terms of
MI and ST rates (4.3% vs 5.9%, \( p<0.001 \)) [7]. How-
ever, an important increase in moderate or severe
bleeding was seen in continued DAPT (2.5% vs 1.6%,
\( p<0.001 \)), and concerns arose from the higher rates
of non-cardiovascular death (1.0% vs 0.5%, \( p=0.002 \)).
This increase in non-cardiovascular death was also
shown in a meta-analysis of RCTs that compared
short (3–12 months) to long (12–36 months) DAPT
in patients treated with DES [hazard ratio (HR) 0.67,
95% confidence interval (CI) 0.51–0.89] [16]. In the
trials included in this meta-analysis, over half of the
patients had chronic coronary syndromes (CCS).
Bare metal stents or first-generation DES were still
frequently used and patients were predominantly
treated with clopidogrel (and not the stronger agents
ticagrelor or prasugrel) in addition to aspirin [16].
Thus, these trials may not adequately portray the
contemporary treatment of patients admitted with
ACS.

A better representation of the modern-day post-
ACS patient is provided by the Prevention of Coron-
ary-vascular Events in Patients with Prior Heart Attack
Using Ticagrelor Compared to Placebo on a Back-
ground of Aspirin–Thrombolysis in Myocardial In-
farction 54 (PEGASUS-TIMI 54) trial, the largest RCT
to date investigating extended DAPT use, although in
this trial only a minority continued DAPT while most
patients restarted DAPT [6]. In this trial, 21,162 pa-
tients who had had a MI 1–3 years earlier and had
at least one additional high-risk feature (i.e. age
≥65 years, diabetes mellitus requiring medication,
more than one prior MI, multivessel disease or renal
impairment) were randomly assigned, in a double-
blind 1:1:1 fashion, to ticagrelor 90 mg twice daily,
60 mg twice daily or placebo. All patients were on
low-dose aspirin and were followed for a median
of 33 months. Both ticagrelor doses reduced the
composite of cardiovascular death, MI or stroke (at
3 years, 7.85% with ticagrelor 90 mg and 7.77% with
ticagrelor 60 mg) as compared to 9.04% with placebo
(HR for 90 mg 0.85, 95% CI 0.75–0.96, \( p=0.008 \); HR for
60 mg 0.84, 95% CI 0.74–0.95, \( p=0.004 \)). Thrombolyis
in myocardial infarction (TIMI) major bleeding was
higher with ticagrelor (2.60% with 90 mg and 2.30% with
60 mg) than with placebo (1.06%) (\( p<0.001 \) for
each dose vs placebo). The rate of death from any
cause was not reduced with ticagrelor. Intracranial
haemorrhage or fatal bleeding in the three groups was
0.63%, 0.71% and 0.60%, respectively. Thus, because
the decrease in thrombotic events and the increase in
bleeding events were quite similar in magnitude, not
all patients at 1 year post-MI should be treated with
a longer duration of DAPT. An interesting subanaly-
ysis of the PEGASUS-TIMI 54 adds to the selection
of patients that may benefit from extended-duration
DAPT, demonstrating that patients who continue
DAPT without interruption show a greater benefit
than patients who restarted DAPT after an initial
discontinuation 1 year post-MI [17].

A meta-analysis investigated 33,435 patients that
had had a prior MI and were randomised to extended
DAPT (low-dose aspirin plus clopidogrel, prasugrel
or ticagrelor beyond 1 year) (\( n=20,203 \)) or to aspirin
alone (\( n=13,232 \)) [14]. Extended DAPT decreased the
composite of cardiovascular death, non-fatal MI and
non-fatal stroke compared with aspirin alone [6.4% vs
7.5%; risk ratio (RR) 0.78, 95% CI 0.67–0.90; \( p=0.001 \)]
and reduced cardiovascular death (2.3% vs 2.6%; RR
0.85, 95% CI 0.74–0.98; \( p=0.03 \)), with no increase in
non-cardiovascular death (RR 1.03, 95% CI 0.86–1.23;
\( p=0.76 \)). Extended DAPT also reduced MI (RR 0.70,
95% CI 0.55–0.88; \( p=0.003 \)), stroke (RR 0.81, 95% CI
0.68–0.97; \( p=0.02 \)), and ST (RR 0.50, 95% CI 0.28–0.89;
\( p=0.02 \)). There was an increase in major bleeding
(1.85% vs 1.09%; RR 1.73, 95% CI 1.19–2.50; \( p=0.004 \))
but not fatal bleeding (0.14% vs 0.17%; RR 0.91, 95% CI
0.53–1.58; \( p=0.75 \)). A second, aggregate meta-anal-
ysis on extended DAPT, which is more contemporary
because it included only patients after DES implanta-
tion (\( n=21,475 \)), compared short (6–12 months) to
extended (18–48 months) DAPT and stratified patients
according to clinical presentation (CCS and ACS) [15].
In this analysis, similar results were found with in-
creased rates of MI, ST and the composite of death,
MI and stroke in patients with short DAPT, but higher
rates of major bleeding and non-cardiac death in pa-
tients with extended DAPT [15]. However, this ad-
verse effect was primarily driven by patients with CCS.
Very important to the discussion about residual risk
at 1 year post-ACS is that extended DAPT in ACS pa-
tients showed no significant increase in major bleed-
ing (HR 0.94, 95% CI 0.48–1.81) and non-cardiac death
(HR 0.94, 95% CI 0.59–1.52), and reduced the rates of
death, MI, stroke and major bleeding combined (6.0% vs
4.4%, \( p<0.0001 \)) with a number needed to treat of
61 to achieve a net clinical benefit. These meta-anal-
yses teach us that to be candidates for a longer duration
of DAPT patients should at least have had a spontane-
ous MI or ACS, while the risk of bleeding due to
extended DAPT seems to be less of an issue in ACS
patients than in CCS patients. Consequently, the lat-
long-term residual cardiovascular risk after acute coronary syndrome

est guidelines of the European Society of Cardiology (ESC) conclude that extended DAPT should be considered in ACS patients at high ischaemic risk without increased risk for major or life-threatening bleeding (class IIa, level of evidence A) [12].

### Long-term treatment with low-dose factor Xa inhibitor and aspirin

Oral anticoagulants reduce the risk of arterial thrombotic events. For example, in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial, additional low-dose rivaroxaban (2.5 mg twice daily) reduced the incidence of cardiovascular death, MI and stroke at 2 years post-ACS in patients mostly treated with low-dose aspirin and clopidogrel with a median duration of rivaroxaban use of 13.3 months. However, an important increase in bleeding, but not fatal bleeding, was found [8]. In a meta-analysis of patients with recent ACS and treated with DAPT, the addition of direct oral anticoagulant (DOAC) drugs to antiplatelet therapy led to a modest reduction of cardiovascular events (HR 0.87, 95% CI 0.80–0.95), but more than doubled the risk of major bleeding (HR 2.34, 95% CI 2.06–2.66) [18]. The ischaemia/bleeding risk trade-off was better in patients with additional DOAC use and aspirin alone. In the years following these trials, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was completed, which may be more relevant to the discussion about how to treat residual risk at 1 year. In this double-blind trial, 27,395 patients with stable coronary syndromes or peripheral artery disease received rivaroxaban (2.5 mg twice daily) plus low-dose aspirin, rivaroxaban (5 mg twice daily) or low-dose aspirin [9]. The composite of cardiovascular death, stroke or MI occurred less often with rivaroxaban plus aspirin than with aspirin alone (4.1% vs 5.4%; HR 0.76, 95% CI 0.66–0.86; p < 0.001), with the greatest effect in the reduction of stroke (HR 0.58, 95% CI 0.44–0.76). Concurrently, major bleeding occurred more with rivaroxaban plus aspirin (3.1%) than with aspirin alone (1.9%; HR 1.70, 95% CI 1.40–2.05; p < 0.001). There was no significant difference in intracranial or fatal bleeding with rivaroxaban plus aspirin. Death occurred in 3.4% with rivaroxaban plus aspirin as compared with 4.1% with aspirin alone (HR 0.82, 95% CI 0.71–0.96; p = 0.01; threshold p-value for significance 0.0025). The rate of the primary outcome was not significantly lower with rivaroxaban alone than with aspirin alone, but major bleeding occurred more with rivaroxaban alone. The study was stopped because of the superiority of rivaroxaban plus aspirin after a mean follow-up of 23 months. Greater absolute risk reductions with rivaroxaban plus aspirin were found in patients at high ischaemic risk (e.g. both coronary artery disease and peripheral artery disease or concomitant diabetes) [19]. Although patients with CCS and not ACS were included in the COMPASS trial, a large group of patients (62%) had a prior MI. Therefore, the 2020 ESC guidelines for the management of ACS patients without persistent ST-segment elevation state that rivaroxaban 2.5 mg twice daily in addition to aspirin should be considered in patients at high thrombotic risk and without an increased risk for major or life-threatening bleeding, and may be considered in patients with a moderately high thrombotic risk [12].

### How to select patients benefitting from extended antithrombotic treatment beyond 1 year post-ACS

Although the above literature clearly shows that there is evidence for extended antithrombotic therapy at 1 year post-ACS in patients with a higher thrombotic risk, we still struggle with how to define this ‘higher thrombotic risk’, how to balance the increased bleeding risk (many patients with a higher thrombotic risk also have a higher bleeding risk) and finally how to

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**Table 1** Antithrombotic treatment options for extended therapy beyond 1 year after an acute coronary syndrome (ACS).

| Extended dual antithrombotic treatment | Dose of additional drug | Continue/start treatment | Eligible patients | NNT (ischaemic events) | NNH (bleeding events) |
|----------------------------------------|-------------------------|--------------------------|------------------|-----------------------|----------------------|
| Aspirin + clopidogrel                   | 75 mg, once per day      | At 1 year post-ACS       | One year uneventful DAPT use | 63                     | 105                  |
| Aspirin + prasugrel                     | 50/10 mg, once per day   | At 1 year post-ACS + PCI | One year uneventful DAPT use | 63                     | 105                  |
| Aspirin + ticagrelor                    | 60/90 mg, twice per day  | At 1 year post-ACS + PCI | One year uneventful DAPT use | 84                     | 81                   |
| Aspirin + rivaroxaban                   | 2.5 mg, twice per day    | At 1 year or more post-ACS | High residual ischaemic risk<sup>a</sup> | 77                     | 84                   |

<sup>a</sup>The reduced prasugrel dose is only for patients with a body weight below 60 kg or age above 75 years.

<sup>b</sup>For criteria for high ischaemic risk, see Tab. 2.

**ARC-HBR** Academic Research Consortium for High Bleeding Risk. **DAPT** dual antiplatelet therapy. **NNH** number needed to harm. **NNT** number needed to treat. **PCI** percutaneous coronary intervention. **PRECISE-DAPT** PREdicting bleeding Complications in Patients undergoing Stent implantation and subsequent Dual Antiplatelet Therapy.
choose between continuing DAPT or switching to low-dose DOAC added to aspirin. Nevertheless, below we give our personal preference and describe how we treat residual antithrombotic risk in daily practice. An overview of the options for extended dual antithrombotic therapy is listed in Tab. 1. It should be noted that the numbers needed to treat or to harm listed for either ischaemic or bleeding events are derived from the original studies without initial risk stratification. In practice, careful risk assessment should be made first before extending dual antithrombotic therapy. In patients with ACS [11, 12]. This risk stratification should involve both thrombotic and bleeding event (Fig. 1). The current guidelines advise the use of either the DAPT score, the criteria used in the PEGASUS-TIMI 54 study or other scores [22]. Further, the ARC-HBR score was not developed to tailor DAPT duration. The PRECISE-DAPT score (consisting of the variables haemoglobin, age, creatinine clearance, white blood cell count and previous spontaneous bleeding) can be used to reduce the duration of DAPT to less than the standard 1 year [20]. In patients with a high PRECISE-DAPT score (≥25), standard-1-year DAPT is associated with no reduction in ischaemic events, but with a strong increase in bleeding [20]. These high bleeding risk patients should receive shorter DAPT (≤6 months), even those patients with a concomitant high ischaemic risk [23]. However, in selected patients with complex PCI (e.g. bifurcation stenting, ST), 12 months of DAPT may be considered after consultation with the interventional cardiologist who performed the PCI (Fig. 1). Patients without a high bleeding risk (e.g. PRECISE-DAPT score <25) should be treated with standard 1-year DAPT. Further, residual thrombotic risk should be assessed at 1 year in all patients that tolerated DAPT and did not suffer a thrombotic or bleeding event (Fig. 1). The current guidelines advise the use of either the DAPT score, the criteria used in the PEGASUS-TIMI 54 study or the criteria for high ischaemic risk in the ESC guidelines, which consist of clinical and angiographical/procedural risk factors (i.e. diabetes mellitus requiring medication, polyvascular disease, bifurcation stenting etc.), to select patients that may benefit from extended DAPT beyond 1 year post-ACS (Tab. 2; [11, 12]). The DAPT score is a combined score of both ischaemic and bleeding risk (Tab. 2; [24]). In patients with a high score (≥2), extended DAPT (12–30 months) resulted in reductions in the incidence of MI or ST [absolute risk difference (ARD) −3.0%; 95% CI −4.1 to −2.1, p<0.001] with a number needed to treat of 34, and no increase

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**Table 2** Risk scores and criteria for high ischaemic risk and eligibility for extended dual antithrombotic therapy. Use these criteria at 1 year after acute coronary syndrome (ACS) or myocardial infarction (MI). MI is defined as spontaneous MI. Multivessel coronary artery disease (CAD) is defined as stenosis of ≥50% in two major coronary territories (i.e. left anterior descending artery, intermediate artery, left circumflex artery, right coronary artery, left main coronary artery, a major branch or bypass graft), including revascularised arteries.

| Risk score/criteria | DAPT score | PEGASUS-TIMI 54 criteria | High ischaemic risk — ESC 2020 |
|---------------------|------------|--------------------------|-----------------------------|
| **Variables**       |            |                          |                             |
| Age: ≥ 75 years     | −2 pts     | Prior MI last 1–3 years and | Complex CAD<sup>a</sup> and |
| Age: 65–74 years    | −1 pt      | Age: ≥ 50 years and         | ≥ 1 of the following:       |
| Age: ≤ 64 years     | 0 pt       | ≥ 1 of the following:       | – Risk enhancers:           |
| Smoking (last 2 years) | +1 pt      | – Age: ≥ 65 years          | – DM requiring medication   |
| Diabetes mellitus   | +1 pt      | – DM requiring medication  | History of recurrent MI     |
| MI at presentation  | +1 pt      | – A second prior MI         | Any multivessel CAD         |
| Prior PCI or prior MI | +1 pt     | – Multivessel CAD           | Polymorphous disease (CAD + PAD) |
| Stent diameter <3 mm | +1 pt      | – CKD with eGFR <60 m<sub>l</sub>/min per 1.73 m<sup>2</sup> | Premature (<45 years)/accelerated<sup>b</sup>CAD |
| CHF or LVEF <30%    | +2 pts     |                          | Systemic inflammatory disease<sup>c</sup> |
| Vein graft stenting | +2 pts     |                          | CKD with eGFR 15–59 ml/min  |

| High ischaemic risk defined as: Total DAPT score: ≥ 2 | All 3 criteria should be met | Complex CAD +1 or more criteria (risk enhancer or technical aspect) should be met |

<sup>a</sup>Complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy

<sup>b</sup>Accelerated CAD is defined as a new lesion within a 2-year timeframe

<sup>c</sup>For example, human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis

<sup>d</sup>Left main stenting, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel

<sup>e</sup>CHF congestive heart failure, CKD chronic kidney disease, DAPT dual antiplatelet therapy, DM diabetes mellitus, eGFR estimated glomerular filtration rate

ESC European Society of Cardiology, LVEF left ventricular ejection fraction, PAD peripheral artery disease, PEGASUS-TIMI 54 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, PCI percutaneous coronary intervention, ST stent thrombosis
Review Article

Fig. 1 Flowchart of bleeding and ischaemic risk assessment following acute coronary syndrome (ACS) or myocardial infarction (MI). Bleeding risk should be assessed during hospital admission. Bleeding risk is assessed by use of the PRECISE-DAPT score or the ARC-HBR criteria [20, 21]. In patients at high bleeding risk, a short duration (≤6 months) of dual antiplatelet therapy (DAPT) should be considered. In patients at high bleeding risk and with a complex percutaneous coronary intervention (PCI), the standard DAPT duration may be considered. In patients without a high bleeding risk and who have tolerated DAPT in the first 12 months, the ischaemic risk should be assessed (see Tab. 2). In patients at high ischaemic risk extended DAPT or dual pathway inhibition (DPI) should be considered.

in moderate or severe bleeding (ARD +0.4%; 95% CI -0.3% to +1.0%, p=0.26) with a number needed to harm of 272. In patients with a low score (<2), extended DAPT was associated with an increase in moderate or severe bleeding events, without reductions in ischaemic events. Thus, only patients with a high DAPT score should be treated with extended DAPT. Also, the PEGASUS-TIMI 54 inclusion criteria could be used (Tab. 2). A third option is to apply the criteria for high ischaemic risk in the latest ESC guidelines (Tab. 2; [12]). These criteria were selected based on the combined evidence of the COMPASS, DAPT and PEGASUS-TIMI 54 studies in addition to observational evidence from large observational registries [6, 7, 9, 25–27]. Our personal preference is the DAPT score because it is easy to use and can be calculated at discharge. Thus it does not take up extra time at a busy outpatient clinic when the decision regarding the continuation of DAPT has to be made together with the patient. It is noteworthy that the ESC criteria have not yet been validated externally, as opposed to the DAPT score [28] and the PEGASUS-TIMI 54 criteria [29].

Finally, to assess whether patients with a high thrombotic risk benefit more from extending DAPT or combining low-dose rivaroxaban with aspirin is not possible, as these therapies have not been compared head-to-head. Intuitively, one would keep the patient on DAPT when this is well tolerated and start low-dose rivaroxaban in a patient with a high thrombotic risk treated with aspirin alone. We start low-dose rivaroxaban in patients with characteristics that are in line with the inclusion criteria of the COMPASS trial, especially those with peripheral arterial disease and/or carotid artery disease. Both long-term DAPT with low-dose ticagrelor (60 mg b.i.d.) and low-dose rivaroxaban (2.5 mg b.i.d.) with aspirin have proven to be cost-effective compared to aspirin alone [30, 31]. Discontinuation rates were higher for low-dose ticagrelor in the PEGASUS-TIMI-54 trial compared to the COMPASS trial (29% at 33 months and 16.5% at a mean follow-up duration of 23 months, respectively) [9, 32]. Low-dose ticagrelor was discontinued due to adverse events in 16% of patients, mainly because of non-major bleeding (6.2%) and dyspnoea (4.6%); in the majority this occurred early after randomisation. Details on rates and reasons for discontinuation in the COMPASS trial have not been published. The duration of extended treatment should depend on the patients’ tolerance. The current literature only supports the use of extended dual antithrombotic therapy from 2 to 4 years post-ACS or post-MI, but some patients at a continuous high ischaemic risk may have an indication for lifelong intensified antithrombotic treatment. It is advised that information on any bleeding complications while on dual antithrombotic therapy should be obtained in the outpatient setting and that patients’ bleeding risk and ischaemic risk should be reassessed yearly.

Long-term residual cardiovascular risk after acute coronary syndrome
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Conflict of interest  D.R.P.P. Chan Pin Yin declares that he has no competing interests. J.M. ten Berg reports institutional grants and personal fees from AstraZeneca, grants from ZonMw, and personal fees from Boehringer Ingelheim, Bayer and Ferrer outside the scope of the submitted work.

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