Antiplatelet agents in uncertain clinical scenarios—a bleeding nightmare

Sean Esmonde¹, Divyesh Sharma¹, Aaron Peace¹²

¹Department of Cardiology, Altnagelvin Area Hospital, Western Health and Social Care Trust, Derry/Londonderry, Northern Ireland, UK; ²Northern Ireland Centre for Stratified Medicine, Ulster University, C-TRIC, Derry/Londonderry, Northern Ireland, UK

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Aaron Peace. Department of Cardiology, Altnagelvin Area Hospital, Derry/Londonderry, BT47 6SB Northern Ireland, UK. Email: aaron.peace@westerntrust.hscni.net.

Abstract: Despite over 40 years since the first percutaneous coronary intervention (PCI) was performed, the optimal dual antiplatelet therapy (DAPT) regime poses a significant challenge for clinicians, especially in certain scenarios. DAPT is the standard of care in PCI following an acute coronary syndrome (ACS) or for elective patients with obstructive coronary artery disease (CAD). There remains significant uncertainty regarding DAPT in patients at high risk of bleeding, such as the elderly and patients requiring anticoagulation. More and more clinicians are faced with a dilemma of weighing risks and benefits from the increasing list of potent, new antiplatelet agents and direct oral anticoagulants (DOACs) in a growing, aging population. Historically, most studies failed to recognize bleeding risk, instead focusing on ischemic risk. In recent years however, bleeding has been recognized as a very significant driver of morbidity and mortality in patients undergoing PCI. There is a paucity of data in this cohort leading to divergent and sometimes conflicting recommendations, largely based on expert consensus of opinion. In the current review, we critically evaluate the available evidence in these uncertain scenarios.

Keywords: Antiplatelet; dual antiplatelet therapy (DAPT); bleeding; elderly; anticoagulation

Submitted Mar 13, 2018. Accepted for publication Jun 28, 2018. doi: 10.21037/cdt.2018.06.09

View this article at: http://dx.doi.org/10.21037/cdt.2018.06.09

Introduction

Antiplatelet therapy has been one of the most widely researched areas of medicine since the introduction of Aspirin in the 1960s (1,2) and Ticlopidine in the 1970s (3). Despite over 30 years of experience of using dual antiplatelet therapy (DAPT), significant uncertainties remain in how best to manage various distinct clinical scenarios. While studies have helped to provide many answers, virtually all of these same studies have raised further questions through a lack of uniformity in study design and definitions (4-6). These uncertainties have been magnified by an ever-growing, aging population, who invariably have never been definitively studied, tend to have complex coronary disease, and have many other co-morbidities which invariably influence our clinical decision making (7).

In particular, the aging population has led to an increased number of cases of patients with AF requiring PCI (8). The optimal regime for this challenging group of patients remains elusive, and is made even more complicated when one considers the expanding list of newer anticoagulant choices aside from Warfarin. Additionally, each of these new anticoagulants require tailoring to the individual based on such characteristics as renal function, age and weight (9).

In this review, we will focus mainly on the importance of bleeding in patients undergoing PCI, since it is largely our concerns with the risk of bleeding that guides the
Prescription of antiplatelet therapy. We will discuss the time at which bleeding tends to occur following PCI, the location of bleeding, the lack of standardisation of bleeding classification, the issue of bleeding in specific groups, especially the elderly and those taking concomitant oral anticoagulation, the failure of platelet function testing to help guide clinical decision making, and what potential measures could be considered to modify risk.

**The ‘Catch 22’ scenario**

Patients who are at high risk of bleeding that require DAPT post PCI represent a ‘Catch-22’ scenario. A ‘Catch 22’ scenario is defined as a dilemma or difficult circumstance(s) from which there is no escape because of mutually conflicting or dependent conditions. Not infrequently, the reaction to bleeding is to modify DAPT, thereby reducing the risk of bleeding whilst increasing the risk of thrombosis, thus increasing the risk of major adverse cardiovascular events (MACE) (10,11). This is every cardiologist’s nightmare. The difficulty faced by clinicians is that they, currently, do not have any robust barometer to safely guide modification of antiplatelet or anticoagulant therapy, such that the appropriate balance between bleeding and thrombosis is achieved.

**The significance and classification of bleeding—‘the lack of standard’**

It is only in recent years that the implications of bleeding post PCI have been fully recognized by clinicians and the regulatory authorities (12-14). In fact, early PCI studies did not appear to fully appreciate the issue at all (15-20). Some clinicians may have presumed that if someone bled this could simply be remedied by giving a blood transfusion. However, we now know that this is not the case as even moderate bleeding translates into a worse outcome, and indeed the simple act of transfusing blood itself is associated with a significantly worse outcome (13,21,22). Even minor bleeding can result in the interruption of DAPT (10) which can have prognostic significance; with previous evidence suggesting that there is a 90-fold increase in stent thrombosis (ST) for patients following premature antiplatelet discontinuation (11).

Before considering PCI, it is crucial to reassess a patient’s symptoms to ensure that their symptoms do indeed sound ischemic and that these symptoms are likely to be alleviated by the combination of a ‘stent for life’ and DAPT. The latter will undoubtedly increase bleeding risk for 1, 6, 12 months or indeed 3 years depending on the chosen duration. As clinicians, it is essential to thoroughly assess bleeding risk in every case and if the risk is unacceptably high, PCI may need to be reconsidered.

It may be difficult to resist the temptation of stent implantation especially for enthusiastic fellows in training when an apparently angiographically significant lesion is identified. PCI has become increasingly accessible, and has delivered such favorable, well-publicised outcomes, that the medical community may have forgotten the potentially devastating consequences of bleeding. It is therefore mandatory that cardiologists use every tool available such as non-invasive ischaemic assessment, fractional flow reserve, instantaneous wave-free ratio and intravascular modalities to validate the need for PCI. If bleeding risk is high, objective evidence should be sought beforehand to justify PCI.

Simply put, bleeding is bad, and clinicians are therefore obliged to be fully aware of the features that increase the risk of bleeding (21-24). Special attention must be given to the aging population as they are considered high risk and the proportion of patients over the age of 75, undergoing PCI, appears to be steadily increasing (25). This elderly population has not been definitively studied in the context of DAPT strategies, nor indeed in general (26-31). Some might say that this is ironic since elderly patients are the majority users of healthcare. This will be discussed in detail later.

There are multiple bleeding classifications such as TIMI, GUSTO, ISTH, PLATO and BARC (32-37) to name but a few. The variance in these classifications, highlighted in Table 1, makes it virtually impossible for clinicians to compare studies. Such is the lack of agreement between classifications that in one study it is possible to classify the same type of bleeding for an individual as either major or minor, depending on which classification is used. Therefore, it is extremely difficult to implement any approach to avoid or reduce rates of bleeding without agreed criteria. Ideally all future research should agree on a single bleeding classification(s) at the study design phase to bring consistency to this ever-puzzling area.

**Predicting who is more likely to bleed**

This is again a “Catch-22”, as those at risk of bleeding are also at risk of MACE. Table 2 illustrates the shared features that we see in many patients. How should clinicians decide which guideline to follow or what to do for patients who have equally high bleeding and ischemic risk, such as the
<table>
<thead>
<tr>
<th>No.</th>
<th>BARC</th>
<th>TIMI</th>
<th>GUSTO</th>
<th>ISTH</th>
<th>PLATO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No bleeding</td>
<td>Minimal</td>
<td>Mild</td>
<td>Non-clinically bleeding not requiring intervention/admission</td>
<td>Minimal</td>
</tr>
<tr>
<td>1</td>
<td>Bleeding is not actionable</td>
<td></td>
<td></td>
<td>Bleeding not requiring intervention</td>
<td>Bleeding not requiring intervention</td>
</tr>
<tr>
<td>2</td>
<td>Any overt, actionable bleed</td>
<td>Minor</td>
<td>Moderate</td>
<td>Overt bleeding that does not meet the criteria for major bleeding, does do require a response in at least one of the following: a hospital admission for bleeding; a physician guided medical or surgical treatment for bleeding; a change in antithrombotic therapy (including interruption or discontinuation of study drug)</td>
<td>Minor</td>
</tr>
<tr>
<td>3a</td>
<td>Overt bleeding plus hemoglobin drop 3 to ≤5 g/dL and any transfusion with overt bleeding</td>
<td>Major</td>
<td>Severe or life-threatening hemorrhage or bleeding that causes hemodynamic compromise and requires intervention</td>
<td>Major</td>
<td>Major</td>
</tr>
<tr>
<td>3b</td>
<td>Overt bleeding plus hemoglobin drop ≥5 g/dL; includes cardiac tamponade and bleeding requiring surgical intervention or vasoactive agents</td>
<td>Major</td>
<td></td>
<td>Any of the following: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells</td>
<td>Any of the following: significantly disabling hemoglobin drop of 3 to 5 g/dL; requiring transfusion of 2 to 3 units of whole blood or red cells</td>
</tr>
<tr>
<td>3c</td>
<td>Intracranial or intraocular bleed compromising vision</td>
<td>Major</td>
<td></td>
<td>Life-threatening</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CABG-related bleeding: perioperative intracranial bleeding within 48 h; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of ≥5 U whole blood or packed red blood cells within 48 h; chest tube output ≥2 L within 24 h</td>
<td>Major</td>
<td></td>
<td>Any of the following: fatal; intracranial; intrapericardial with cardiac tamponade; resulting in shock requiring vasopressors or surgery; hemoglobin drop of ≥5 g/dL; requiring transfusion of ≥4 units of whole blood or red cells</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Fatal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
elderly diabetic with renal dysfunction? This is certainly not a rare case in current clinical practice.

Risk prediction calculators, such as the PRECISE-DAPT or PARIS risk scores (45) may be useful for clinicians to predict bleeding post PCI. Ideally a risk prediction score would not only aid clinicians to identify high-risk patients, but should also help to determine the DAPT regime and duration. There is a paucity of prospective data evaluating the clinical utility of these scores (46). Recent data, however, suggests that these scores have moderate predicative power at best, with the PARIS score out-performing the PRECISE-DAPT score (47). While there appears to be promise from the PARIS risk score more work is needed to find better risk prediction models.

In the ACS population, early bleeding may be reduced by minimizing the duration of low molecular weight heparin (LMWH). Providing more expedient access to PCI following NSTEMI may reduce the exposure to LMWH thereby decreasing rates of early bleeding. The use of glycoprotein IIB/III A inhibitors (GPI) has fallen in certain parts (48). One might speculate that GPI usage is less relevant now with the advent of Prasugrel and Ticagrelor and that avoidance of GPI may be associated with lower risk of bleeding.

In the elective population it appears that the bleeding rates are lower compared to the ACS population particularly in the first 30 days (48). Previous data shows that pre-treatment of elective patients with DAPT reduces MACE, however the duration of pre-treatment is short in most studies being significantly less than 30 days (49-51). Anecdotally, DAPT does tend in cases to unmask occult malignancies and this may be an unexpected benefit for the patient if it leads to early detection and rapid, effective treatment of a malignancy. One might speculate that a longer duration of pre-treatment with DAPT may not only be efficacious, but may unmask the potential for patients to bleed; even those not perceived to be high-risk, thus avoiding PCI and exposure to DAPT. In summary, identifying the time at which most bleeding occurs may help to implement strategies that will reduce bleeding risk. Once a stent is deployed in a coronary artery, clinicians are committed to a course of antiplatelet therapy and this may be too late.

In both the elective and ACS population chronic kidney disease is an area of particular interest as these patients are also at a higher risk of both ischemic and bleeding events, although the data is conflicting as recent studies suggest it has less of an impact than previously reported (52,53). Post-hoc analysis of PLATO suggests that Ticagrelor may be more effective than Clopidogrel in patients with ACS and concomitant renal dysfunction (54).

### The timing of bleeding—when does bleeding occur?

Virtually every study that has examined rates of bleeding has used a wide variety of pre-determined time-points at which bleeding is reported. Studies have evaluated bleeding events at 30 days, 3 months, 6 months, 1 year, and indeed 3 years depending on the study (4,6,30,55,56). Similar to the issue mentioned above about bleeding classification, the visible lack of standardization of time-points across such studies again makes it challenging to compare studies. It is however important to review, where possible, when bleeding actually occurs.

A recent systematic review, of over half a million participants post-PCI, found that major bleeding increased
overall mortality by 3-fold, whilst also increasing the risk of MACE by a similar degree (12). This same review looked at a very large number of patients mainly drawn from a registry of 280,390 participants (24). One potential criticism of this review is that the follow-up period for over half of these patients was less than 30 days, which is surprisingly short. However, this did highlight that many events and indeed fatal events occur in the first 30 days following PCI, with an adjusted risk of mortality odds ratio of 2.91 (95% CI, 2.77–3.05) if major bleeding occurs (24). Similarly several randomized trials also report that the vast majority of bleeding occurs in the first 30 days, with rates of major bleeding as high as 8% by 30 days in patients with ACS (5,57-60). While the rate of bleeding beyond 30 days increased to 12%, the rate of increase was much less marked (6). Landmark analysis of more recent data from PLATO shows that almost half of all major bleeds occurred within the first 30 days, with both Ticagrelor and Clopidogrel having high early major bleeding rates (13,61). Given that a very significant amount of bleeding occurs in the first 30 days following PCI and that the shortest possible duration of antiplatelet therapy post PCI is 1 month, it may be impossible to significantly impact on bleeding in the first 30 days. Maybe the site of the bleed is more important to focus on as bleeding risk is modifiable depending on the site.

**What sites do patients bleed from?**

While there is a lack of standardization amongst the multitude of bleeding classifications each one does agree that intracranial haemorrhage (ICH) is life-threatening, with an incidence ranging from 0.1% to 0.34% with DAPT (4–6). The rest of the bleeding that occurs seems to be split between gastrointestinal (GI) and non-GI bleeding; the latter split between epistaxis, genitourinary bleeding, vascular access, and indeterminate. It is generally accepted that, while it is devastating, ICH is relatively uncommon and virtually impossible to predict. Reducing the risk of ICH remains a challenge aside from identifying those with previous history of ICH and carefully assessing need for PCI and therefore DAPT.

In contrast, bleeding that arises from vascular access is clearly modifiable (62-67). Historically, vascular access site has been a major driver of bleeding in many studies, although this influence has decreased for several reasons. Measures such as reduction in the sheath size, use of slender technologies, greater attention to the femoral puncture site has been a major driver of bleeding in many studies, although this influence has decreased for several reasons. Measures such as reduction in the sheath size, use of slender technologies, greater attention to the femoral puncture

**Antiplatelet therapy in the elderly population—a double edged sword?**

Undoubtedly, the most challenging population to treat are the elderly given their co-morbidities and frailty. GI bleeding in under 75 years old patients is remarkable, but in the over the 75 years old population who have undergone PCI, it is even more notable, rising to 53.8% (73). Strikingly, major GI bleeds, in patients over 75 years on DAPT are frequently fatal or disabling [based on the modified Rankin score (74)] (73). Recent work shows that the numbers needed to treat with a proton pump inhibitor to prevent one major upper GI bleed at 1 year mortality (95% CI, 3.07–5.15, P<0.0001) (72). The issue of GI bleeding becomes even more striking in the elderly discussed below.
together in older patients (75-79) further increasing bleeding risk. With increasing life expectancy and improvements in healthcare, older patients represent a growing population among those who undergo PCI (25).

**Lack of evidence for DAPT in the elderly**

While improvement in stent technology and optimal antithrombotic therapies have further improved clinical outcomes, the management of DAPT in advanced age remains challenging. This is primarily due to the scarcity of evidence to guide clinical decisions. Although over 75 years old patients represent one-third of patients admitted with MI, and two-thirds of all patients that die from MI (80), they are significantly under-represented in ACS trials (81).

Moreover, extrapolating findings from current randomized trials to this elderly population is extremely challenging, as they have the most undesirable trait of having an increased risk of both ischemia and bleeding. This is due to different pharmacokinetics and pharmacodynamics as compared with younger patients (25). Other contributing factors include the presence of multiple comorbidities, frailty, concomitant use of anticoagulation and non-steroidal anti-inflammatory drugs (NSAIDs), age-related reduction in renal and hepatic function, reduced mobility, poly-pharmacy, and higher peri-procedural bleeding complications (82,83). In the Oxford Vascular Study (84), almost 50% of patients who bled were aged >75 years, with advancing age associated with increased risk of fatal bleeding [hazard ratio (HR) 5.53; 95% CI, 2.65–11.54, P<0.0001], major bleeding (HR 3.10; 95% CI, 2.27–4.24, P<0.0001), and major upper GI bleeding (HR 4.13; 95% CI, 2.60–6.57, P<0.0001). As mentioned, bleeding events have important prognostic implications and, in many cases, lead to death (85).

Bleeding complications are usually perceived to be higher in these fragile patients, which may lead to sub-optimal treatment, with a reduced threshold by clinicians to prematurely discontinue DAPT even in the case of minor bleeding. Furthermore elderly patients are less likely to receive drug eluting stents due to concerns about prolonged DAPT (10,86-88). The complex, calcified lesions in elderly patients are technically more challenging to treat with PCI, and have a higher peri-procedural complication rate (89). In addition, advanced age is independently associated with a reduced effectiveness of adenosine diphosphate (ADP) antagonists and a higher rate of high residual on-treatment platelet reactivity in patients receiving DAPT (90).

**Do antiplatelets work in an elderly population?**

In CURE (4), the combination of Aspirin and Clopidogrel for 12 months reduced the composite endpoints of cardiovascular death, MI, or stroke as compared to Aspirin alone [relative risk (RR) 0.80; 95% CI, 0.72–0.90, P<0.001] but in the over 65 population major bleeding was increased (RR 1.38; 95% CI, 1.13–1.60, P<0.001). In the PLATO trial, 18,624 ACS patients received either Ticagrelor or Clopidogrel with Aspirin for up to 12 months. Overall, the ischemic events and total mortality were lower with Ticagrelor (6). This was consistent among older patients, with numerically greater absolute mortality reduction in patients aged ≥75 years. There was no significant increase in major bleeding rates in the older subgroup. The PLATO study did not find a significant difference in age-matched cohorts (6), however the study was not powered to answer this. TRITON-TIMI 38 randomized 13,608 ACS patients undergoing PCI to either Prasugrel or Clopidogrel in combination with Aspirin for a median of 14.5 months. In 1,769 (13%) patients aged ≥75 years, there was 6% RR reduction in MACE at a cost of increased non-CABG related TIMI major bleeding with Prasugrel (HR 1.32; 95% CI, 1.03–1.6, P<0.03) especially in patients ≥75 years. Patients ≥75 years had no net benefit (death, MI, stroke, or non-CABG-related TIMI major bleeding; HR 0.99; 95% CI, 0.81–1.21) (5). Data like this highlights the need for further work in elderly patients.

Recent guidelines recommend Clopidogrel on top of Aspirin for up to 1 year after elective PCI in the elderly (91). They also recommend that Clopidogrel, should be considered if bleeding risk is high in patients with ACS, though Ticagrelor is still recommended in most elderly ACS patients. In light of the above data, the European Society of Cardiology (ESC) suggests that the use of Prasugrel is cautioned in patients ≥75 years and is contraindicated for those with prior stroke/TIA.

The CRUSADE Registry looked at the rates of bleeding, MACE and all-cause mortality at 1, 12 and 30 months in patients post NSTEMI who underwent PCI and found a significant rise in MACE in patients ≥65 years (22). A recent subgroup analysis of a multicentre, prospective registry of PCI patients highlighted that the risk of the combined bleeding and MACE at 30 days in patients ≥80 years of age was significantly higher if the patients were taking Ticagrelor and Aspirin, compared to Clopidogrel and Aspirin (12.9% vs. 7.2%; P=0.02) (92,93). Clearly, the optimal regime for the elderly remains unknown.


DAPT duration and stent choice in the elderly

The recent After Eighty RCT looked at treatment strategy in the elderly, comparing PCI with optimum medical therapy (OMT) vs. OMT alone in ACS patients ≥ 80 years old. It found a significant reduction in the composite end-point of all-cause mortality and MACE in patients undergoing PCI. However, After Eighty was limited by the small number of patients they were able to recruit (n=457).

The LEADERS-FREE trial, which compared the use of BioFreedom DES vs. bare metal stent (BMS) in high-risk patients (mean age of 75.7), found a significant reduction in MACE with BioFreedom and only 1 month of DAPT (26). The SENIOR study, which compared the use of a SYNERGY DES vs. a BMS and shortened DAPT regimens, in 1,200 patients aged over 75 years, found a significant reduction in MACE at 1 year in those treated with a DES (RR 0.71; 95% CI, 0.52–0.94, P=0.02), with no difference in bleeding (27). SENIOR had BARC 3–5 bleeding rates of 3.3% at 1 year, which is much lower than the 13.7% seen in LEADERS-FREE (26). This may be because LEADERS-FREE had a higher rate of anticoagulation, lower rate of transradial access and deliberately targeted a high bleeding risk population. In SENIOR, patients were also treated with shortened lengths of DAPT; 1 month for stable presentations and 6 months for ACS, with the authors concluding that a shortened regimen, along with a DES, was an attractive strategy for elderly patients (27).

A meta-analysis has looked at the impact of age in RCTs where they compared 3–6 months DAPT vs. 12-month DAPT after PCI with DES implantation (30). It concluded that shorter DAPT was non-inferior for ischemic composite endpoints of MI, ST, or stroke in elderly patients, but was safer than 12-month DAPT due to reduced bleeding. As highlighted, almost all patients received Clopidogrel, limiting the generalization of these findings to Ticagrelor or Prasugrel, and most used Zotarolimus- and Everolimus-DES (94). These results may not be applicable to high-risk bleeding or high-risk ACS populations.

The above seems to suggest that that Biofreedom or Synergy may be useful to facilitate shorter DAPT in the elderly.

Thrombocytopenia

A low platelet count defined as <150x10⁹/L is more commonly seen in patients undergoing ACS with figures as high as 5% and higher in the elderly (95). Thrombocytopenia was excluded in most of the major studies (5,6). It does appear that the approach to these patients undergoing PCI is inconsistent and poorly understood due to a lack of guidance. There is a belief that low platelets and DAPT means increased risk of bleeding, but this is not always the case as it depends on severity.

Depending on the etiology of the thrombocytopenia, platelet populations may co-exist which may be pro-thrombotic to compensate for decreased numbers as evidenced by the presence of immature platelets known as reticulo-platelets. The presence of these types of platelets may be underappreciated and so thrombocytopenic patients may indeed be undertreated. Looking to platelet function testing may again be ineffective, as the commercially available tests appear to have little application in the presence of low platelet counts. This is an area that requires exploration.

Platelet function testing to guide DAPT—the promise unrealised

Clinicians hoped that by using platelet function tests, they might be able to personalise DAPT for an individual to prevent thrombotic events, however this approach disappointingly failed (95-100). In 2009, Cuisset et al. (101) suggested that platelet function testing could also be used to identify patients at higher risk of bleeding by identifying hyper-responsiveness to the effects of Clopidogrel. Unfortunately, the findings of ANTARCTIC have further stifled the approach to personalize antiplatelet therapy (102). The only guidance as to how best to manage high bleeding risk comes largely from consensus of opinion (103,104). While this is helpful it is arguably not ideal when considering the complexity and significance of this particular clinical decision.

The adverse effects of thrombosis in relation to DAPT has long been recognized, but there is a growing body of literature to say that bleeding has a very significant impact on a patient’s morbidity and mortality (12-14). It is, therefore, crucial for us to re-examine the issue of bleeding in certain clinical scenarios in light of the expanding literature and to examine whether it is possible to reduce bleeding risk where possible.

Bleeding avoidance strategies

Figure 1 represents the bleeding avoidance strategies we would recommend. Recent trials of newer stents, such
as LEADERS-FREE and SENIOR, provide promising evidence for the use of biodegradable polymers with shorter DAPT duration, in high risk individuals (26,27). Concerns still exist for bleeding from intracranial, genitourinary and indeterminate sites. RCTs into antiplatelet continuation vs. interruption in bleeding patients are critically needed but may be impossible to conduct.

**Guidance on active bleeding and DAPT interruption**

Patients who bleed on DAPT are possibly the most uncertain group of all. There are guidelines and statements in relation to this (103-105), however, there is a paucity of randomized data or otherwise to support any recommendations. This is of major concern when one considers the potentially devastating outcomes from interruption of DAPT.

The recent ESC guidelines and consensus group document recognize the difficulty in balancing ischaemic and bleeding risk, thus a flow chart is provided making recommendations to clinicians which vary depending on the severity of bleeding (103,104). Trials are notably lacking in terms of continuation vs. interruption, duration of interruption, and choice of single antiplatelet agent to use following a bleed. A Cochrane systematic review is currently underway for non-cardiac surgery patients (106), although another meta-analysis has admitted the paucity of evidence in these patients (107). Clearly, robust evidence is required to determine the best approach, ideally with the creation of a better scoring calculator to help physicians in their decision-making.

**Antiplatelet therapy and concurrent anticoagulation**

Almost 10% of patients undergoing PCI have an indication for oral anticoagulation, most commonly AF (108-110). There is a 2- to 3-fold increase in bleeding rate with the addition of DAPT to an anticoagulant, referred to as triple therapy (TT) (111), yet this is the current gold standard in the European and American guidelines (47,103). Patients on TT have a 5% to 15% rate of major bleeding at 1 year, and major bleeding is associated with a 2- to 8-fold rise in the risk of death and MACE (23). AF rates are expected to increase with the epidemic of aging, because in those aged 75–84, the prevalence of AF is as high as 12%, while in those aged over 85 it is as high as 33% (8,112). The Framingham heart study found a lifetime risk of AF in those aged 70 of 23–24.3%, and that MI was an independent risk factor (113). Decisions in this area are difficult balancing acts, weighing up the risks of thrombosis with those of bleeding (114). We must note the different pathogenic processes of coronary/ST compared with thromboembolism formation in AF, though recognizing the shared influence of thrombin (115,116).

This is an evolving area of research given the emergence of direct oral anticoagulants (DOACs), previously referred to as novel oral anticoagulants (NOACs) for non-valvular atrial fibrillation (NVAF), beginning with the WOEST trial from 2013 (117), continuing with the recently published PIONEER AF-PCI and RE-DUAL PCI papers (118,119), and awaiting the AUGUSTUS and ENTRUST-AF PCI trials (NCT02415400, NCT02866175).

Given the myriad of trials, and the heterogeneity of their definitions, criteria and regimens, it is again challenging to draw comparisons to enable us to best treat our patients. However, comparisons must be drawn; in particular in how the trials defined bleeding, what proportion of PPIs were used, and the different drug regimens used. Each trial uses bleeding as its primary endpoint, and MACE as a secondary endpoint. It is worth summarizing the data to date.

The WOEST trial was a Prospective Randomized, Open-label, Blinded Endpoint (PROBE) study of 573 patients who were randomized to TT with Warfarin, Aspirin and Clopidogrel compared to double therapy (DT) with Warfarin and Clopidogrel. The TT group had significantly more bleeding than the DT group, without a rise in MACE in the latter (117). Importantly, this study included metallic heart valves, unlike all others. A landmark analysis of bleeding in the TT group showed that 26.1%
of patients bled within the first 30 days, while MACE, including all-cause mortality, occurred in 4.2% during that time. This showed that over half of those that bled on TT did so in the first 30 days. Meta-analysis has also reinforced the efficacy and safety of DT (120).

It is therefore noteworthy that the current ESC guidelines suggest that TT should be prescribed in the first month after PCI in the face of significant 30-day bleeding rates using the TT strategy. Surely there is merit in initially prescribing TT with the view to stopping Aspirin as soon as the patient’s international normalised ratio (INR) is therapeutic. This is likely to further reduce the exposure to TT in these patients.

PIONEER AF-PCI was a larger PROBE trial of 2,124 participants with three arms consisting of (I) Rivaroxaban and a P2Y12 inhibitor, (II) low-dose, twice daily Rivaroxaban with DAPT and (III) TT with Warfarin. It reported a lower bleeding rate in both Rivaroxaban arms over TT, without a rise in MACE (118).

The RE-DUAL PCI trial was another PROBE study of 2,725 patients with three regimens consisting of (I) low- or high-dose Dabigatran with a P2Y12 inhibitor, and (II) TT using Warfarin. Again, it found a lower incidence of bleeding in the Dabigatran arms, with no rise in MACE. Of note, it had a higher rate of PPI usage than other trials (60.2% vs. 36.5–38.1%) (119).

Twelve months of TT has consistently been shown to significantly increase bleeding rate without an improvement in mortality or MACE. However, the dual therapy DOAC regimens using Rivaroxaban and Dabigatran are arguably unfair in that they were compared to TT, when DT using Warfarin and a P2Y12 inhibitor is clearly safer. The latest ESC antiplatelet guidelines also do not advise longer than 6 months of TT (103), though a year of TT was used in some patients in PIONEER AF-PCI. The PIONEER AF-PCI trial is comparing Rivaroxaban to a TT regimen that is no longer used in clinical practice, and it also reflected the WOEST finding of a higher bleeding rate in the first 30 days in patients receiving Warfarin plus DAPT. Furthermore, it found a significant rise in stroke events in those prescribed low-dose Rivaroxaban and DAPT at 6 months (P=0.02), and there were multiple subgroups within the Rivaroxaban arms depending on the length of DAPT (118). As such, its application to real-world practice appears limited.

Additionally, RE-DUAL PCI suffers from significant limitations, most importantly that it used Warfarin TT. The original RE-LY trial, which was powered for MACE, also showed a significant rise in MIs in patients taking 150 mg Dabigatran vs. those on Warfarin alone (0.74% vs. 0.53%; P=0.048) (119,121).

The first meta-analysis of the above three trials plus ISAR-TRIPLE, which had the goal of evaluating the optimal length of TT with Warfarin (122), was published this year. Six thousand and thirty-six patients were included, with AF being the commonest indication (95.4%). It found that DT had a significantly less major and minor bleeding, without a rise in MACE. It concluded that DT using a P2Y12 inhibitor and a DOAC, particularly in high bleeding risk cases, is the preferred treatment strategy (122). However, the newer anticoagulants do not yet have the real-world registry data as seen with Warfarin (123,124). In an effort to further reduce the bleeding it may be that Clopidogrel should be used in any DT regime in preference to Prasugrel or Ticagrelor. The AUGUSTUS and ENTRUST AF-PCI studies do involve a Warfarin and P2Y12 DT arm, which should shine some light on this area.

Table 3 provides a comparison of the published trials, while Table 4 represents what is known about those that are, currently, unpublished. It highlights the similarities and differences in these studies, allowing us to see the heterogeneity amongst the three published studies, particularly in bleeding definition, regime and PPI usage. The ISTH bleeding definition is being used in AUGUSTUS and ENTRUST AF-PCI, which may enable comparison between them and RE-DUAL PCI. AUGUSTUS is attractive given its larger size, placebo-containing arms and crossover design, allowing better comparison of the impact of Aspirin.

Given that the first 30 days is the period in which the number of bleeds is highest, how do the guidelines justify a recommendation that TT should be used routinely in these patients? Surely, if the patient were on Warfarin it would be advantageous to discontinue Aspirin as soon as the patient’s INR is therapeutic. Indeed, if the patient is already on therapeutic Warfarin, and is going to have a PCI performed through trans-radial access, then the question must be asked if there is a need for any Aspirin at all, particularly when one consider the signals coming from older anticoagulation studies, showed that rates of MI were numerically lower (121,125-127). Clinicians need to be mindful that thrombin is a powerful platelet aggregator, and that antagonism of this is extremely effective at reducing arterial thrombosis (128).

Once the AUGUSTUS and ENTRUST AF-PCI results are published, practice will need to be reviewed once again.
However, they will not answer all questions, particularly for those with indications for anticoagulation other than NVAF, such as mechanical valve replacements, chronic thromboembolic disease and AF with mitral stenosis. There are at least five trials involving DOACs and either trans-aortic valve replacements or biological prosthesis (NCT03284827, NCT03183843, NCT02833948, NCT02664649 and NCT02247128). To our knowledge there are no studies exploring combinations in patients with metallic valves, and clearly research is needed but this will be more challenging. In addition, the WOEST 2 Registry data (NCT02635230) is a prospective, multi-centre cohort study intending to provide data on 2,200 patients requiring anticoagulation and coronary revascularization.

Assessment of the patient’s ischemic and bleeding risks is recommended along with early discontinuation of Aspirin once the INR is therapeutic (i.e., 2–3 for NVAF) to avoid any prolonged duration TT. Achieving a therapeutic INR should be done using a slow induction protocol to avoid high INRs (70). Recommendations to tightly control the INR between 2.0–2.5 are notoriously difficult to achieve in the real-world setting most likely requiring more frequent monitoring. One must bear in mind that the time within the therapeutic range (TTR), i.e., an INR of between 2.0 and 3.0 was only achieved in approximately 60% of the cases for the DOAC studies (121,125-127), making it improbable to

Table 3 Summary of published OAC/PCI trials (117-119)

<table>
<thead>
<tr>
<th>Study</th>
<th>WOEST</th>
<th>PIONEER AF-PCI</th>
<th>RE-DUAL PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>573</td>
<td>2,124</td>
<td>2,725</td>
</tr>
<tr>
<td>Age (mean), years old</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Sex</td>
<td>70% male</td>
<td>75% male</td>
<td>76% male</td>
</tr>
<tr>
<td>Dose of OAC</td>
<td>INR 2–3 (NVAF)</td>
<td>10–15 mg OD 2.5 mg BD</td>
<td>INR 2–3</td>
</tr>
<tr>
<td>Notes</td>
<td>–</td>
<td>–</td>
<td>– A for 1–3 months</td>
</tr>
<tr>
<td>PPI usage (%)</td>
<td>36.5</td>
<td>38.1</td>
<td>60.2</td>
</tr>
<tr>
<td>Bleeding definition</td>
<td>TIMI/GUSTO/BARC</td>
<td>TIMI/BRMA</td>
<td>ISTH</td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>19.4</td>
<td>44.4</td>
<td>16.8</td>
</tr>
<tr>
<td>MACE (%)</td>
<td>11.1</td>
<td>17.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Notes: A for 1–3 months

Table 4 Summary of unpublished OAC/PCI trials

<table>
<thead>
<tr>
<th>Study</th>
<th>AUGUSTUS</th>
<th>ENTRUST AF-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Number</td>
<td>4,600</td>
<td>1,500</td>
</tr>
<tr>
<td>Dose of OAC</td>
<td>2.5–5 mg BD</td>
<td>INR 2–3</td>
</tr>
<tr>
<td>Notes</td>
<td>P for 6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Bleeding definition</td>
<td>ISTH</td>
<td>ISTH</td>
</tr>
</tbody>
</table>

Notes: P for 6 months
achieve an even more narrow therapeutic window of 2.0–2.5. One year after PCI the patient should remain on lifelong Warfarin which can be switched to DOAC if good Warfarin control of >65% in the TTR cannot be achieved.

If antiplatelet therapy in combination with Warfarin was not suitable, currently available evidence would favor the use of Dabigatran 110 mg BD with Clopidogrel alone in the NVAF patients, although a subsequent meta-analysis did suggest that the higher dose (Dabigatran 150 mg BD) should be given in light of the non-significant trend toward ST in the low dose group (122). The significant rise in MIs in the 150 mg Dabigatran cohort in the original RE-LY trial, which was powered for MACE is notable and difficult to explain fully (121). Nevertheless concomitant PPI therapy seems very reasonable with any combined antiplatelet and anticoagulation regime.

Conclusions

The risk vs. benefit exercise still troubles clinicians and it is becoming even more challenging with an increasingly complex, older patient. While bleeding was once seen as a minor reversible problem, we now know that it carries significant mortality and morbidity. Efforts to reduce bleeding risk, such as transradial access, PPI usage, and optimal stent/medication strategies must be used, along with reacting appropriately to those who do bleed. Our increasingly elderly, frail and complex population are, paradoxically, not a group at all, but individuals who require a personalised approach to manage their risk to achieve best outcomes. They are less well studied than other cohorts, though this is a recognized issue and hopefully, will become clearer soon. Concurrent anticoagulation with DAPT provides the greatest risk for bleeding, and with the introduction of DOACs it has become more difficult for the clinician to select the best option. Hopefully the days of extended TT are numbered as this is clearly an undesirable strategy. Further work in all these areas is desperately needed if we are to make informed decisions with our patients for their benefit.

Acknowledgements

None.

Footnote

Conflicts of Interest: A Peace has received honoraria from Bayer, Pfizer, BMS, Astra-Zeneca, Boehringer, Elli Lily, Medtronic, Boston Scientic, Biosensors, Abbott, St Jude. The other authors have no conflicts of interest to declare.

References

9. Webster E, Gil M. Advances in anticoagulation therapy. JAAPA 2018;31:30-5.


Cite this article as: Esmonde S, Sharma D, Peace A. Antiplatelet agents in uncertain clinical scenarios—a bleeding nightmare. Cardiovasc Diagn Ther 2018;8(5):647-662. doi: 10.21037/cdt.2018.06.09