Drug coated balloons or drug eluting stents: determining an optimum strategy for the high bleeding risk patients

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Abstract

The management of patients who require percutaneous coronary intervention and are at high risk of bleeding continues to be challenging; balancing thrombotic versus bleeding risk to determine the safest duration of dual antiplatelet (DAPT).

With recent efforts to determine safety in one-month duration of dual antiplatelet therapy after implantation of a drug eluting stent (DES), alternative strategies such as drug coated balloons (DCB) have also been explored as both have been shown superior to bare metal stent (BMS) which has historically been used for high bleeding risk patients.

We sought to review the literature surrounding safety profile and bleeding events with both DCB and DES and conclude whilst DCB and DES offer safety of cessation of DAPT after one-month, DCBs offer lower MACE events after one-month duration of DAPT.

Background

Coronary artery disease is the leading cause of morbidity and mortality globally [1]. Dual antiplatelet therapy (DAPT) in the form of aspirin and a $P2Y_{12}$ inhibitor is the mainstay of pharmacotherapeutic treatment for an acute coronary syndrome (ACS) and prevention of stent thrombosis after PCI for ACS or stable coronary disease. DAPT with ticlopidine plus aspirin was first shown to be superior to anticoagulation and aspirin for patients undergoing percutaneous coronary intervention (PCI) in 1996 [2]. Subsequently, DAPT (clopidogrel plus aspirin) has been shown to be superior to aspirin alone with a relative risk reduction of 26.9% of major adverse cardiovascular outcomes (MACE) [3]. DAPT has since become one of the most extensively investigated treatment strategies in cardiology with over 35 RCTs and 225,000 patients and is increasingly important given the volume of patients requiring DAPT. In 2015 European based population estimates suggested that 1.4-2.2 million patients require DAPT per year [1].

The duration of DAPT has evolved with the introduction of second and now third generation drug eluting stents. The first-generation drug eluting stents raised the concern of very late stent thrombosis after one year[4] with evidence supporting a prolonged duration of DAPT preventing subsequent spontaneous myocardial infarction (MI) [5] and led to RCTs investigating prolonged duration of DAPT. The trade-off of reducing ischaemic sequelae is always balanced with the risk of bleeding with evidence supporting a significant increase in bleeding events with greater than twelve months of DAPT with minimal reduction in MACE results, with 2.5% v 1.6% major bleeding ($p<0.001$).[6]

Identifying bleeding risk/ risk stratification

Given the aging population with increasingly complex co-morbidities that we are seeing, the risk of bleeding is greater. This has led to the introduction of bleeding risk stratification scoring systems both for clinical and research purposes. Both the DAPT [7] and PARIS [8] risk stratification scores were introduced based on prediction of events during the index admission or shortly after. Neither of these looked at the duration of DAPT in relation to bleeding risk. The most comprehensive scoring system to date is the PRECISE-DAPT scoring system and is recommended in the European Society of Cardiology (ESC) guidelines as a IIb A recommendation for use [1]. The PRECISE-DAPT study showed that if patients considered at a high risk of bleeding were given a prolonged (> 12 months) duration of DAPT, there was no ischaemic benefit but a significantly higher bleeding risk with a number needed to harm (NNH) of 38 [9].

Guidelines

DAPT guidelines are different for ACS as opposed to PCI in stable coronary disease. Regardless of bleeding risk, DAPT is recommended for 12 months for all patients after an ACS [1].

However, for patients undergoing PCI for stable coronary disease, the evidence is less cohesive. This becomes relevant for two reasons:

- As a stable group, there is time to plan the intervention strategy, assess bleeding risk and determine an appropriate approach to an individual patient
- There is less clear-cut evidence on the duration of DAPT for this cohort

The current ESC guidelines for stable coronary disease and DAPT (shown in Figure 1) advise that for stable coronary disease treated with DES/BMS or DCB, for patients not at a high risk of bleeding, a 6-month duration of DAPT comes with a Class I A recommendation with a class IIb A recommendation to continue DAPT for a further 6 months (DAPT consisting of aspirin and clopidogrel). For patients at a high risk of bleeding treated with DES/ BMS or DCB, a one-month duration of DAPT has a Class IIb C recommendation with 3-months of DAPT having a class IIa B recommendation.

Figure 1: The ESC recommendations for DAPT after PCI for stable coronary disease

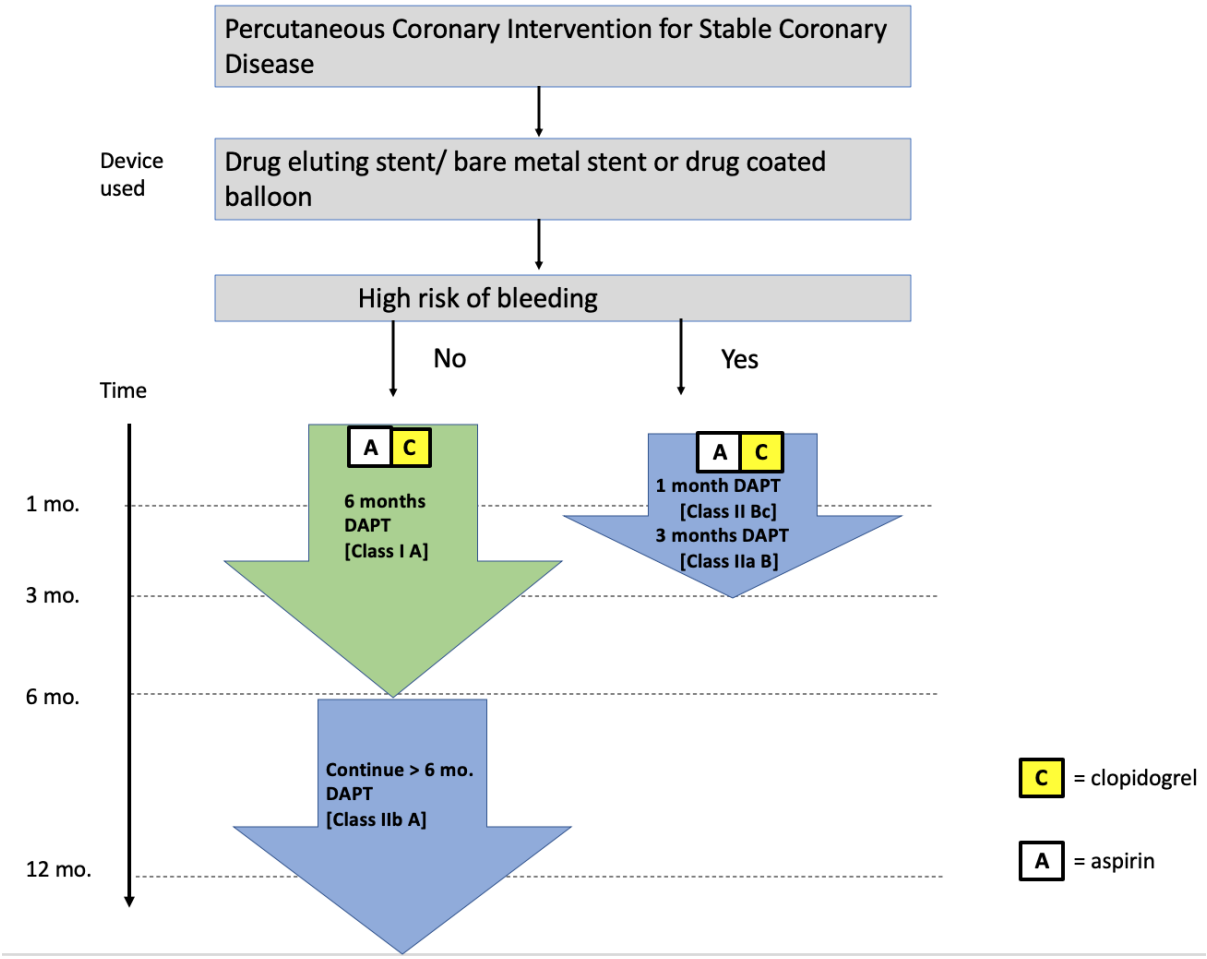


Figure 1 visualising the current ESC guideline recommendations for DAPT therapy

Despite these guidelines, routine clinical practice remains giving a 12-month duration of DAPT for patients receiving a DES for stable coronary disease unless there are significant bleeding sequelae [10].

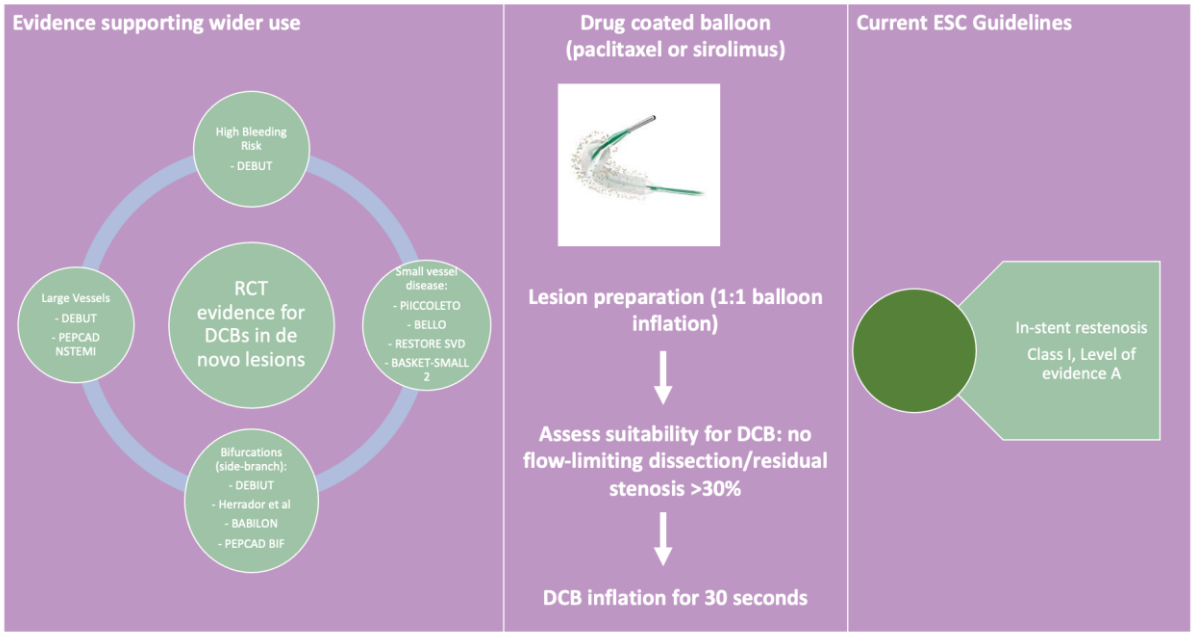
A systematic review and meta-analysis (17 studies, 46 864 patients) compared short-term (≤ 6-months but excluded those with ≤ one-month) with standard duration of DAPT (12 months) and long duration DAPT (≥12 months) for drug eluting stents. This included all patients with ACS and stable coronary disease. It showed a statistically significant increase in all-cause mortality and major bleeding in the long duration DAPT group and an increase in any bleeding in standard duration DAPT as compared to short-term duration DAPT with no statistically significant difference in major adverse cardiovascular outcomes (MACE) [11]. This indicates a safety in 6-month duration of DAPT but for those patients who may benefit from a shorter duration again, the evidence is less clear. This also did not identify whether patients were at a higher risk of bleeding.

Drug coated balloons: a practical alternative

Drug-coated balloons (DCB) are an attractive proposition for cardiology interventionalists who subscribe to the "leave nothing behind" philosophy [12]. The use of DCBs are currently recommended in ESC guidelines for small vessel disease and in-stent restenosis. However, over the past two years, the evidence supporting the role of DCBs in wider circumstances has increased [13–16].

One significant benefit of a DCB strategy is the proposed shorter duration of DAPT required. Previous consensus groups have all recommended a one-month duration of DAPT for stable coronary disease [17–19]. This recommendation was changed by the 2017 ESC Focused DAPT Update, which recommended a 6-month duration of DAPT after DCB angioplasty [1]. In response to this, we interrogated our registry database of a large, real world population. We reported 303 patients treated with one-month DAPT after elective DCB angioplasty, with no occurrence of major adverse cardiovascular events (MACE) at six-months and found that one-month duration of DAPT appears safe after DCB angioplasty for stable coronary disease[20].

Figure 2: A visual representation of the role of DCBs, their indication for use and evidence supporting their use in de novo coronary disease.



Having established the safety of one-month duration after DCB angioplasty in stable coronary disease, we sought to review the evidence for shorter duration DAPT in terms of

bleeding rates, clinical outcomes and safety profiles for both DCB and DES. Table 1 provides a summary of all papers included in the review.

Table 1: Summary of all randomised controlled trials included in discussion

Study name	Experimental arm	Control arm	Study population	Primary outcome
DES:				
LEADERS-FREE [21]	2nd generation DES	BMS	n=2466 ACS & stable coronary disease (high bleeding risk)	MACE (CD, MI, ST) at 390 days
ZEUS [22]	2nd generation DES	BMS	n=1606 ACS & stable coronary disease (high bleeding risk, high thrombotic risk or low restenosis risk)	MACE (all-cause mortality, MI, TVR) at 12 months
SENIOR [23]	2nd generation DES	BMS	n=1200 >75 ACS & stable angina	MACE (all-cause mortality, stroke, MI, TLR) at 12 months
ONYX-ONE [24]	Onyx Zotorolimus eluting stent	Biofreedom stent	n=2000 ACS & stable coronary disease (high bleeding risk)	MACE (CD, MI, ST) at 12 months
STOP-DAPT2 [25]	DES with one-month DAPT	DES with 12 months DAPT	n=3045 ACS & stable coronary disease	Combined cardiovascular and bleeding composite endpoint
DCB:				
DEBUT [15]	DCB	BMS	n=208 ACS & stable coronary disease (high bleeding risk)	MACE (CD, MI, TLR)
Basket-Small 2 [13]	DCB	DES	n=758 ACS & stable coronary disease (one-month DAPT only in stable group)	MACE (CD, MI, TVR) at 12 months

Where DES= drug eluting stent, BMS= bare metal stent, n=number of participants, MACE= major adverse cardiovascular outcomes, CD= cardiac death, MI= myocardial infarction, ST= stent thrombosis, TVR= target vessel revascularisation, TLR= target lesion revascularisation

DES with one-month duration of DAPT with improved safety profile

There has been recent emphasis on identifying safety in one month duration of DAPT for DES given that studies suggest at least 15% of patients undergoing PCI are at high risk of bleeding [26]. Until recently, bare metal stents (BMS) were considered an appropriate strategy for patients at a high risk of bleeding as a one-month duration was deemed safe and adequate. This was despite all of the evidence showing superiority of DES compared to BMS, particularly in terms of target lesion revascularisation [27]. In addition, there had been no safety/ efficacy data supporting the use of DES for one-month only. As such, significant advancements have been made in stent technology in improving safety profile for a shorter duration of DAPT. This includes newer generation DES, bioresorbable polymer and faster re-endothelization combined with thinner struts which all influence rates of stent thrombosis [28]. Subsequently, the LEADERS-FREE, ZEUS and SENIOR trials all changed perspective on this as showing that DES was superior in terms of safety and efficacy over BMS with one-month duration of DAPT [22,23,29]. LEADERS-FREE randomised 2466 patients, including those with ACS and stable coronary disease, to either second generation DES or BMS with one-month duration of DAPT. A primary safety end point of cardiac death, MI or stent thrombosis showed DES to be superior to BMS (9.4% v 12.9%, HR: 0.71(0.56-0.91), p=0.005). There was no statistical significance between bleeding events of BARC 3-5 (7.2v7.3%, p=0.96). [29]
The ZEUS study compared second generation DES with BMS in a more heterogeneous population- those at high bleeding risk, high thrombotic risk or low restenosis risk. A subgroup analysis of patients at a high bleeding risk (828) favoured DES over BMS with a primary composite outcome of death, MI or TVR (HR: 0.74 (0.57-0.97)). [22]

The SENIOR trial randomised 1200 patients over the age of 75 to either DES or BMS and gave a one-month duration of DAPT for stable angina and six months for ACS. Although

these patients were not specifically at high risk of bleeding, their age does contribute to bleeding risk. The primary endpoint was a composite of all-cause mortality, MI, stroke or ischaemia driven TLR and results favoured DES (12% v 16%, RR: 0.71 (CI: 0.52-0.94), p=0.02). Bleeding complications occurred in 5% of both arms. [23]

These three studies have shown superiority of DES over BMS in patients at high risk of bleeding who would benefit from a shorter duration of DAPT. Having identified that DES is superior to BMS in this situation, further studies have sought to evaluate safety of one-month duration of DAPT compared to a longer duration.

The more recent ONYX One trial comparing the Onyx Zotorolimus eluting stent with the biofreedom stent showed non-inferiority with one-month duration of DAPT, although, event rates were notably high with primary composite safety end point (cardiac death, MI, ST) at one year of 17.1% v 16.9% [30].

STOP-DAPT 2 randomised 3045 patients in Japan to either one-month or one-year DAPT after PCI (of which 38% were ACS). A primary composite endpoint of cardiovascular and bleeding events (cardiac death, MI, definite ST, ischaemic or haemorrhagic stroke or TIMI major or minor bleeding) showed superiority of one-month DAPT (2.36% v 3.7%, HR:0.64 (0.42-0.98), p=0.04) [25]. Of note, the majority of patients were low to intermediate risk of bleeding.

DCBs and one-month duration DAPT

Two prospective studies have been conducted reporting cardiovascular outcomes and bleeding events using DCB in one arm.

The first study, the DEBUT trial, was a randomised control trial comparing bare metal stent (BMS) with DCB in patients at high risk of bleeding. This included patients with stable coronary disease or ACS in the form of NSTEMI/ unstable angina but excluded STEMI. The occurrence of a primary outcome of MACE in stable angina was 0% in DCB v 11% (HR: 0.35, 95%CI: 0.11-1.09, p=0.069). DEBUT also reported a 13% bleeding rate at 9-months in DCB patients with 11% in BMS group (p=0.59). This was in a high-risk of bleeding cohort with 58% (DCB cohort) on an oral anticoagulant and 29% (DCB cohort) anaemic with additional risk factors for bleeding including old age (>80 years old), CKD3 or more, thrombocytopenia, frailty, synthetic liver dysfunction and previous ICH or CVA [15].

The second study was the BASKET-Small 2 trial [13]. This was an RCT comparing DES with DCB for small vessel disease in patients with ACS and stable coronary disease in which 758 patients were randomised to either DCB or DES, powered to detect non-inferiority in DCB. The patients who received DCB for stable coronary disease were given a one-month duration of DAPT and those who had an ACS were given 12 months. The majority of patients included were those with stable coronary disease (70% in the DCB patients and 73% in the DES patients). Risk of bleeding criteria were not specified in the patient cohort. MACE events at 12 months were 7.3% in the DCB v 7.5% in the DES arm (0·97, 0·58–1·64; p=0·9180). Major bleeding rates were low, at 1.1 v 2.4% with a p-value of 0.46. The lower rates occurred in the DCB cohort but this was not of statistical significance [13].

Finally, our own retrospective database analysis of all patients receiving one-month duration of DAPT showing no occurrence of MACE at six months further strengthens the safety argument for the use of DCBs in those at high risk of bleeding [20].

Whilst the current ESC guidelines recommend DCB only for small vessel disease and in-stent restenosis[31], there is an increasing body of evidence supporting the use of DCBs in large vessels [32,33]. With upcoming RCTs to further investigate the use of DCBs in large vessels, their role in high bleeding risk patients is thought to increase.

Acute Coronary Syndromes and duration of DAPT

The current guidelines still recommend a 12 month duration of DAPT for all ACS patients, regardless of treatment strategy [1]. Although the purpose of this review is to focus on stable coronary disease, it is worth briefly mentioning the evidence for DCB and DES for ACS one-month DAPT. Within the DES RCTs, ACS patients made up a significant proportion of the numbers: 41% in LEADERS-FREE [21], 63% in ZEUS [22], 46% in SENIOR [23], 52% in ONYX-ONE [24] and 38% in STOP-DAPT 2 [24]. In comparison, the only data for one-month DAPT in DCB in ACS is in DEBUT, where ACS patients account for 46% of patients [15] BASKET-SMALL 2 gave a 12 month duration of DAPT to all ACS patients. Therefore, although the clinical outcomes in DEBUT are excellent for DCB, there is currently a smaller body of evidence supporting the use of one-month DAPT in ACS patients with DCB.

Discussion

When comparing the DEBUT data (DCB) with the LEADERS-FREE trial[29] (DES v BMS in high risk bleeding patients), the DEBUT bleeding rates reported are not as high as those reported

in the LEADERS-FREE trial, where bleeding events (BARC 1-5) were 18.1 v 19.1% (DES v BMS) compared to 13 v 11% in DEBUT. Although the DEBUT numbers are smaller, both studies are looking at high risk of bleeding. In comparison, the BASKET-Small 2 trial reported lower bleeding events at 4 v 9% (DCB v DES) but this patient group was not identified as being at a higher risk of bleeding, which may explain the lower bleeding rates.

Of particular interest however is the fact that although the bleeding rates were slightly lower in DEBUT compared to LEADERS-FREE, the MACE rates were significantly lower in the DEBUT trial (1% for DCB) than both the LEADERS-FREE trial (9.4%) and the Onyx One trial (17.1% for the Zotorolimus eluting stent) [24]. Of course, these MACE rates cannot be directly compared, however it certainly adds strength to the concept that DCB is a very appealing strategy for patients at high risk of bleeding. This is backed up by our registry data with 0% MACE rates at 6-months in patients who received one-month of DAPT [20].

Where the LEADERS-FREE, SENIOR and ONYX-ONE all report high MACE occurrence in the DES arm (9.4%, 12% and 17.1%), the results of the Japanese STOP-DAPT 2 were significantly lower with MACE rates at 2.36%. One hypothesis for this could be the use of intracoronary imaging to optimise stent sizing in almost all patients, which is not standard western practice.

With the exception of the STOP-DAPT 2 trial, DCB studies show a significantly lower MACE rate when compared with DES or BMS. This adds weight to the argument that DCB is an attractive proposition for patients who are at a higher risk of bleeding, particularly in the stable angina cohort where bleeding risk can be assessed pre-procedure and angioplasty strategy planned accordingly.

Limitations

Whilst all of the included DES studies have been conducted with large numbers, the sample size in DEBUT and Basket-Small 2 is smaller although both studies were adequately powered to answer their primary outcome. As the population in all of the included studies vary from those at high risk of bleeding to a heterogeneous cohort, no definitive subgroup meta-analysis can be conducted that would add any weight to the available data.

Conclusion

In conclusion, we are increasingly faced with a more complex patient cohort with higher risk of bleeding associated with DAPT. Although it is clear that a 6-month duration of DAPT can be given with adequate effects on MACE with DES, the MACE rates remain high with only one-month of DAPT in the DES RCTs. In comparison, a one-month duration of DAPT with DCB in the DEBUT study and our own series shows significantly lower MACE rates than the contemporaneous DES studies. This strengthens the viewpoint that DCB is a very attractive proposition for all patients with stable coronary disease identified as being at a high risk of bleeding.

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