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Development of a concept for a personalized approach in the perioperative antiplatelet therapy administration/discontinuation management based on multiple electrode aggregometry in patients undergoing coronary artery surgery

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Abstract

Objectives

In patients undergoing coronary artery surgery (CAS), improvements in clinical outcomes currently rely on continued refinements of the surgical technique and modulation of adjuvant pharmacotherapy. Despite medical and technological advances, negligible rate of bleeding and ischemic events still persist necessitating further improvements in patient management. Platelet function testing (PFT) might play an important role in meticulous balancing between the risk of bleeding and thrombotic events. A suitable balance can be achieved by implementing a personalized, PFT based approach in antiplatelet therapy (APT) administration/discontinuation management. Despite emerging evidence on the widespread variability in platelet inhibitory response to APT, numerous PFT devices and heterogeneity in reporting study results hamper pooling of the evidence which in turn results with a lack of consensus in "on treatment" platelet reactivity associated with ischemic and bleeding events in perioperative phase.

Methods

The literature on multiple electrode aggregometry (Multiplate® ; Roche Diagnostics, Mannheim, Germany) in coronary artery disease patients was reviewed systematically. Based on the evidence evaluating the relationship between "drug specific" PFT and bleeding or adverse ischemic events, we sought to define therapeutic window for the most commonly administered antiplatelet drugs such as aspirin (ASPI test) and adenosine-diphosphate receptor blockers (ADP test).

Results

Preoperatively, APT administration was primarily focused to avoid bleeding complications. ASPI test value of 20 AUC and ADP test value of <73 AUC were set as cut-off values that delineate bleeding tendency. Postoperatively, "therapeutic window" was set to avoid both

bleeding and adverse ischemic events. Therapeutic ranges were as follows: 20 AUC<ASPItest≤30 AUC and 19AUC<ADP≤46AUC, respectively.

Conclusion

This is the first attempt to define PFT based “therapeutic window” according to, perioperative APT administration/discontinuation management would be targeted.

It seems that the “one-size-fits-all” concept of perioperative APT administration management is outdated and further development of PFT based, personalized APT administration/discontinuation management is desirable.

This concept therefore presents a possible step forward in patient care and provides a platform for further interventional trials whereby the impact of its application on clinical outcomes would be validated.

Keywords: Aspirin resistance; Multiple electrode aggregometry; Platelet aggregation inhibitors; Coronary artery bypass surgery; platelet function ; hemorrhage

Introduction

Optimizing outcomes in patients undergoing coronary artery surgery (CAS) requires amongst others, meticulous balancing between the risks of thrombotic and bleeding events. Optimal balance between the risks of thrombotic and bleeding complications may differ extremely between individuals, and the reason for this may be in the fact that individuals platelet inhibitory response to antiplatelet therapy (APT) varies widely, from profound platelet inhibition to high degree of residual platelet reactivity. Therefore, it can be expected that occurrence of CAS related bleeding complications as well as ischemic adverse events is strongly influenced by the management of antithrombotic therapy both in the pre- and post-CAS period.

Despite medical and technological advances, hemorrhage in accordance to cardiac surgery continues to be a persistent problem. Prediction, prevention and adequate treatment of excessive bleeding in adult cardiac surgery require a comprehensive approach. It has been noted that 90% of blood products transfused in cardiac surgery are consumed by only 10% of patients being operated on[1]. It is therefore of utmost importance to identify patients who are at risk of excessive bleeding.

There are three main causes of excessive postoperative bleeding as recently described by Besser et al[1]: 1) Surgical bleeding ; 2) Coagulopathy bleeding; and 3) Bleeding due to preoperative conditions such as pre-operative undiagnosed or untreated coagulopathy, thrombocytopenia or administration of anticoagulants or APT in close proximity to surgery. Preoperative APT management is a modifiable risk factor for excessive bleeding and should therefore be subject to further improvements and modifications directed towards the minimization of bleeding complications.

Variability in platelet reactivity while on APT ranges from pronounced platelet inhibition to a high degree of residual platelet reactivity, which is often considered as

resistance to APT. Resistance to APT is an important phenomenon that certainly affects clinical outcome and as such, should strongly influence APT administration/discontinuation management. While it remains much easier to decide to proceed with surgery without drug cessation if high residual platelet reactivity exists, far less is known about the postoperative management of high residual platelet reactivity[2]. The clinical relevance of and challenges in management of APT resistance in cardiac surgery patients have already been discussed within our working group[2].

APT management affects both adverse ischemic events and bleeding events, therefore, the risk of bleeding and thrombotic events should be inextricably evaluated when deciding about APT administration/discontinuation management.

There are several point-of-care platelet function analyzers that have different measuring principles but are able to provide drug specific platelet function testing[3]. Different point-of-care platelet function analyzers available, together with a lack of standardization in designing trials and defining outcomes makes it somewhat difficult to pool the evidence. Consequently, with class IIb and level B of evidence, platelet function testing has the status "May be considered" which in the absence of stronger evidence somehow underestimates the real possibilities of this kind of technology in patient care. While much of the literature on point-of-care platelet function tests focuses on assessing their utility in guiding long term APT, these devices have an additional role in cardiac surgery as they can assess bleeding risk and transfusion requirements[4-6]. The evidence for a therapeutic window targeting optimal on-treatment platelet reactivity to prevent both bleeding and ischemic events is emerging. Nowadays, heterogeneity in study settings, different devices used as well as the absence of the large scale prospective clinical trials to define a therapeutic window all create a barrier to the implementation of a personalized approach in administration of APT in routine clinical practice.

Is it however apparent that minimization of bleeding and adverse ischemic events through personalized APT administration management should be based on platelet function testing. This would provide reliable information about the achieved level of platelet inhibition while on APT. In order to optimize patient outcomes, a personalized approach is required both in pre- and in postoperative period aiming to minimize early postoperative complications as well as bleeding and ischemic complications associated with chronic APT use. Efforts to create a therapeutic window using a single platelet function analyzer that are based on the published evidence are desirable as new "cutting edge" steps in development of personalized approach. Such a therapeutic window is a very valuable concept and may be used as platform for further randomized clinical trials resulting in further refinements of such a concept.

Based upon our own clinical and research experience using multiple electrode aggregometry (MEA) (Multiplate® ; Roche Diagnostics, Mannheim, Germany) in this particular field[2-13], we sought to define pre- and post CAS therapeutic window for the most commonly administered APT such as aspirin and adenosine di-phosphate receptor blockers. Such a therapeutic window presents a concept for a personalized APT administration management based on drug-specific platelet function testing which may minimize the occurrence of intraoperative bleeding complications and transfusion requirements caused by preoperative APT, as well as occurrence of bleeding and adverse ischemic events while on chronic APT in postoperative phase.

To the best of our knowledge, this is the first definition concept for a perioperative APT therapeutic window based on point-of-care drug specific platelet function testing in patients undergoing CAS.

Preoperative considerations

Nowadays, preoperative management of APT is not standardized and varies among different centers.

Even though it is apparent that a “one-size-fits-all” strategy seems obsolete as it does not account for wide interindividual variability in platelet inhibitory response to APT, the fact is that current guidelines as well as previous guidelines typically rely on this “one size fits all” strategy.

Guidelines on antiplatelet and anticoagulation management published in 2008. recommended cessation of clopidogrel 5-7 days before surgery, if clinical condition allows[14]. The same guidelines recommend stopping aspirin 2-10 days before elective cardiac surgery while patients undergoing urgent cardiac surgery with an acute coronary syndrome should continue aspirin up to the day of surgery[14]. Despite the current guidelines, many centers continue to use APT until the day of surgery, disregarding the recommendations for a drug-free interval before surgery. For example, data from 2,858 acute coronary syndrome patients in the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse Outcomes with Early implementation of the ACC/AHA Guidelines) initiative demonstrated that 87% of CLO-treated patients underwent CAS surgery within 5 days after APT cessation[15].

Interestingly, 2011 ACCF/AHA CAS guidelines suggest preoperative administration of aspirin (100 mg to 325 mg daily) [16]. Clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days[16]. In patients referred for urgent CAS, clopidogrel and ticagrelor should be discontinued for at least 24 hours[16], therefore suggesting that it may be reasonable to perform surgery in less than 5 days after drug cessation[16].

In 2012, Update to the Society of Thoracic Surgeons Guideline on use of APT in patients having cardiac operations[17], broader discussion of point-of-care testing to monitor platelet function is provided[17]. In this updated guideline[17], the authors suggest stopping APT before the operation[17]. However, the interval between discontinuation of APT and

operation remained uncertain[17]. In the same update[17] it is suggested (Class IIb (Level B)) to use preoperative point-of-care tests to assess the bleeding risk because of their high negative predictive values expressed in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, who can undergo operation without elevated bleeding risk. However, the type of point-of-care platelet function test devices as well as cut-of values that would direct preoperative APT management were not provided.

In contrast to chronic postoperative administration of APT where attention should be paid equally to both bleeding and thrombotic complications, preoperative APT administration/discontinuation management should primarily be focused to minimize bleeding events. Preoperative APT administration/discontinuation management pertains to the short time period from establishing an indication for surgery to performing the surgical procedure. Considering the reasonably short time in between, it is rational to make the prevention of bleeding events associated with preoperative use of APT a priority. For the short term preoperative period, the risk of excessive bleeding certainly outweighs the risk of adverse ischemic events and therefore measures to prevent excessive bleeding should be the primary focus. If pronounced platelet inhibition occurs in elective cases, there should be enough time to wait until platelet recovery. Furthermore, the rate of ischemic events may even be lower if patients , with documented high residual platelet reactivity with platelet function being above the cutoff that delineate bleeding tendency, continue to receive APT up to the day of surgery. This personalized approach may therefore provide more favorable outcomes in terms of both bleeding and adverse ischemic events. According to the Society of Thoracic Surgery (STS) practice guidelines (Class I, Level of evidence B), screening for bleeding risk factors is indicated preoperatively to intervene and modify risk factors , if possible[17]. Management of APT is certainly one of the modifiable risk factors that may be modified after platelet function testing.

Notably, particular attention should be paid to the rest of the risk factors that may lead to increased bleeding and blood transfusion: 1) advanced age, 2) anemia , 3) complex procedures, 4) urgent procedures and 5) chronic patient comorbidities. Majority of these factors may be considered as a subject of preoperative intervention. Herein we will be focused on APT administration/discontinuation management based on drug specific platelet function testing.

In line with this standpoint, we have performed a prospective observational study aiming to define cut-of values that delineate bleeding tendency in patients undergoing isolated CAS[4]. Using drug specific platelet function tests we have defined cut-of values that delineate risk for excessive postoperative bleeding[4]. The receiver operating curve revealed an ASPI test (sensitive to the effect of aspirin) value of <20 area under curve (AUC) units (AUC 0.603, p = 0.023) and an ADP test (sensitive to the effect of thienopyridines) <73 AUC (AUC 0.611, p = 0.009) as a determinants of bleeding complications[4].

A tailored approach in APT management based on these cut-of values may not only diminish bleeding risks attributable to platelet inhibitory effect of APT, but also may reduce the risk for adverse ischemic events by suggesting to continue APT up to the day of surgery in cases with measured high residual platelet reactivity with observed values exceeding cut-of values[4]. The preoperative period in which we may modify APT with the aim to avoid early postoperative bleeding is narrow, so our aim is primarily to avoid excessive bleeding. Antiplatelet drug with measured drug specific platelet function below the cut-of point should be discontinued and repetitive measurements should be done on a daily basis to confirm adequate platelet recovery. *Vice versa*, antiplatelet drug with high "on treatment" platelet reactivity (values of drug specific platelet function test above cut-of value) should be continued up to the day of surgery assuming that such an approach leads to minimum risk for both bleeding and ischemic events (Figure 1).

Postoperative considerations:

While on chronic APT in postoperative phase, the same attention should be paid to bleeding and adverse ischemic events. Therefore, it seems reasonable to develop an "antiplatelet drug specific therapeutic window", framed by a lower bound indicating bleeding tendency and an upper bound indicating proclivity towards ischemic events.

Using MEA ASPI test, our working group defined resistance to aspirin in patients undergoing CAS[9]. In addition to this, we have evaluated the perioperative dynamics of platelet reactivity and have found that patients have hyperactive platelets in early postoperative phase resulting in a significant increase in prevalence of aspirin resistance in the early postoperative phase[10] . Furthermore, we evaluated the clinical relevance of aspirin resistance[11] as well as the treatment modalities to overcome aspirin resistance[2,7,8]. Although some studies performed by our working group were actually underpowered to reliably evaluate association between on treatment platelet reactivity and relatively infrequent adverse outcomes, the findings that we gained through our research help us to establish the platform for the "therapeutic window" concept. To propose a "therapeutic window" concept in postoperative APT management, we relied on our own results as well as on results published by colleagues evaluating APT management in coronary artery disease patients based on the same platelet function device that we used.

There is limited literature evidence pertaining to the definition and management of aspirin resistance following CAS. Our working group has defined aspirin resistance using MEA[9] in patients undergoing CAS[9]. ASPI test value of ≥30 AUC indicated aspirin resistance. Values above pre-defined ASPI test of ≥30 AUC warrant APT regimen modification. Distinguishing between CAS patients in whom APT resistance is permanent from those in whom it may be a transient phenomenon may hold practical value. The clear distinction between "permanent resistance" and "temporary resistance" can be done by performing both pre- and post-

operative platelet function testing. The aspirin resistance is likely a permanent one if detected both pre- and postoperatively. However, if a patient has adequate platelet inhibitory response preoperatively, but aspirin resistance occurs in postoperative phase, this resistance may be considered as transient phenomenon. This is of particular practical value as permanent aspirin resistance requires permanent APT modification whereas temporary aspirin resistance warrants temporary APT adjustments.

Ideal modality of APT adjustments in aspirin resistant patients remains elusive. At present, there is no established therapeutic approach to manage aspirin resistance that has been shown in large trials to provide clinical benefit. The current guidelines on postoperative APT management recommend the initiation of 100 to 325 mg of aspirin within 6 hours of surgery[14]. In between this range, we suggest stepwise increase in aspirin dose aiming to achieve adequate platelet inhibitory response. Further increases in aspirin dose are not recommended because of possible worsening of endothelial mediated arterial dilatation[18]. If aspirin resistance occurs after relatively high doses of aspirin being administered, addition of another, supplemental, antiplatelet agent is rational. Recently, our working group has evaluated the impact of clopidogrel addition on outcomes among aspirin resistant patients following CAS[8]. A subgroup analysis revealed that dAPT led to lower rates of adverse events in patients with a body mass index >30 kg/m(2) (0% vs 18%, p <0.01) and those <65 years (0% vs 10%, p = 0.02) [8]. This was the first prospective randomized study to address the clinical impact of dual APT after CAS in patients with aggregometry-documented aspirin resistance[8]. We cannot reliably exclude the possibility that this study may have been underpowered and the addition of clopidogrel would result generally in better outcomes if we have had larger patient cohort recruited[8]. However, our results may provide an impetus for the conduct of a larger scale multicentric study of a similar design that would address all the shortcomings of our study. Awidi et al[19] have shown that dual APT with clopidogrel and

aspirin was found to have greater inhibitory effect on platelet aggregation than either agent alone [19]. Later, this phenomenon has been corroborated by Wang et al[20]. Authors[20] conducted a randomized control trial[20] with the aim to investigate whether clopidogrel can improve aspirin response. Dual APT with clopidogrel addition resulted in a significantly lower incidence of aspirin resistance[20]. Finally, authors concluded that clopidogrel reduces the incidence of aspirin resistance in early post CAS phase[20]. Furthermore, when administering clopidogrel, the objective measurement of platelet inhibitory response to clopidogrel therapy would be desirable as there is evidence on negligible rate of resistance to clopidogrel[2]. Youn et al[21] have recently shown that platelet reactivity on clopidogrel is associated with the risk of adverse events after CAS[21]. Routine measurement of platelet reactivity and thorough monitoring of patients with clopidogrel resistance is certainly warranted[21]. It seems that longitudinal follow up based on drug specific platelet function testing that would lead to periodical APT adjustments, rather than adjustments performed in single time point, should be an integral part of a personalized APT administration management[22].

Although variability in platelet inhibitory response to aspirin varies widely, reflecting proclivity towards ischemic or bleeding complications, incidence and clinical relevance of increased or accentuated response to aspirin therapy is far less explored. Based on our experience [4] we defined the therapeutic window lower bound value of ASPI test to be <20 AUC. Although this specific cut-of value corresponds to early postoperative bleeding events, we decided to use that value in the absence of studies reporting the data specifically in relation to non-surgery related bleeding events. Therefore, postoperative aspirin therapeutic window, as assessed by Multiplate ASPI test ranges between 20 and 30 AUC. ASPI test values above or below the pre-defined therapeutic range require aspirin treatment regimen modification.

Our working group did not perform studies to define clopidogrel resistance or to propose a therapeutic window for long term clopidogrel administration in postoperative phase. Therefore, in designing the concept for development of postoperative clopidogrel therapeutic window, we completely relied on the findings published by Sibbing et al[23]. Using the MEA ADP test, the authors defined the clopidogrel therapeutic window for coronary artery disease patients undergoing percutaneous coronary intervention[23]. Clopidogrel therapeutic window was framed by an upper bound value of 46 AUC and lower bound value of 19 AUC using Multiplate ADP test[23]. Long term administration of clopidogrel should be targeted to achieve a therapeutic window as assessed by Multiplate ADP test. Again, longitudinal follow up with subsequent dose regimen adjustments is rational. Our working group recently found that serial clopidogrel dose adjustments targeted after platelet function testing improve outcomes of patients undergoing percutaneous coronary intervention with high on-treatment platelet reactivity[22]. Although this approach has not specifically been validated in post-CAS setting, it sounds reasonable to implement a longitudinal follow up of platelet function in a personalized concept of APT management.

Implications for everyday clinical practice

To the best of our knowledge, this is the first attempt to develop pre- and postoperative therapeutic window for the most commonly used antiplatelet drugs in both pre- and postoperative period for patients undergoing CAS.

This concept provides a shift towards a personalized approach in perioperative APT management. There are numerous studies describing the variability in platelet inhibitory response to APT, but different devices used as well as different study settings hamper the pooling of the results. Therefore, it is not surprising that present literature lacks an APT "therapeutic window".

The "therapeutic window" concept in pre- and post-CAS APT administration management seems desirable and could easily be incorporated into routine practice. Considering the preoperative management, if platelet function testing reveals value that is below the lower bound cut-of value, it seems reasonable to discontinue APT and re-schedule surgery until platelets recovery. Repetitive measurements should quantify and confirm platelet recovery. Recently, Di Dedda et al conducted a study with aim to assess the rate and time of platelet recovery after discontinuation of thienopyridines, in the setting of patients scheduled for cardiac operations[24]. In their study, platelet aggregation values high enough to avoid major bleeding were reached 3 days after drug discontinuation (95% confidence interval: 2-4 days) [24]. Within the observed cohort the MEA ADP test results significantly increased (P = 0.001) with increasing numbers of elapsed days following thienopyridine discontinuation[24]. The mean daily ADP test increase was 12 U[24]. These results hold practical value as it is possible to estimate the time needed to achieve platelet recovery after values below the lower bound cut-of are detected preoperatively. For instance, a patient on clopidogrel treatment and with observed ADP test value of 37 AUC should have 3 days drug free interval in order to avoid excessive bleeding by achieving sufficient ADP reactivity (37 AUC+ (12 AUC daily

recovery rate*3 days) =73 AUC). *Vice versa*, if platelet function testing reveals a value exceeding the lower bound cut-of point (that delineates bleeding tendency), it seems reasonable to continue with APT assuming that patients have "on treatment" residual platelet reactivity sufficient to achieve adequate hemostasis. At the same time, by avoiding unnecessary discontinuation of APT, we may further minimize the risk for adverse ischemic events onset.

However, whereas administration/discontinuation management of preoperative APT relies on single cut-of value delineating bleeding tendency, the postoperative APT management should be tailored to achieve the range of platelet reactivity defined by the "therapeutic window". If bleeding occurs while on chronic APT, platelet function should be performed and APT should be discontinued until bleeding stops and platelet recovery is documented (Figure 1). In general, platelet function should fit the pre-defined therapeutic range. However, due to different sources of bleeding events as well as different anatomical background for bleeding, we may sometimes target APT management after a clinical picture is established.

Although more investigated, less is known about management of APT resistance in postoperative phase[2]. If values of drug specific platelet function tests are above the upper bound value of a pre-defined therapeutic window, it is very important to: 1) increase the drug dose if possible or administer additional antiplatelet drug, and 2) provide platelet function testing longitudinal follow up[22]. Both high "on treatment" residual platelet reactivity and pronounced platelet inhibition may be transient phenomenons requiring temporary adjustments. Thus, using longitudinal follow up it is possible to continuously keep platelet function within the predefined therapeutic range[22]. The lack of longitudinal follow up may result in a switch from the risk of ischemic events to the risks of bleeding events and *vice versa*. If longitudinal follow up is not feasible for some reason, distinction between "permanently" and "temporary" resistance could help in tailoring APT management. As we

have previously shown[10], patients may express platelet reactivity turnaround in the early postoperative phase resulting in higher proportion of aspirin resistant patients. The resistance is probably a permanent one if detected both pre- and postoperatively[10]. If platelets respond to aspirin adequately in preoperative phase, but acquire aspirin resistance in the early postoperative period, this resistance is more likely to be transient[10]. Evidently, permanent resistance requires permanent APT adjustments whereas transient resistance requires transient APT adjustment. In the absence of the possibility to perform longitudinal periodical follow up, this seems an acceptable strategy. However, such a strategy requires prospective observational studies to define longevity of such a temporary resistance to APT that would in turn define longevity of temporary APT adjustments.

Such a concept for a personalized approach in the perioperative APT administration/discontinuation management based on multiple electrode aggregometry, has some limitations (Table 1). When measuring platelet function, one should be aware that global aggregation measure approach is usually less specific to the effect of certain antiplatelet drug. On the other hand, analysis of the drug effect with high specificity (drug specific platelet function analysis) provides less information regarding the overall platelet aggregation status. Very recently, Ranucci et al showed that in patients taking P2Y12 receptor inhibitors, residual platelet reactivity to thrombin stimulation limits the risk of severe postoperative bleeding[25]. In order to make the concept more complex and precise, one should consider using not just drug specific platelet function assays but also assays representing in some degree general platelet reactivity.

When developing "therapeutic window concept" based on point-of-care platelet function analyzers, one should consider possibility for high variation coefficients in the reproducibility check of the numerical values that analyzers produce. This may be very important particularly in scenarios with narrow therapeutic window range. Very recently, Karon et al [26] came out

with comparative study evaluating precision and reliability of 5 different platelet function tests in healthy volunteers donors on daily APT, with aim to distinguish their efficacy for titrating APT [26]. Tests were compared for intraassay precision (duplicate analysis from a single blood draw), interassay precision (samples from two separate blood draws) and reliability coefficient. Authors assessed arachidonic acid induced and ADP induced platelet function by light transmission aggregometry (LTA), Multiplate® Impedance aggregometry, Verify Now, and Platelet Mapping by thromboelastography [26]. Put briefly, based on their findings, authors concluded that thromboelastography-platelet mapping was least suited to monitor effects of APT. Multiplate® impedance aggregometry was the only method to demonstrate an acceptable reliability coefficient among healthy volunteers and donors on both aspirin and clopidogrel therapy.

When we look at the present "therapeutic window" for postoperative aspirin management based on ASPI test, one could consider proposed "therapeutic window" as too narrow, in particular when excluding normal variation. Several issues should be considered when defining aspirin "therapeutic window". Firstly, the fact is that testing the efficacy of aspirin is methodologically more complicated and less reliable than measuring the effects of ADP receptor blockers [27-9]. Secondly, there is scarce evidence evaluating the level of aspirin sensitive platelet function test results that would delineate non-surgery related bleeding events as well as ischemic events while on chronic aspirin therapy.

To date, the level of aspirin sensitive platelet function test value that would delineate non-surgery related bleeding complications in patients on chronic postoperative aspirin treatment, has not yet been defined. Therefore, we alternatively decided to use cut-of value that delineates early postoperative bleeding complications[4].

The definition of aspirin resistance in present paper is "laboratory based". To assess the clinical relevance of aspirin resistance, we evaluated its impact on outcomes among patients

following CAS [11]. However, we may assume that the most appropriate way would be to define “clinically based” aspirin resistance, that would be considered as the level of aspirin sensitive platelet function test value that is associated with significantly higher occurrence of adverse ischemic events. Such an approach could possibly result with higher cut-of values, thus wider therapeutic range than that defined in present manuscript. In that regard, it sounds reasonable that each laboratory/center define its own therapeutic window range for the various platelet function assays. Such a “local” therapeutic window should , however, be defined in high volume centers, or should be defined through multicenter collaboration. In possible multicenter collaboration, the pre-analytical factors such as the anticoagulant used (hirudin, citrate , and heparin) and the time delay between sampling and analysis should inevitably be standardized as may alter results [30].

Conclusion

It seems that current “one-size-fits-all” concept of perioperative APT administration management is outdated. Point-of-care measurements of platelet function level are far more reliable predictors of bleeding complications than the more arbitrary use of specified period of surgical delay or drug free interval. In addition to this, discontinuation of antiplatelet drugs based on a pre-specified period of time may in patients with high residual “on treatment” platelet reactivity cause rebound platelet reactivity following drug cessation which may cause adverse ischemic events[31].

The risk for excessive bleeding associated with APT must always be weighed against the risk for adverse ischemic events and those risks should be inextricably assessed.

The clinical use of such a “therapeutic window” concept is not always possible as timing of surgery is not always feasible because of clinical conditions. This presents the drawback of such a concept. In such cases, use of this concept may at least identify patients that may proceed with surgery with a high risk of bleeding. Identification of patients proceeding to surgery with high risk of bleeding may warrant more aggressive hemostatic management based on intraoperative point-of-care assessment of viscoelastic blood clot properties. For such cases, we advise intraoperative use of rotational thromboelastometry to optimize hemostatic blood properties and to provide more efficient transfusion of procoagulant blood components. One should be aware that optimal hemostatic management requires a comprehensive approach with measures such as intraoperative blood salvage, topical hemostatic agents, the use of antifibrinolytic agents and intraoperative transfusion algorithms based on point-of-care hemostatic tests which all may minimize bleeding risk owing to platelet dysfunction. We have published an algorithm for intraoperative hemostatic management and this point-of-care based algorithm should particularly be used in patients that are considered to be at higher risk of bleeding[3].

Whether guidance on APT treatment based on platelet function testing proves useful for avoiding bleeding and adverse ischemic events both in pre- and postoperative phase warrants further investigation. To date, this is the first concept of perioperative APT management based on a “therapeutic window” and at present provides a step forward in patient care and the platform for further interventional trials that should evaluate its influence on clinical outcomes.

Conflict of interest: none declared.

Figure legends:

Figure 1.

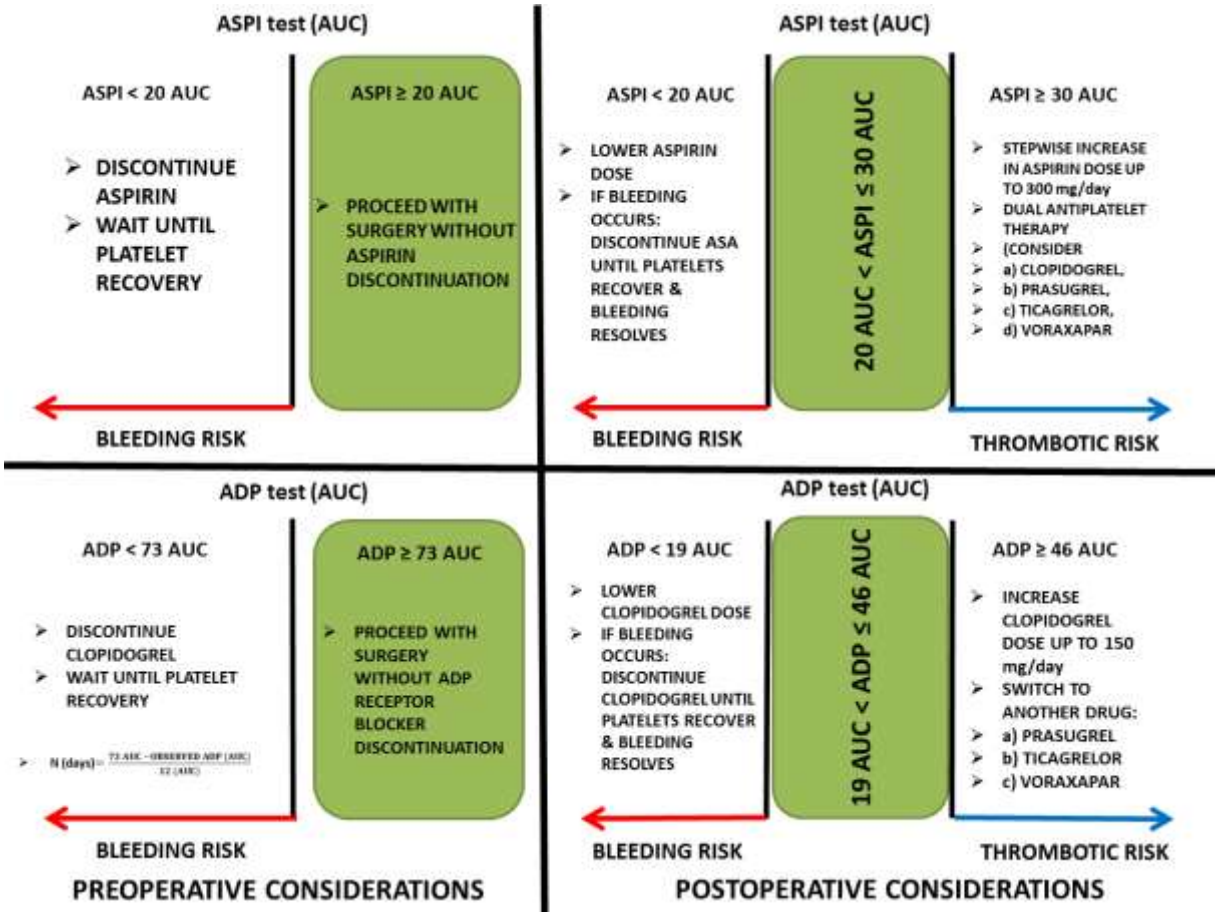
Illustration of "therapeutic window" concept in management of antiplatelet therapy in patients undergoing coronary artery surgery.

Abbreviations:

ASPI test – cyclooxygenase-1-dependent platelet aggregation, sensitive to the effect of aspirin

ADP test – adenosine di-phosphate induced platelet aggregation, sensitive to the effect of thienopyridines

AUC – area under the curve units



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Tables

Table 1.

Development of a concept for a personalized approach in the perioperative antiplatelet therapy administration/discontinuation management based on multiple electrode aggregometry: Pros and Cons

Abbreviations: APT – antiplatelet therapy ; PFT- Platelet function testing

PROS
Reasonable approach to manage widespread variability in platelet inhibitory response to APT.
"One-size-fits-all" concept of perioperative APT administration management is outdated and further development of PFT based, personalized APT administration/discontinuation management is desirable both in pre- and postoperative period.
Possible step forward in patient care. Such an approach could reduce the incidence of bleeding and ischemic complications.
Point-of-care measurements of platelet function level are far more reliable predictors of bleeding complications than more arbitrary use of specified period of surgical delay or drug free interval.
Avoidance of poor platelet function caused by platelet inhibitory response to APT may theoretically reduce the incidence of bleeding complications.
Appropriate management of high residual "on-treatment" platelet reactivity may theoretically reduce the incidence of adverse ischemic events.
CONS
When measuring platelet function, one should be aware that global aggregation measure approach is usually less specific to the effect of certain antiplatelet drug. On the other hand, analysis of the drug effect with high specificity (drug specific platelet function analysis) provides less information regarding the overall platelet aggregation status.
Lack of consensus in defining the level of "on-treatment" platelet reactivity associated with ischemic and bleeding events in both pre- and postoperative period.
"Therapeutic window" should be "device specific" and , if possible, "center specific", or defined throughout multicentric studies with inevitable sandardization on pre-analytical parameters.
Several point-of-care platelet function analyzers available on the market express a high inter-assay variability.
Intraassay precision and reliability limits the value of such approach if platelet function analyzer has low reliability coefficient/high coefficient of variation in repetitive measurements.