REVIEW ARTICLE

Antiplatelet therapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures

Key messages for clinical practice

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KEY WORDS

acetylsalicylic acid, atherosclerotic coronary artery disease, clopidogrel, gastrointestinal endoscopy, risk assessment

ABSTRACT

Should we interrupt antiplatelet therapy (acetylsalicylic acid [ASA] alone or in combination with clopidogrel) in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal (GI) procedures? The relevant evidence was critically appraised in a recent White Paper from the American College of Gastroenterology and the American College of Cardiology. Clinicians need to qualify and compare 2 competing risks: the increased risk of bleeding if antiplatelet therapy is maintained during the endoscopic GI procedure, vs. the increased risk of cardiovascular (CV) thrombosis if antiplatelet therapy is interrupted or modified in the periprocedural period. ASA treatment may be continued for all endoscopic GI procedures, provided that there is no pre-existing bleeding disorder. Clopidogrel administration could be maintained for low-risk endoscopic GI procedures, such as diagnostic endoscopy of the upper or lower GI tract with or without biopsies. For patients on clopidogrel undergoing high-risk endoscopic GI procedures, such as polypectomy or sphincterotomy, the individualized risk of CV complications from clopidogrel discontinuation should be assessed. During the first month following bare-metal stent implantation or the first 6 (possibly 12) months following drug-eluting stent placement the CV risk is particularly high, therefore elective high-risk endoscopic GI procedures should be deferred accordingly. In all other clinical situations requiring clopidogrel treatment, the risk of CV events is lower than above. Therefore, clopidogrel treatment could be interrupted for 7 to 10 days before the procedure (and restarted as soon as possible after the procedure), provided that ASA treatment is maintained.

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Introduction With the rising incidence and prevalence of atherosclerotic coronary artery disease worldwide, an ever-increasing proportion of the population is using antiplatelet therapies such as acetylsalicylic acid (ASA) and/or clopidrogrel. Meanwhile, elective endoscopic gastrointestinal (GI) procedures, such as screening colonoscopy or endoscopic examination of the GI tract for nonurgent indications, are becoming more accessible and ubiquitous. This means that, nowadays, physicians, and the patients who are undergoing elective endoscopic GI procedures, are increasingly confronted by the dilemma of whether to adjust, or even interrupt, antiplatelet therapy in the periprocedural period.

These concerns were addressed in the recent White Paper on the "Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures".[1,2]

This paper was authored by a team of opinion leaders in gastroenterology and cardiology in collaboration with the American College of Gastroenterology (ACG) and the American College of Cardiology (ACC) and was co-published in the respective official journals. In 2008, the above mentioned colleges in collaboration with the American Heart Association (AHA) developed an Expert Consensus Document on reducing the GI risks of antiplatelet therapy and nonsteroidal anti-inflammatory drugs, which included recommendations relating to endoscopy procedures in patients on antiplatelet therapy.[3,4] The British Society of Gastroenterology published guidelines in the same year,[5] while the American Society for Gastrointestinal Endoscopy (ASGE) published their own guidelines a few years ago.[6] The recent ACC/ACG White Paper was not intended to be a consensus statement; it rather builds on the 2008 Consensus Document. The ACC/ACG White Paper is more focused, therefore allowing for a more detailed appraisal of the available evidence. Furthermore, it elaborates equally on the GI and the cardiovascular (CV) perspective, since a decision regarding discontinuation of antiplatelet therapy before an elective endoscopic GI procedure requires quantification of both the risk of a thrombotic event during temporary discontinuation of therapy and the risk of periprocedural bleeding if treatment is continued or when it is resumed.[1,2]

Indications for, and cardiovascular risks of discontinuing antiplatelet therapy Non-cardiologists need to be familiar with the indications for, and the minimum duration of, single (i.e., ASA alone) and dual antiplatelet therapy (i.e., ASA and clopidogrel) in patients with atherosclerotic coronary artery disease, as highlighted by the ACC and AHA.[7]

1 All patients with ST-segment elevation myocardial infarction should receive dual antiplatelet therapy for at least 2 weeks.

2 Patients with unstable angina or non-ST elevated myocardial infarction (MI) who do not undergo percutaneous coronary intervention should receive dual antiplatelet (and anticoagulant) therapy for 1 to 12 months.

3 patients receiving a bare-metal stent (BMS) implantation should be given dual antiplatelet therapy for 1–12 months

4 Patients receiving a drug-eluting stent (DES) implantation should be given dual antiplatelet therapy for at least 12 months.

5 In patients with stable coronary artery disease, single antiplatelet therapy with ASA is recommended.

Observational studies have shown that, in patients with atherosclerotic coronary artery disease who are appropriately on antiplatelet therapy, discontinuation of all antiplatelet agents for scheduled surgery is associated with increased 30-day risk of MI and death.[8] This applies both to withdrawal of ASA in patients on single-agent antiplatelet therapy (CV events occur in 10 days on average following withdrawal), as well as to withdrawal of ASA and clopidogrel in patients on dual antiplatelet therapy (CV events occur in 7–10 days on average following withdrawal). With regards to partial discontinuation of dual antiplatelet therapy (i.e., stopping clopidogrel while ASA is continued) in patients without coronary stents, short-term discontinuation of clopidogrel alone is not associated with a major increase of CV risk. However, in patients with coronary stents, discontinuation of clopidogrel alone earlier than the minimum indicated duration as per the type of stent is associated with a high risk of CV events due to stent thrombosis.

Inherent risk of bleeding from elective endoscopic gastrointestinal procedures It is important to stratify the endoscopic GI procedures into low and high risk for bleeding based on inherent risk for bleeding. The ACC/ACG White Paper endorsed the classification previously developed by the ASGE.[6]

Low-risk procedures are considered the following:

1 diagnostic endoscopy (esophagogastroduodenoscopy [EGD], flexible sigmoidoscopy, colonoscopy or enteroscopy) with or without biopsies

2 endoscopic retrograde cholangiopancreatography without endoscopic sphincterotomy

3 biliary/pancreatic stenting without sphincterotomy

4 endoscopic ultrasound (EUS) without fine needle aspiration (FNA).

The baseline risk of bleeding is less than 0.13% in diagnostic EGD with or without biopsies and less than 0.02% in diagnostic colonoscopy with or without biopsies.[9]

High-risk procedures are:

1 polypectomy

2 biliary sphincterotomy

3 pneumatic or bougie dilation

4 percutaneous endoscopic gastrostomy

5 EUS-guided FNA

6 laser ablation and coagulation

7 treatment of varices

8 endoscopic mucosal resection.

Colonoscopic polypectomy is by far the most commonly performed high-risk endoscopic GI procedure. It may be complicated by bleeding, which can be either immediate or delayed. In general, immediate bleeding is less problematic since it can be recognized and managed during the index colonoscopy. However, delayed post-polypectomy bleeding may occur up to 14 days after the index colonoscopy. The overall risk of post-polypectomy bleeding is less than 1%, but the risk is relatively increased with increasing polyp size, advancing age, systemic hypertension, and probably other chronic comorbidities.[10]

Incremental risk of bleeding from antiplatelet therapy in patients undergoing elective endoscopic gastrointestinal procedures Although it is plausible

that antiplatelet therapy may further increase the risk of bleeding in patients undergoing elective endoscopic GI procedures, it is unclear whether the magnitude of the incremental risk is clinically important; there is paucity of high-quality evidence on this. With the best available evidence coming from retrospective observational studies, ASA use has not been associated with a statistically significant increase in the risk of bleeding in patients undergoing polypectomy. Regarding the safety of clopidogrel in patients undergoing endoscopic GI procedures, only indirect evidence is available: clopidogrel use has been associated with a dramatically increased risk of bleeding from other, non-GI, endoscopic procedures, including transbronchial lung biopsy.

Strategies to reduce bleeding in patients on antiplatelet therapy undergoing elective endoscopic GI procedures[1,2,5,6]

1 Periprocedural discontinuation of ASA is not required for any endoscopic GI procedure (low or high risk), provided that there is no pre-existing bleeding disorder.

2 Clopidogrel administration need not to be stopped for low-risk endoscopic GI procedures.[5,6]

3 In patients on clopidogrel requiring high-risk endoscopic GI procedures, the individualized risk of CV complications from clopidogrel discontinuation should be evaluated.

a If the CV risk is high, i.e., within the first month following BMS placement or within the first 6 (possibly 12) months following DES placement, elective high-risk endoscopic GI procedures should be deferred until the CV risk is reduced.

b In all other clinical situations requiring clopidogrel treatment, the risk of CV events is lower than above. Therefore, it is relatively safe to stop clopidogrel 7 to 10 days before the procedure, as long as ASA treatment is not interrupted. Clopidogrel inhibits platelet aggregation by irreversibly blocking the adenosine diphosphate receptor P2Y12. Therefore, its pharmacodynamic effect is gradually attenuated as the platelet pool is replenished. Clopidogrel should be restarted as soon as possible after the procedure. The decision to resume clopidogrel treatment with a maintenance dose, which requires several days to achieve full pharmacodynamic effect, or a loading dose should be individualized depending on the trade-off between the CV risk and the post-procedural delayed bleeding risk. We would like to emphasise that there is still a residual risk of stent thrombosis during the 7 or 10 days of clopidogrel discontinuation. Although the median time from discontinuation of clopidogrel therapy to stent thrombosis is 14 days for the first 6 months after DES implantation, the inter-quartile range is 5 to 26 days.[11] This implies that a dichotomous approach, (i.e., either continuation of clopidogrel or interruption for 7–10 days), may not always be the best option. In clinical practice the most appropriate option for some patients may be a compromise, such as interruption for 5 to 7 days. For example, this may apply in patients who have completed at least 1 month of antiplatelet therapy following BMS placement or at least 12 months following DES placement and require a "high-risk" GI procedure, but the clinician estimates that either the individualized risk of thrombosis is higher than expected, or the individualized risk of bleeding is lower than expected.

4 Although bridging therapy appears an attractive strategy, it cannot currently be recommended. Observational studies have not shown any benefit from heparin bridging, there are only very limited data available on bridging with glycoprotein IIb/IIIa receptor antagonists, and there are no data on bridging with new short-acting platelet P2Y12 inhibitors (currently under investigation).

5 Since the value of measuring the individualized risk of bleeding with the use of platelet function tests (laboratory based or point-of-care whole blood tests) has not been studied as yet, no recommendations can be made on this issue.

Quality of supporting evidence Increasingly, the GRADE approach is being used to develop and present recommendations for management of patients.[12] This approach classifies the quality of supporting evidence as high, moderate, low and very low. Evidence derived from randomized controlled trials (RCTs) is labeled as high-quality, but may be downgraded by 1 or more levels in case of study limitations, inconsistency of results, indirectness of evidence, imprecision, or reporting bias. Observational studies (cohort and case-control) start as low-quality evidence but may be upgraded one or more levels if there is a large magnitude of effect, a dose-response gradient, or if all plausible biases would decrease the demonstrated effect. Although this approach is primarily used in the development of consensus guidelines, it may be appropriate to use this framework to assess and interpret the strength of supporting evidence for the ACC/AHA White Paper. With the exception of the evidence on the indications for and length of treatment of antiplatelet therapy (which could be graded as high-quality), the evidence for all other areas addressed in the paper ranges from medium to very low. This does not undermine the value of the ACC/AHA White Paper, which has provided a comprehensive review of the best available evidence. Along with previously published guidelines, the ACC/AHA White Paper can assist clinicians with decision regarding continuation or discontinuation of antiplatelet therapy before an elective endoscopic GI procedure. However, the lack of high-quality evidence weakens our confidence in the assessment and underscores the need for further research.

Patient's values and preferences Consensus statements and White Papers are not intended to promote "cookbook medicine" and should not replace clinical judgment. A clinician should individualize management plan taking into account a patient's values, preferences, and expressed needs. The concept of shared decision making becomes even more important in circumstances where the evidence for the benefit of a treatment option is of low quality or where much variation exists.

For example, Devereaux et al.[13] conducted a prospective observational study evaluating trade-offs in physicians and patients between the risk of stroke and the risk of GI bleeding when antithrombotic treatment is being considered. The study showed that patients may be more averse to the potential consequences of stroke and less concerned about the side effects, including GI bleeding risk, of antithrombotic treatment than their physicians. The findings of their study are consistent with other observational studies that have compared the preferences of patients and healthcare professionals when they are faced with choices about treatment. This is precisely the reason why health professionals should explicitly seek patients' views when making decisions about treatment.

Among patients with high CV risk undergoing high-risk endoscopic GI procedures, there may be diversity in values and preferences. For example, some patients may place a higher value on avoiding a CV event, and may be more ready to accept a small risk of bleeding with antiplatelet therapy. These patients may prefer to continue dual antiplatelet therapy in the periprocedural period without any interruption of therapy. To optimize quality of care, patients' preferences and values should be incorporated into decisions about how to manage antiplatelet therapy for the purpose of an elective endoscopic GI procedure. The use of decision aids in this setting may facilitate shared decision making.

Implications for further research There is a need for observational studies (that are appropriately adjusted for confounders and adequately powered) to accurately quantify the baseline risk of bleeding from high risk endoscopic GI procedures, the risk modifiers (including alternative endoscopic methods), the attributable risk of bleeding from antiplatelet therapy, the reduction of bleeding risk from discontinuation of antiplatelet therapy, and the optimal duration of antiplatelet therapy interruption. RCTs could also be designed to address some, although not all, of the above issues.

The risk of CV complications from interruption of antiplatelet therapy and the relevant risk modifiers also requires better quantification.

RCTs are needed to assess whether the periprocedural administration of proton pump inhibitors (PPIs) reduces the risk of bleeding from high-risk upper GI procedures in patients on dual antiplatelet therapy. Previously raised concerns regarding the clinical significance of the clopidogrel-PPI interaction have recently been questioned.[14,15]

Bridging strategies with glycoprotein IIb/IIIa receptor antagonists or new short-acting platelet P2Y12 inhibitors, and the utility of platelet function testing in individual patients should also be assessed in RCTs.

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CONFLICT OF INTERESTS

Grigorios I. Leontiadis has received honoraria and consultancy fees from AstraZeneca, Sanofi-Aventis, Janssen-Cilag, and GlaxoSmithKline. He is currently an Associate Editor for the American Journal of Gastroenterology.

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ARTYKUŁ POGLĄDOWY

Leczenie przeciwpłytkowe u chorych na chorobę wieńcową o podłożu miażdżycowym poddawanych planowym zabiegom endoskopowym w obrębie przewodu pokarmowego

Główne przesłania dla praktyki klinicznej

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SŁOWA KLUCZOWE

choroba wieńcowa na podłożu miażdżycowym, endoskopia przewodu pokarmowego, klopidogrel, kwas acetylosalicylowy, ocena ryzyka

STRESZCZENIE

Czy powinniśmy przerywać leczenie przeciwpłytkowe (samym kwasem acetylosalicylowym [*acetylsalicylic acid* – ASA] lub w skojarzeniu z klopidogrelem) u chorych na chorobę wieńcową o podłożu miażdżycowym poddawanych planowym zabiegom endoskopowym w obrębie przewodu pokarmowego? Dane dotyczące tego zagadnienia poddano krytycznej ocenie w niedawno opublikowanych wytycznych American College of Gastroenterology i American College of Cardiology. Lekarze potrzebują ocenić ilościowo i porównać dwa konkurujące ryzyka: zwiększone ryzyko krwawienia w razie kontynuacji leczenia przeciwpłytkowego podczas zabiegów endoskopowych w obrębie przewodu pokarmowego i zwiększone ryzyko zdarzeń sercowo-naczyniowych z powodu zakrzepicy w przypadku przerwania lub modyfikacji leczenia przeciwpłytkowego w okresie okołozabiegowym. Leczenie ASA można kontynuować podczas wszystkich zabiegów endoskopowych w obrębie przewodu pokarmowego, jeśli tylko nie istnieje choroba będąca przyczyną krwawienia. Leczenie klopidogrelem można utrzymać w przypadku zabiegów endoskopowych w obrębie przewodu pokarmowego związanych z małym ryzykiem, takich jak endoskopia diagnostyczna górnego lub dolnego odcinka przewodu pokarmowego z biopsjami lub bez biopsji. U chorych leczonych klopidogrelem poddawanych zabiegom endoskopowym w obrębie przewodu pokarmowego związanym z dużym ryzykiem, takim jak polipektomia lub sfinkterotomia, należy ocenić indywidualne ryzyko powikłań sercowo-naczyniowych związanych z przerwaniem stosowania klopidogrelu. Ryzyko sercowo-naczyniowe jest szczególnie duże w ciągu pierwszego miesiąca po wszczepieniu stentu niepowlekanego i w ciągu pierwszych 6 (być może 12) miesięcy po wszczepieniu stentu uwalniającego lek, dlatego też należy odpowiednio opóźnić planowe zabiegi endoskopowe w obrębie przewodu pokarmowego o dużym ryzyku. We wszystkich sytuacjach klinicznych wymagających stosowania klopidogrelu innych niż opisana powyżej ryzyko zdarzeń sercowo-naczyniowych jest mniejsze. Dlatego też w takich przypadkach leczenie klopidogrelem można przerwać na 7–10 dni przed zabiegiem (i wdrożyć ponownie jak najszybciej po zabiegu), pod warunkiem kontynuowania stosowania ASA.

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