

# Endoscopic Procedures in Patients under Clopidogrel/Dual Antiplatelet Therapy: To Do or Not to Do?

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## ABSTRACT

**Background:** Dual antiplatelet therapy has to be used for at least one month after placement of bare metal coronary stents and for a minimum of one year after placement of drug eluting stents. Because of the higher risk of bleeding, guidelines recommend cessation of clopidogrel seven days prior to high-risk endoscopic procedures and to delay elective surgery/endoscopy until dual antiplatelet therapy is ended. Premature cessation of clopidogrel however, may lead to catastrophic cardiovascular sequelae.

**Methods:** We searched the MEDLINE database, EMBASE, and the Cochrane Library for English-language literature up to October 2012 to identify clinical trials on the bleeding risk of gastrointestinal endoscopic procedures in patients on uninterrupted clopidogrel/dual antiplatelet therapy.

**Results:** Six studies (high-risk endoscopic procedures: 5, low-risk endoscopic procedures: 1) on this issue were identified through the literature search. A total of 1,245 endoscopic procedures were performed under clopidogrel. Thirteen bleeding complications occurred (1%). None of the patients required angiographic or surgical intervention and there were no long-term sequelae.

**Conclusion:** To date, data published on this issue are scarce and of poor quality. Nevertheless, there is no evidence to support the recommendations of the current guidelines to stop clopidogrel for at least one week prior to high-risk endoscopic procedures. In this setting, the clinical decision making should take place on an individual basis.

**Key words:** Dual antiplatelet therapy – clopidogrel – endoscopic procedures.

## INTRODUCTION

Guidelines of the British Society of Gastroenterology [1] and the American Society of Gastrointestinal Endoscopy [2] recommend cessation of clopidogrel seven days prior to high-risk endoscopic procedures. However, antiplatelet therapy has to be used for up to one year after placement of coronary stents.

Premature discontinuation of antiplatelet medication during this period is associated with increased risk for stent thrombosis with severe or even fatal consequences [3]. Moreover, recent data suggest that even after one year of antiplatelet

therapy, clopidogrel cessation may result in rebound platelet hyperactivity contributing to increased thromboembolic complications in this setting [4].

## AIM

To search for any data supporting the recommendation of the current guidelines regarding clopidogrel cessation for at least seven days prior to high-risk endoscopic procedures. The aim of this systematic review therefore was to determine the bleeding risk of gastrointestinal endoscopic procedures performed in patients under clopidogrel/dual antiplatelet therapy.

## METHODS

We searched the MEDLINE database, EMBASE, and the Cochrane Library for English-language literature up to October 2012 to identify clinical trials on the bleeding risk of endoscopic procedures in patients on uninterrupted clopidogrel/dual antiplatelet therapy.

The search terms were clopidogrel, antiplatelet therapy, dual antiplatelet therapy, bleeding risk, endoscopy, colonoscopy, polypectomy, post polypectomy bleeding (PPB), endoscopic sphincterotomy (ES), biopsies, percutaneous endoscopic gastrostomy (PEG), and endoscopic mucosal resection (EMR).

All publications regardless of methodology, design, or size were included.

Date extracted from each article included aim, study design, patient's characteristics, type of the endoscopic procedure performed, and the number of patients under uninterrupted clopidogrel/dual antiplatelet therapy. Data on bleeding complications in this group were also extracted and analysed according to the following criteria: definition of bleeding; immediate bleeding; delayed bleeding; and necessity of endoscopic intervention, re-hospitalization, or transfusion of packed red blood cells (PRBC).

## RESULTS

Altogether, six studies (Table I) on the safety of endoscopic procedures in patients under clopidogrel/dual antiplatelet therapy were identified by the literature search [5-10]. Several study designs were employed (retrospective design: 2, retrospective case-control: 3, prospective single-blind randomized: 1).

Five publications were designed to address bleeding complications in high-risk endoscopic procedures (endoscopic polypectomy: 3, endoscopic sphincterotomy: 1, percutaneous endoscopic gastrostomy: 1). One study investigated this issue in low-risk procedures (gastroduodenal biopsies).

A total of 1,245 endoscopic procedures were performed under clopidogrel (860 endoscopic polypectomies, 350 gastroduodenal forceps biopsies, 27 percutaneous endoscopic gastrostomy, and 8 endoscopic sphincterotomy). The mean

age of patients ranged between 65 and 70 years except for one study, which included healthy adult volunteers with a mean age of 40 years.

Thirteen bleeding episodes (1%) were documented, six immediate and seven delayed. However, relevant bleeding requiring re-hospitalization and/or transfusion of PRBC occurred in only four patients. Nine bleeding complications occurred under dual antiplatelet therapy.

### Endoscopic polypectomy in patients under clopidogrel/dual antiplatelet therapy

So far, three retrospective studies were published on the risk of bleeding in patients undergoing colonoscopy with polypectomy under clopidogrel/dual antiplatelet therapy [5-7].

The average size of removed polyps in the study of Friedland et al [5] was 5.4 mm (size range 3 – 12 mm). Most of the polyps were removed using the cold snare technique (73 %). The largest polyp removed in the study of Feagins et al [6] was 40 mm in size. The average size of the largest polyp removed per patient was 6.54 mm. Polyps of 10 mm or larger were removed in 14.4% of cases. Most polyps were removed with the cold forceps technique (70.8 %).

The majority of polyps [59 %] removed in the study of Singh et al [7] were under 5 mm in size, while 29 % of the removed polyps were between 5 and 9 mm, and only 12 % were 10 mm or larger. The largest polyp removed was of 30 mm. Most of the polyps were removed using the hot snare technique (60%).

## DISCUSSION

Coronary stenting has become an established treatment of ischemic heart disease. Current guidelines recommend the use of dual antiplatelet therapy for at least one month after the placement of bare metal stents and at least one year after

**Table I.** Studies on bleeding risk of gastrointestinal endoscopic procedures in patients under clopidogrel/dual antiplatelet therapy

Reference	Design	Endoscopic procedure	No of procedures	No of patients (M/F)	Average of age of patients	No of procedures under Clopidogrel	No of patients under dual antiplatelet therapy	Immediate bleeding	Delayed bleeding	Remarks
Friedland et al [5]	Retrospective analysis	Polypectomy	125	60 (60/0)	65	125	10 (17%)	3 (5%)	1 (1,7%)	
Feagins et al [6]	Retrospective case control	Polypectomy	360	118 (118/0)	65	360	93 (78%)	Not assessed	1 (0,8%)	
Singh et al [7]	Retrospective case control	Polypectomy	375	142 (99/43)	66	375	77 (54%)	3 (2%)	5 (3,5%)	
Abdel Samie et al [8]	Retrospective analysis	Endoscopic sphincterotomy	8	8 (4/4)	65	8	8 (100%)	0	0	
Whitson et al [9]	Prospective single blind randomized	Gastroduodenal forceps biopsy	630	45 (18/27)	40	350	0	0	0	Healthy adult volunteers
Richter JA [10]	Retrospective cohort	PEG	990	990 (525/465)	70	27	0	0		Bleeding in the first 48 hours following PEG

PEG: percutaneous endoscopic gastrostomy

the placement of drug eluting stents [11]. Discontinuation of antiplatelet therapy was the most powerful predictor of drug eluting stent thrombosis in a prospective study including 3,021 patients [12].

However, the risk of gastrointestinal bleeding may increase by 2 – 3 fold in patients on aspirin and clopidogrel compared with aspirin alone as shown in randomized trials [13]. Data regarding the management of patients on clopidogrel/combined antiplatelet therapy undergoing endoscopic procedures are limited and current guidelines dealing with this common clinical scenario are mainly based on expert opinion. The incidence of bleeding following gastrointestinal endoscopy varies depending on the procedure. High-risk procedures which may be associated with increased incidence of bleeding include polypectomy, endoscopic sphincterotomy (ES), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), dilation of strictures, percutaneous endoscopic gastrostomy (PEG), and endosonography guided fine-needle aspiration (EUS-FNA) [1, 2].

In patients on dual antiplatelet therapy clopidogrel should be stopped seven days prior to high-risk procedures, while aspirin can be continued [1]. However, before stopping clopidogrel in high-risk conditions, such as recently implanted drug eluting stents, consultation with the patient's cardiologist is mandatory. As a general principle, the risk of thromboembolism needs to be balanced against the risk of bleeding during an endoscopic interventional procedure.

To date, no prospective data exist in respect of the bleeding risk in patients under clopidogrel/dual antiplatelet therapy undergoing high-risk gastrointestinal endoscopic procedures. The risk of bleeding under dual antiplatelet therapy was studied prospectively in patients undergoing transbronchial biopsies, yet the study was stopped early because of severe bleeding in both the clopidogrel alone and combined aspirin/clopidogrel group compared to controls. Bleeding occurred in all patients (12 patients: moderate bleeding in 6 cases and severe bleeding in 6 cases) on uninterrupted dual antiplatelet therapy [14].

In a prospective, single blind, randomized trial including 45 healthy adult volunteers 350 gastroduodenal biopsies were performed under clopidogrel. In this recently published study no significant bleeding occurred in the clopidogrel group [9]. The study from Whitson et al is the first prospective study on this issue in the gastroenterological literature; nevertheless, gastroduodenal biopsy is considered to be a low-risk endoscopic procedure. Furthermore, the study included healthy volunteers. In "real life", patients on clopidogrel/dual antiplatelet therapy often exhibit relevant comorbidities and require comedication, which may influence not only the efficacy of the antiplatelet therapy but also the bleeding risk.

Three retrospective studies examined the risk of bleeding in patients undergoing colonoscopy with polypectomy under clopidogrel/dual antiplatelet therapy [5-7].

The primary outcome of interest in the study from Feagins et al was delayed post-polypectomy bleeding (PPB), which was defined as bleeding per rectum occurring within 30 days following polypectomy and requiring hospitalization or treatment. Three hundred and sixty polypectomies were performed in 118 patients under clopidogrel/dual antiplatelet therapy (25/93). Delayed PPB occurred in one patient,

who required hospitalization for two days and endoscopic intervention (clip). Transfusion of PRBC was not needed in this patient, who was under dual antiplatelet therapy (ASA 325 mg). In this study, six PPB were documented in the control group (0.32%). Using the whole sample of 1,967 patients, a logistic regression analysis indicated no significant difference between both groups.

The authors concluded that the thrombotic risk of discontinuing clopidogrel prior to colonoscopy may exceed the risk of post-polypectomy bleeding [6].

In another retrospective case-control study, comprising 142 patients on clopidogrel (375 polypectomies) and 1243 controls (3226 polypectomies) the risk of PPB was significantly higher in patients undergoing the procedure while on clopidogrel and concomitant aspirin/non steroidal anti-inflammatory drugs. However, clopidogrel alone was not an independent risk factor for PPB, and the authors concluded that routine cessation of clopidogrel prior to colonoscopy/polypectomy is not necessary [7].

In the third small retrospective study on this issue [5], 125 polypectomies were performed in 60 patients under clopidogrel/dual antiplatelet therapy (50/10). Four patients experienced PPB (three immediate and one delayed).

However, none of these patients required transfusion of PRBC or re-hospitalization. The average size of removed polyps was 5.4 mm (3-12 mm). This is comparable to the size of polyps removed in the former two studies, so that the safety of removing larger polyps without stopping clopidogrel remains unresolved.

In this study, prophylactic clip application was performed in all patients, and most of the polyps were removed using the cold snare technique (73%). The authors hypothesized that, although unproven, both techniques may have contributed to the low bleeding rate in this study.

There are no published data on the risk of hemorrhage under clopidogrel/dual antiplatelet therapy in patients undergoing ES.

A case-control retrospective study, including 40 patients and 86 controls demonstrated that antiplatelet agents do not significantly increase the risk of clinically relevant bleeding following endoscopic sphincterotomy; however, due to the limited number of patients on clopidogrel (one patient in the case group?) in this study, no definitive recommendation regarding the use of clopidogrel in patients undergoing ES can be made [15]. In a retrospective study conducted by the authors of this paper ES was performed safely in eight consecutive patients on uninterrupted combined antiplatelet therapy. Neither endoscopically relevant immediate nor clinically significant delayed bleeding was observed [8]. The widely used Endo-Cut mode in ES with alternating cutting and coagulation cycles may be beneficial for reducing the bleeding risk during ES.

Regarding the bleeding risk, percutaneous endoscopic gastrostomy (PEG) is also considered to be a high-risk procedure. In a retrospective cohort study from Richter et al 27 procedures were performed in patients under clopidogrel. No bleeding related to the procedure occurred in the first 48 hours following PEG placement [10].

To our knowledge there are no published data on the risk of bleeding in patients undergoing EUS-FNA or EMR while

on clopidogrel/dual antiplatelet therapy and only one small study regarding endoscopic sphincterotomy [8]. Although the above mentioned study does not prove that clopidogrel/dual antiplatelet therapy increases the bleeding risk in patients undergoing endoscopic sphincterotomy while on dual antiplatelet therapy, it is too limited to assert the opposite,

## CONCLUSION

To date, data published on the bleeding risk of gastrointestinal endoscopic procedures in patients under clopidogrel/antiplatelet therapy are scarce and of poor quality. Nevertheless, there is no evidence to support the recommendations of the current guidelines to stop clopidogrel for at least one week prior to high risk-endoscopic procedures. Moreover, cessation of antiplatelet therapy in patients with a high thromboembolic risk may lead to catastrophic cardiovascular sequelae. Hence, in this setting the clinical decision making should take place on an individual basis.

As the number of patients under clopidogrel/dual antiplatelet therapy is predicted to further increase in an aging population, a prospective, multicenter study on this problem is absolutely necessary.

**Conflicts of interest:** No conflicts of interest exist.

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