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Bleeding and management of bleeding

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Clopidogrel is an effective antiplatelet drug for preventing cardiovascular events and death but also increases the risk of bleeding. There is emerging evidence that bleeding is associated with an increased risk of recurrent ischaemic events and death, even when the bleeding is not severe enough to be considered life-threatening. Reducing the risk of bleeding has the potential to improve clinical outcomes, but it is important to ensure that strategies aimed at reducing the risk of bleeding do not compromise the net clinical benefit of clopidogrel that has been demonstrated in clinical trials. Possible strategies to reduce the risk of bleeding during clopidogrel treatment include appropriate dosing of concomitant antithrombotic drugs and their avoidance unless they are of proven benefit, careful selection of patient for invasive procedures, and discontinuation of clopidogrel at least 5 days prior to coronary artery bypass graft surgery, except in unstable or very high risk patients. Management of bleeding in patients treated with clopidogrel may include temporary discontinuation of antithrombotic drugs, resuscitation with intravenous fluid, packed red cell transfusion, and surgical or other procedures to control the bleeding. The only way to overcome the antiplatelet effect of clopidogrel is with platelet transfusions because clopidogrel irreversibly inhibits platelet function for the life of the platelet, and there is no known antidote. Future research efforts should be directed towards establishing whether or not the association between bleeding and recurrent ischaemic events and death is causal and to determine the mechanism(s) responsible for the association.

Introduction

Clopidogrel is an effective antiplatelet drug for preventing myocardial infarction, stroke, and death in high-risk patients with symptomatic cardiovascular disease.[1–8] Like all effective antithrombotic agents, clopidogrel use increases the risk of bleeding, which can be spontaneous or occur at sites of compromised vascular integrity. In the past, clinicians have discounted bleeding complications in patients with acute coronary syndromes, provided that the antithrombotic regimens are effective in preventing irreversible ischaemia. The reason being that ischaemic events cause irreversible complication, whereas even severe bleeding is rarely associated with permanent morbidity. The notion that haemorrhagic complications do not result in irreversible damage is now being challenged by emerging evidence that bleeding is associated with an increased risk of recurrent ischaemic events and death, even when the bleeding is not severe enough to be considered life-threatening.[9] Further, with the increasing use of aggressive antithrombotic therapies and invasive revascularization procedures, the incidence of bleeding is increasing.[10–12] These two observations highlight the need to re-examine the importance of bleeding in cardiovascular patients treated with antithrombotic drugs.

This article reviews the mechanisms and incidence of bleeding in patients treated with clopidogrel, the emerging evidence of a relation between bleeding and

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recurrent ischaemic events and death, and implications of bleeding for clinical practice and future research.

What is the mechanism of bleeding in patients treated with clopidogrel?

Antiplatelet drugs predispose to bleeding by impairing physiological haemostatic processes. This untoward effect is an inevitable consequence of the ability of these drugs to prevent thrombosis.[13,14] Platelets adhere to exposed subendothelial proteins at the site of vessel injury, become activated, undergo shape change, release vasoactive and thrombogenic substances such as ADP, and recruit additional platelets to form a haemostatic plug. Activated platelets also provide a phospholipid surface on which the amplification and propagation of fibrin clot formation take place.[15,16] An active metabolite of clopidogrel binds to, and irreversibly blocks, the platelet P_2Y_{12} ADP receptor, thereby inhibiting ADP-induced platelet activation and aggregation for the life-span of the platelet.[17] When clopidogrel is combined with other antithrombotic agents, multiple platelet-mediated and non-platelet-mediated haemostatic pathways are simultaneously inhibited, thereby increasing further the risk of bleeding.[12]

The most common site of spontaneous bleeding in patients treated with clopidogrel is the gastrointestinal tract. Bleeding is common at puncture and surgical sites in patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery.[18,19] Intracerebral bleeding is uncommon but is associated with the highest mortality.[1,3,8]

What is the incidence of bleeding in patients treated with clopidogrel?

The reported incidence of bleeding with clopidogrel is influenced by patient-related factors, by the use of additional antithrombotic drugs, and by the study design (*Table 1*). In general, estimates of bleeding can be obtained from randomized trials or population studies. Estimates of bleeding risk due to clopidogrel obtained from randomized trials are reliable because baseline characteristics and other unknown potential confounders are balanced between the treatment groups.[20] However, randomized trials generally exclude patients at highest risk of bleeding and may therefore underestimate the true frequency of bleeding associated with clopidogrel use in the general population. In contrast, population studies do not have the same restrictive inclusion criteria as randomized trials but are limited because they do not separate the risk of bleeding due to clopidogrel from the risks of bleeding incurred by the use of other antithrombotic treatments or of invasive procedures.

The definition of bleeding is an important determinant of the reported incidence of major bleeding. Bleeding is usually classified according to clinical or laboratory criteria as major (life-threatening, severe) or minor bleeding (*Table 2*).[20–24] However, bleeding that is defined as 'minor' in one study may be classified as 'major' in another; different definitions of bleeding can lead to as much as a three-fold difference in the reported incidence of major bleeding.[25] In 2005, the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis proposed a single standard definition of bleeding for use in non-surgical studies (*Table 2*).[20] Although the adoption of a single standardized definition will facilitate comparison of bleeding events across studies, it remains to be established whether the proposed ISTH definition is more reliable than existing definitions for identifying clinically relevant bleeding episodes.

Randomized trials

The incidences of major bleeding reported in randomized trials of clopidogrel or clopidogrel-containing dual

Table 1 Determinants of reported bleeding incidence in randomized trials and population studies

Factor	Details
Study-related	
Study design	Randomized trials may include patients at lower risk of bleeding. Community studies or population data may more accurately reflect clinical bleeding risk
Definition of bleeding	More stringent definitions that do not take into account less severe bleeding may underestimate the frequency of clinically important bleeding
Patient factors	
Demographics	Increasing age, female sex
Comorbidities	Diabetes, hypertension, previous stroke, renal impairment, other major organ dysfunction (cardiac, respiratory, hepatic), haemostatic disorders
Treatment factors	
Concomitant therapies	Anticoagulant, antiplatelet, fibrinolytic drugs
Invasive procedures	Angiography, PCI, surgery, intra-aortic balloon pump
Timing of drug administration	Timing of drug administration in relation to procedures

Table 2 Definitions of major or severe bleeding

Name	Definition
GUSTO[21]	Haemodynamic compromise or intracranial haemorrhage
OASIS[22]	Requiring at least 2 unit transfusion, disabling, leading to surgery, intracranial, fatal
TIMI[a23]	Overt bleeding with drop in haemoglobin >5 g/dL or intracranial haemorrhage
ISTH[b20]	Fall in haemoglobin of 2 g/dL or transfusion or leading to a transfusion of 2 or more units or symptomatic in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) or fatal

The GUSTO definition classifies bleeding as severe, moderate, or mild; the TIMI definition classifies bleeding as major, minor, or minimal; and the OASIS definition classifies bleeding as major or minor.

[a]Various modifications of the TIMI criteria have been used.

[b]Definition proposed by the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (2005) for use in clinical investigations of antihaemostatic medicinal products in non-surgical patients.[20]

antiplatelet therapy are summarized in *Table 3*. The absolute increase in bleeding with clopidogrel compared with placebo or control in these trials is up to 1.0%; this risk is likely to be higher in the elderly, female patients, and those with renal impairment or other major comorbidities, some of whom are often not included in randomized trials.

Clopidogrel vs. aspirin

The clopidogrel vs. aspirin in patients at risk of ischaemic events (CAPRIE) randomized trial[1] demonstrated a reduced risk of gastrointestinal bleeding with clopidogrel compared with aspirin (*Table 1*). However, aspirin in this study was given at a dose of 325 mg/day, which is higher than the presently recommended 75–150 mg/day.[13,14] Higher doses of aspirin have not been shown to improve antithrombotic efficacy but increase the risk of bleeding.[26,27]

Clopidogrel plus aspirin vs. aspirin

Five large ($n \geq 1000$) randomized trials involving a combined total of more than 75 000 patients have compared the combination of clopidogrel 75 mg/day (usually preceded by a 300 mg loading dose) and aspirin 75–325 mg/day with aspirin 75–325 mg/day in patients at high risk of future cardiovascular events (*Table 1*).[3,5,6,8,28] Over a mean or median follow-up period of up to 28 months, there were between six and 48 major bleeds for every 1000 patients treated with dual antiplatelet therapy, compared with between six and 38 major bleeds for every 1000 patients treated with aspirin alone. Pre-treatment with clopidogrel was not associated with a reported excess of major bleeding among acute coronary syndrome patients who had PCI.[4,7]

Other clopidogrel studies

The risk of bleeding with aspirin plus clopidogrel is similar to the risk with aspirin plus ticlopidine (*Table 3*).[2] In the MATCH randomized trial comparing the combination of aspirin and clopidogrel with clopidogrel alone in patients with recent ischaemic stroke or transient ischaemic attack,[29] there was a relative increase of 97% and an absolute increase of 13 life-threatening bleeds for every 1000 patients treated with the combination of clopidogrel and aspirin for 18 months.

Observational studies

Subgroup analyses of randomized trials and registry studies have demonstrated an increase in major bleeding with clopidogrel plus aspirin compared with aspirin alone in patients undergoing coronary artery bypass graft surgery, which is similar in magnitude to the increase in risk demonstrated in randomized trials.[18,30–32] In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, there was about a 30% increase in major bleeding with the combination of clopidogrel and aspirin compared with aspirin alone in patients undergoing coronary artery bypass graft surgery. The risk of bleeding was greater when patients continued clopidogrel treatment to within 5 days of surgery; major bleeding occurred during the first week after surgery in 44 per 1000 patients who stopped clopidogrel at least 5 days before surgery, 93 per 1000 patients who stopped clopidogrel 3 days before surgery, and 111 per 1000 patients who stopped clopidogrel the day before the surgery.[30]

Population studies

The Global Registry of Acute Coronary Events (GRACE), involving 94 hospitals in 14 countries, reported a 3.9% incidence of major bleeding in hospital among 24 045 patients with acute coronary syndromes studied between 1999 and 2002 (4.8% in patients with STEMI, 4.7% in patients with NSTEMI, and 2.3% in patients with unstable angina).[10] Patients included in this registry received one or more of the following antithrombotic treatments: aspirin, glycoprotein IIb/IIIa inhibitors, unfractionated heparin, low-molecular-weight heparin, and thrombolysis. The proportion receiving treatment with a thienopyridine was not reported but, except in patients undergoing PCI, is likely to have been low because most data were collected before there was definitive evidence of the effectiveness of clopidogrel in patients with acute coronary syndromes not undergoing an invasive procedure. The 'Can Rapid Risk Stratification of Unstable Angina Patients Suppress

Table 3 Incidence of bleeding in large ($n \geq 1000$) randomized trials of clopidogrel

Trial	Indication	*N*	Patient characteristics					Major bleeding (as defined in the trials)			
			Age[a]	Sex (%)	Concomitant Rx[b]	PCI or CABG (%)	Treatment duration	Clopidogrel (%)	Control (%)	RR(95% CI)	Absolute excess (%)
Clopidogrel vs. aspirin											
CAPRIE[1]	High risk	19 185	62	28	—	NR	1.9 years	2.0[c]	2.7[c]	0.75 (0.62–0.90)	−0.7
Clopidogrel plus aspirin vs. aspirin											
CHARISMA[28]	High risk	15 603	65	30	—	NR	28 months	1.7	1.3	1.25 (0.97–1.61)	—
CLARITY[6]	STEMI	3 491	57	20	Hp or LMWH[d]	100	8 days	1.3	1.1	1.20 (0.66–2.20)	0.2
COMMIT[8]	STEMI	45 852	61	28	Hep[d]	NR	28 days	0.6	0.6	1.07 (0.84–1.36)	—
CREDO[5]	PCI	2 116	62	29	Hep	100	12 months	4.8[e]	3.8[e]	1.29 (0.86–1.93)	1.0
CURE[3]	ACS	12 562	64	38	Hep or LMWH	36	9 months	3.7	2.7	1.38 (1.13–1.67)	1.0
PCI CLARITY[7]	PCI	1 863	57	18	Hep or LMWH[f]	100	30 days	1.1	0.5	0.50 (0.17–1.45)	0.6
PCI CURE[4]	PCI	2 658	62	30	Hep or LMWH[f]	100	30 days	1.6	1.4	1.13 (0.61–2.10)	0.2
Clopidogrel plus aspirin vs. ticlopidine plus aspirin											
CLASSICS[2]	PCI	1 020	60	23	Hep	100	28 days	1.2	1.3	1.12 (0.35–3.63)	—
Clopidogrel plus aspirin vs. clopidogrel											
MATCH[29]	Stroke	7 599	66	37	—	—	18 months	2.6[g]	1.3[g]	1.97 (1.40–2.77)	1.3

A denotes aspirin; ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; Creat, creatinine; F, female; Hep, heparin; LMWH, low-molecular-weight heparin; NR, not reported; PCI, percutaneous coronary intervention; STEMI, ST elevation acute coronary syndrome; W, warfarin.

[a]Mean unless indicated otherwise.

[b]Other antithrombotic drugs used in at least 50% of patients.

[c]Gastrointestinal bleeding. Intracranial bleeding occurred in 0.35% of patients treated with clopidogrel and 0.49% treated with aspirin ($P = \text{NS}$).

[d]Also treated with fibrinolysis.

[e]At 28 days. All patients received clopidogrel 75 mg daily during this time.

[f]More than 80% of patients received open label clopidogrel after PCI.

[g]Life-threatening bleeding. Major bleeding was reported in 1.9% of patients treated with clopidogrel and aspirin vs. 0.6% of those treated with clopidogrel.

Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines' (CRUSADE) Registry reported major bleeding during 2004 in 11.5% of 23 622 high-risk patients with acute coronary syndromes without ST elevation, who did not undergo coronary artery bypass graft surgery.[11] Patients included in this registry were treated with oral antiplatelet drugs, glycoprotein IIb/IIIa inhibitors, unfractionated heparin, and low-molecular-weight heparin, but specific information on the use of aspirin and clopidogrel was not reported. In a separate CRUSADE analysis, blood transfusion was administered in 14.9% of 85 111 patients and 10.3% of 74 271 patients who did not undergo CABG surgery.[12] The incidence of transfusion increased with the increasing number of antithrombotic drugs used.

In summary, these data indicate that adding clopidogrel to aspirin increases the relative risk of bleeding by up to 50% and the absolute risk by up to 1%, equivalent to an excess of up to 10 major bleeds for every 1000 patients treated. There is a similar relative increase in major bleeding among patients treated with clopidogrel plus aspirin (compared with aspirin) undergoing PCI or coronary artery bypass graft surgery, but the risk is further increased in patients who stop clopidogrel less than 5 days before surgery, equivalent to an excess of up to 50 major bleeds for every 1000 patients treated.

What is the prognostic importance of major bleeding?

Until recently, bleeding that is classified as major but not life-threatening has been thought of as a reversible event that is not associated with long-term sequelae. There is, however, a growing body of evidence that both major and minor bleeding are independently predictive of adverse clinical outcomes, including myocardial infarction, stroke, and death. Major bleeding is associated with a two- to eight-fold increase in the risk of death among patients with acute coronary syndromes[9,10,12,33] or undergoing PCI.[9,34] The relation appears to be consistent, dose-related (increasing severity of bleeding is associated with increased risk of death), and independent of patient baseline characteristics and cointerventions (including the use of clopidogrel), which might potentially confound this relation. A similar relation has been demonstrated between bleeding and ischaemic outcomes, such as myocardial infarction and stroke.[9,33]

Although a causal link between bleeding and adverse outcome has not been established, there are several, biologically plausible mechanisms linking bleeding with an increased risk of ischaemic events and death. First, bleeding can reduce oxygen delivery to the myocardium, either as a result of hypoperfusion or by lowering blood haemoglobin levels.[35] Further, by increasing heart rate and stroke volume, lower haemoglobin levels increase myocardial oxygen demand, thereby exacerbating ischaemia. Secondly, major bleeding usually leads to discontinuation of antithrombotic drugs, thereby increasing the risk of myocardial infarction, stroke, and death; this effect is likely to be greatest in those with more severe bleeding. Thirdly, bleeding can result in platelet activation, which in turn can precipitate recurrent ischaemic events. Fourthly, transfusion may cause adverse outcomes because stored red cells are depleted of intracellular 2,3 diphosphoglycerate, thereby increasing haemoglobin's affinity for oxygen. Stored red cells may, therefore, act as an oxygen sink, pulling oxygen out of tissues and away from normal red blood cells.[36] Stored red cells are also depleted of nitric oxide (NO) and so may act as an NO sink, thereby resulting in vasoconstriction and reduced oxygen carriage of the blood.[37] Red cells stored for a longer period of time are more depleted of 2,3 diphosphoglycerate and NO than cells stored for shorter periods and are more fragile and less distensible.[36] The supernatant plasma in stored blood is replete with cytokines that are capable of activating endothelial cells and inducing tissue factor production, thereby activating coagulation. Despite its biological plausibility, however, results of clinical studies of the association between transfusion and risk of ischaemic events or death are conflicting.[38–40]

What are the implications for clinical practice and future research?

Clinical practice

Bleeding is inconvenient in its mildest form, potentially life-threatening or even fatal when severe, and represents a major health care cost by precipitating or prolonging hospitalization or leading to transfusion or surgical intervention.[41–43] The recent reports of a strong association between major bleeding and ischaemia raise the possibility of an additional disadvantage and suggest that when choosing antithrombotic regimens, clinicians should pay closer attention to the risk of bleeding than they have in the past.

Although clopidogrel increases the risk of bleeding, it is a proven effective antiplatelet drug for preventing myocardial infarction and recurrent ischaemia and is associated with a clear net clinical benefit. Therefore, it should be used either alone or in combination with other antithrombotic agents when indicated, on the basis of evidence from clinical trials. Strategies aimed at reducing the risk of bleeding should ensure that clinical benefit is not compromised. For example, if indicated, aggressive antithrombotic treatment should not be avoided in patients at high risk of bleeding because they are likely also to be at high risk of ischaemic events and thus have the potential to achieve greater absolute benefits from clopidogrel.[44]

Strategies that may reduce the risk of bleeding in patients treated with clopidogrel include: careful selection of patient for invasive procedures;[45] appropriate dosing of concomitant antithrombotic drugs;[11] use of the lowest proven effective dose of aspirin;[26] avoidance of combinations of multiple antithrombotic agents unless they are of proven benefit;[12,46,47] and discontinuation of clopidogrel at least 5 days prior to coronary

artery bypass graft surgery, except in unstable or very high-risk patients.[30,48]

Treatment of acute bleeding

The general principles of management of major bleeding also apply to patients who bleed during clopidogrel treatment and include temporary discontinuation of antithrombotic drugs, resuscitation with intravenous fluid, packed red cell transfusion, and surgical or other procedures to control the bleeding. The only way to overcome the antiplatelet effect of clopidogrel is with platelet transfusions because clopidogrel irreversibly inhibits platelet function for the life of the platelet, and there is no known antidote. In the case of gastrointestinal bleeding, where bleeding can be controlled with endoscopic injection and mechanical methods (e.g. thermal coagulation, placement of a haemoclip), the withdrawal of clopidogrel may not be necessary, particularly in patients at high risk of stent thrombosis. Other treatments that can be considered in patients who develop major bleeding during clopidogrel treatment include DDAVP,[49] antifibrinolytic drugs (aprotinin, aminocaproic acid, tranexamic acid),[50] and recombinant factor VIIa,[51] although none of these treatments directly reverse the platelet-inhibitory effects of clopidogrel.

Research implications

The outstanding research issues are: (i) to establish whether or not the association between bleeding and recurrent ischaemic events or death is causal; and (ii) if causal, to determine the mechanism(s) responsible for the causal relationship.

Establishing causality

Resolving the issue of causation is challenging because patients at increased risk of bleeding are also at increased risk of death from ischaemic causes and therefore cannot be randomized to receive less intensive antithrombotic therapy. In the absence of evidence from randomized trials, a causal association would be strongly supported by showing that the risk of ischaemic events or of death would be reduced by reducing the incidence or severity of bleeding. For example, a causal relation would be suggested if haemostatic agents such as tranexamic acid could be shown to reduce both bleeding and death. A causal association between bleeding and death would also be suggested by demonstrating that the relation is consistent across different studies using different antithrombotic agents or other interventions that cause bleeding, that the association is strong, dose-related, and independent of differences in baseline characteristics and cointerventions.

Exploring mechanisms

Possible putative mechanisms to explain the association can be investigated by collecting descriptive data on the following in patients who did and did not suffer a major bleed: (i) changes in oxygen delivery and demand; (ii) discontinuation of antithrombotic drugs (type and duration of drug discontinued); (iii) extent of platelet activation; and (iv) transfusion of red blood cells (age and number of packs transfused). In addition, randomized trials can be performed in patients who develop major bleeding to compare the effect on clinical outcome of: (i) strategies that optimize myocardial oxygen delivery and uptake with usual care; (ii) early with delayed recommencement of antithrombotic drugs after major bleeding; (iii) the effect of transfusion of recently collected red blood cells (e.g. stored for less than 5 days) with red blood cells that have been stored for an extended period (e.g. stored for more than 5 days); and (iv) restrictive vs. liberal transfusion strategy, by transfusing patients at a lower vs. higher haemoglobin threshold.

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