Coronary Intervention in Patients With Diabetes, Chronic Renal Disease, and the Elderly: Therapeutic Implications

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Patients with diabetes mellitus, chronic renal disease, or advanced age who are undergoing percutaneous coronary intervention are at an increased risk of bleeding and thrombosis. This article reviews the clinical implications of these conditions and discusses the therapeutic options currently available for these patient groups.
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Key words: Percutaneous coronary intervention • Prothrombotic state • Plasminogen activator inhibitor 1 • Diabetes mellitus • Chronic renal disease • Thrombosis

Three groups who present unique challenges during percutaneous coronary intervention (PCI) include patients with diabetes mellitus, patients with chronic renal disease, and the elderly. Although these conditions may coexist, they are each independently associated with an increased risk of death after PCI.[1,2] This review will discuss the implications of risks associated with these conditions, potential mechanisms responsible for the risks, and therapeutic strategies designed to optimize outcomes.

Diabetes Mellitus

Diabetes confers a 2-fold to 3-fold increased risk of myocardial infarction, stroke, and cardiovascular death.[3] The Bypass Angioplasty Revascularization Investigation (BARI) identified diabetes as a condition that is associated with a greater risk of death after coronary intervention (balloon angioplasty) compared with surgical revascularization.[4] Despite advances in technology (stents, drug-eluting stents) and pharmacology, patients with diabetes continue to have a greater risk of cardiovascular events after PCI.[5,6] One factor contributing to a greater risk of complications after coronary intervention is a higher incidence of restenosis due to exaggerated intimal hyperplasia.[5-7] Drug-eluting stents have been an effective strategy to combat the greater incidence of restenosis.[5,6] Another risk factor is a prothrombotic state that increases the risk of thrombosis after coronary intervention in patients with diabetes.[8]

The Prothrombotic State of Diabetes

Diabetes mellitus is a prothrombotic state that not only increases the rate of progression of atherosclerosis, but also increases thrombosis in response to plaque rupture and after coronary intervention.[8-10] Patients with diabetes exhibit increased platelet activity, greater activation of the coagulation cascade, increased thrombin production, and decreased fibrinolysis.

Evidence of increased activity of platelets is reflected by increased concentrations in blood of soluble CD40 (a platelet released mediator of thrombosis and inflammation) and P-selectin (reflecting platelet activation).[11] Patients with diabetes, particularly those with macrovascular disease, have an increased circulating platelet mass and a higher ploidy of megakaryocytes.[12] In addition, platelets isolated from the blood of subjects with diabetes exhibit impaired capacity to mediate vasodilatation.[13,14] The threshold for release of the contents of dense granules in response to thrombin is lower with platelets from patients with diabetes.[15] Thus, platelet activation and aggregation in response to agonists (ie, platelet reactivity) is increased in patients with type 2 diabetes.[15-18] Insulin decreases platelet aggregation and adhesion in patients without diabetes, an effect not seen in those with type 2 diabetes.[17] In addition, the procoagulant capacity of platelets from subjects with diabetes mellitus is increased.[19,20] The generation of coagulation factor Xa and thrombin is increased by 3-fold to 7-fold in blood from patients with diabetes compared with those without diabetes.[20] Accordingly, prothrombotic platelet function contributes to the greater risk of thrombosis seen in patients with diabetes.

One mechanism potentially contributing to greater platelet reactivity in patients with diabetes is osmotic effect of hyperglycemia.[21] Consistent with this observation, the likelihood of no reflow and reocclusion after treatment of acute ST elevation myocardial infarction with PCI is increased in patients with hyperglycemia.[22] Another mechanism potentially contributing to increased platelet reactivity associated with diabetes is reduced bioavailability of nitric oxide.[23]

Activation of the coagulation system leads to the generation of thrombin and thrombin-mediated formation of fibrin, which is converted from fibrinogen. The generation of thrombin depends on activation of procoagulant factors, and is limited by antithrombotic factors and inhibitors. Fibrinopeptide A (FPA), released when fibrinogen is cleaved by thrombin, has a very short half-life in the circulation and is cleared promptly by the kidneys. Thus, FPA is a marker of thrombin activity. Subjects with diabetes mellitus (both type 1 and 2) have increased concentrations of FPA in blood and urine compared with subjects without diabetes.[24-26] The highest concentrations are observed in patients with clinically manifest vascular disease.[24,26]

Patients with type 2 diabetes have increased concentrations of coagulation factors including tissue factor, fibrinogen, factor VII, and factor VIII.[11,27-30] Fibrinogen is strongly associated with the risk of developing cardiovascular disease.[27] Hyperinsulinemia in subjects with insulin resistance associated with obesity and early stages of type 2 diabetes may contribute to increased activity of the coagulation cascade.[31-33]

Insulin resistance, obesity, and type 2 diabetes mellitus are associated with the impairment of fibrinolytic system capacity and increased concentrations of plasminogen activator inhibitor 1 (PAI-1), the primary physiologic inhibitor of fibrinolysis.[34,35] Mechanisms responsible are multifactorial and include increased adipose tissue that produces PAI-1,[36] increased concentrations of cytokines and growth factors that have agonist effects on the expression of PAI-1,[37] and direct effects on expression of PAI-1 by insulin and precursor proinsulin. These mechanisms are additive or synergistic with metabolic abnormalities that include hyperglycemia, hypertriglyceridemia, and increased concentrations of free fatty acids in blood.[38] Increased expression of PAI-1 impairs fibrinolysis and the fibrinolytic response to thrombosis and promotes exaggerated, persistent thrombosis.

In summary, the prothrombotic state of diabetes mellitus exhibits increased platelet activity, acute

activation of the coagulation cascade, and decreased fibrinolysis. Contributing factors include metabolic abnormalities, hormonal dysregulation (insulin resistance), and elevated concentrations of cytokines and growth factors. Expectedly, targeting one component or one contributing factor of the prothrombotic state is not sufficient to neutralize the associated risk. Thus, more intense antithrombotic therapy that combines treatments affecting both the coagulation cascade and platelet activity is likely to be most effective in attenuating the prothrombotic state.

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Therapeutic Implications

Antithrombotic therapy is central to the care of patients with diabetes mellitus because of the prothrombotic state and the associated high prevalence of atherosclerosis. Consensus guidelines recommend primary and secondary prevention with aspirin for patients with type 2 diabetes. Recent results suggest that primary prevention with aspirin may be associated with less beneficial effects in patients with diabetes compared with patients who have other (non-diabetes) cardiovascular risk factors.[39] However, these results do not demonstrate a limited therapeutic effect of aspirin in patients with diabetes or an inadequate suppression of the prothrombotic state. Additional mechanistic studies are required to explain this observation. These results should prompt studies with newer antithrombotic agents, and in the interim, aspirin should be prescribed regularly to patients with diabetes.

Treatment with the combination of aspirin plus clopidogrel is recommended after acute coronary syndromes and coronary stenting. This is because patients with and without diabetes demonstrated a benefit when treated with aspirin plus clopidogrel after an acute coronary syndrome and PCI.[40,41] However, recent results suggest limited therapeutic efficacy of clopidogrel in patients with diabetes, particularly those treated with insulin.[42,43] These results may explain why a greater demonstration of efficacy was not apparent in patients with diabetes.[40,41] Similar to the results with aspirin, these results should prompt additional studies with novel agents and dosing regimens. Until those results are available, however, the combination of aspirin plus clopidogrel should be used in accordance with consensus guidelines after acute coronary syndromes and coronary stenting.

When combined with aspirin plus unfractionated heparin, glycoprotein (GP) IIb/IIIa antagonists exhibited benefit in patients with diabetes. In patients with acute coronary syndromes and diabetes, upstream treatment with tirofiban was associated with a greater reduction in the incidence of cardiac events than in patients who did not have diabetes.[44] Meta-analysis demonstrated that treatment with GP IIb/IIIa antagonists reduced the incidence of death in patients with diabetes and suggested that the majority of the benefit was seen in patients undergoing coronary intervention.[45] Accordingly, unlike aspirin and clopidogrel, GP IIb/IIIa inhibitors have been associated with greater efficacy in patients with diabetes mellitus. One contributing factor to this greater efficacy is that glycation of GP IIb/IIIa decreases the binding rate of fibrinogen to the activated conformer of GP IIb/IIIa without affecting the binding rate of GP IIb/IIIa antagonists.[46] Thus, the extent of inhibition exerted by GP IIb/IIIa antagonists is greater with platelets from patients with diabetes than from those without diabetes.[46]

The greater prevention of ischemic events seen with GP IIb/IIIa antagonists may, however, be dependent upon its use in combination with heparin as the anticoagulant. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, a diagnosis of diabetes (present in approximately 28% of participants) was not associated with a lower incidence of ischemic complications in patients treated with GP IIb/IIIa antagonists. The incidence of ischemic complications was similar in patients randomized to bivalirudin alone compared with heparin plus a GP IIb/IIIa antagonist.[47] Further, the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial demonstrated a similar incidence of ischemic complications after 30 days among patients with and without diabetes who were undergoing PCI.[48] A non-significant trend toward a lower rate of death after 1 year was seen in patients with diabetes treated with bivalirudin.[48]

The mechanism(s) responsible for the seemingly contradictory finding of greater efficacy associated with the use of GP IIb-IIIa antagonists in patients with diabetes who are treated with heparin plus aspirin and clopidogrel yet a similar incidence of ischemic complications in patients with diabetes who were treated with

bivalirudin combined with aspirin and clopidogrel compared with heparin plus a GP IIb-IIIa antagonist combined with aspirin plus clopidogrel has not been defined. As described previously, the prothrombotic state of diabetes exhibits increased activity both of platelets and the coagulation cascade. Thus, one potential explanation for this contradiction is that the greater efficacy of bivalirudin in suppressing thrombin activity in patients with diabetes may offset the effect of GP IIb/IIIa antagonists on platelet aggregation. Accordingly, therapeutic strategies have emerged for patients with diabetes undergoing PCI. All patients should be treated with aspirin plus clopidogrel after acute coronary syndromes and coronary stenting until more effective alternatives are available. When heparin is used as the anticoagulant during PCI, GP IIb/IIIa antagonists are indicated to prevent ischemic complications. A second strategy could be the use of bivalirudin without the addition of GP IIb/IIIa antagonists, which results in a similar incidence of ischemic complications and a lower incidence of bleeding complications.

Chronic Renal Disease

Cardiac disease is the primary cause of death in patients undergoing long-term dialysis. It accounts for 44% of deaths, 50% of which are attributable to acute myocardial infarction.[49] Cardiovascular mortality is more than 10 times greater in patients with end-stage renal disease (ESRD) than in the general population.[50] Patients undergoing long-term dialysis have a particularly poor rate of survival after myocardial infarction.[51] Moreover, the incidence of major adverse cardiac events after percutaneous revascularization and mortality after coronary bypass surgery is increased.[52,53] Bleeding is a common problem in patients with ESRD. Accordingly, patients with chronic renal disease exhibit both deficient hemostasis associated with a greater risk of bleeding and an increased incidence of thrombotic arterial occlusion leading to myocardial infarction.

Thrombosis and Hemostasis in Chronic Renal Disease

In the REPLACE-2 trial, overall, renal impairment (defined as a creatinine clearance < 60 mL/min) was associated with a greater risk of ischemic (hazard ratio, 1.45; $P = .004$) and bleeding events (hazard ratio, 1.72; $P = .028$), regardless of treatment.[54] Consistent with these findings, primary coronary intervention for acute myocardial infarction in patients with renal impairment has been associated with a 2-fold increased risk of bleeding and reocclusion of the infarct-related artery.[55] Accordingly, chronic renal disease is associated with a seemingly contradictory combination of both a greater risk of bleeding and a greater risk of thrombosis.

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Abnormalities of platelet adhesion and aggregation appear to be the major cause of deficient hemostasis associated with uremia.[56-58] Perhaps paradoxically at first glance, platelet reactivity (ie, the propensity of platelets to activate) is increased in patients with ESRD undergoing hemodialysis.[59-61] In addition, dialysis appears to activate platelets.[60,61] However, insight into these effects is provided by experiments in which the components of blood (plasma and isolated platelets) from normal subjects and patients with uremia are mixed. These results demonstrate that abnormalities of plasma proteins contribute to the inability of platelets to adhere and aggregate.[62] Thus, renal impairment appears to alter the function of both plasma proteins and platelet surface proteins and thereby attenuates adhesion and aggregation, which promote bleeding. By contrast, increased platelet reactivity and platelet activation that is induced by hemodialysis promote thrombosis. Thus, the patient with chronic renal disease presents a unique therapeutic challenge because of a greater risk both for bleeding and thrombosis.

Therapeutic Implications

Even mild renal dysfunction is associated with a greater risk of cardiovascular complications after myocardial infarction.[63] Unfortunately, the use of therapies such as aspirin is less common in those with greater impairment of renal function.[63] Clinical results currently available do not clearly demonstrate the efficacy of antithrombotic regimens in patients with renal impairment. Additional studies are needed to define optimal long-term antithrombotic therapy for patients with chronic renal disease. In the interim, consensus recommendations for the use of aspirin and clopidogrel should be implemented.

When patients were treated with GP IIb/IIIa antagonists, a greater extent of renal dysfunction was associated with an increased risk of ischemic complications as well as major and minor bleeding after PCI.[64] A similar finding was apparent in the REPLACE-2 trial.[54] Patients with renal impairment had a greater risk of bleeding. However, the relative

benefit associated with bivalirudin was maintained regardless of the extent of renal dysfunction. A meta-analysis demonstrated that the absolute benefit with respect to the incidence of ischemic and bleeding complications was progressively greater with decreasing creatinine clearance when patients were treated with bivalirudin compared with the combination of heparin plus a GP IIb/IIIa inhibitor.[65] In the ACUITY trial, major bleeding was found to be a powerful predictor of death during the month after PCI.[66] Patients with chronic renal disease undergoing PCI are a group with a high incidence of bleeding and ischemic complications. Bivalirudin is associated with the lowest incidence of complications when bleeding and ischemia are combined. Further, the lower incidence of bleeding complications in patients treated with bivalirudin may have long-term implications on survival. When patients with chronic renal disease are treated with heparin plus a GP IIb/IIIa inhibitor, particularly eptifibatide, dose adjustment is appropriate in an effort to reduce the risk of bleeding.[67]

Advanced Age

Advanced age is a universally identified predictor of an increased risk of major complications, including death. It is an independent predictor of death after myocardial infarction[68,69] and death after PCI.[1] The extensive comorbidities that accompany advanced age are likely responsible for the increase of risk. These include renal impairment that may not be adequately recognized, extensive vascular disease, and concomitant disease of other organ systems. Although the elderly are at an increased risk of death, the incidence of reinfarction does not appear to be increased, and the elderly have not been described as a group exhibiting a prothrombotic state. However, a particularly prominent risk for elderly patients is bleeding.[70]

Risk of Bleeding in the Elderly

Advanced age is a powerful predictor of major bleeding after PCI.[66,71] In the Global Registry of Acute Coronary Events (GRACE), treatment of patients greater than 75 years of age with GP IIb/IIIa antagonists was associated with a high (> 8%) risk of major bleeding complications.[70] As mentioned previously, bleeding was found to be a powerful predictor of mortality in the ACUITY trial.[66] Accordingly, the balance between risk of bleeding and prevention of ischemic complications is particularly important in the elderly.

Therapeutic Implications

The risk of bleeding, including intracranial bleeding, increases with age. Consistent with this observation, the risk of bleeding associated with antithrombotic treatments is greater in the elderly. In the Stroke Prevention in Atrial Fibrillation II trial, treatment with aspirin was associated with a 0.8% incidence of intracranial bleeding in those over age 75 and 0.2% in those under age 75.[72] In light of the beneficial effects of aspirin and the greater prevalence of vascular disease in the elderly, it is generally accepted that the beneficial effects of aspirin outweigh any additional risk.[73] Consistent benefits, such as reduction in the incidence of ischemic events, of clopidogrel without a major increase in the risk of bleeding have also been reported in the elderly.[74] Accordingly, treatment with aspirin plus clopidogrel after an acute coronary syndrome or coronary stenting combined with long-term therapy with aspirin is likely to provide therapeutic benefit, despite a greater risk of bleeding.

Treatment of the elderly with heparin plus a GP IIb/IIIa antagonist is associated with a substantial risk of bleeding.[66,70,71] Because the incidence of ischemic complications is similar in patients treated with bivalirudin or heparin plus a GP IIb/IIIa inhibitor, and the risk of bleeding is significantly lower in patients treated with bivalirudin, adjunctive treatment with bivalirudin during PCI reduces the incidence of complications in the elderly.[47]

Summary

Patients with diabetes, chronic renal disease, and the elderly pose unique challenges during PCI. Patients with diabetes exhibit a prothrombotic state. Limited efficacy of long-term therapy with aspirin and clopidogrel may be addressed with newer antithrombotic regimens. However, GP IIb/IIIa antagonists are indicated in patients with diabetes when heparin is used as the anticoagulant. Recent results suggest that bivalirudin may also be an effective alternative.

Patients with chronic renal disease pose a unique challenge because of the concomitant risk factors of bleeding and thrombosis. A greater benefit is seen in patients treated with bivalirudin who have a more severe impairment of renal function.

Elderly patients are at greater risk of all complications. Because the risk of bleeding increases substantially in patients older than 75 years of age who are treated with heparin plus a GP IIb/IIIa inhibitor, bivalirudin is an alternative that leads to a similar

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Main Points

- In patients who have diabetes mellitus, one factor contributing to a greater risk of complications after coronary intervention is a higher incidence of restenosis due to exaggerated intimal hyperplasia. Another risk factor is a prothrombotic state that increases the risk of thrombosis after coronary intervention in patients with diabetes.
- The prothrombotic state of diabetes mellitus exhibits increased platelet activity, greater activation of the coagulation cascade, and decreased fibrinolysis. Contributing factors include metabolic abnormalities, hormonal dysregulation (insulin resistance), and elevated concentrations of cytokines and growth factors.
- Patients with chronic renal disease exhibit both deficient hemostasis associated with a greater risk of bleeding and an increased incidence of thrombotic arterial occlusion leading to myocardial infarction.
- Advanced age is a universally identified predictor of an increased risk of major complications, including death. It is an independent predictor of death after myocardial infarction and death after percutaneous coronary intervention. The extensive comorbidities responsible for the increase of risk include renal impairment, extensive vascular disease, and concomitant disease of other organ systems.

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