Coping with new challenges in acute coronary syndromes

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The acute coronary syndromes have become well-established clinical entities and are used as working diagnoses tied in with elaborate investigation and treatment practice guidelines. However, these syndromes remain challenging because their prevalence, morbidity and mortality remain high. Furthermore, these syndromes are demanding on the health care system because an early invasive management strategy is recommended for most patients with these conditions. Coping with these challenges requires the following initiatives: stepping beyond current diagnostic and management algorithms to a better performing risk stratification scheme that considers specific patient risk factors in addition to the disease risk, and a reintegration of acute coronary syndromes into the more global perspective of coronary artery disease; more effective antithrombotic therapy that does not further compromise bleeding risk, or drugs that control thrombogenic stimuli; and medical and revascularization therapies targeted to more specific individual pathophysiologies identified by novel blood markers and imaging techniques.

Key Words: Anticoagulants; Antiplatelet drugs; Pathophysiology; Risk stratification; Treatment

Acute coronary syndromes (ACS) have been at the edge of practice in cardiology and of clinical research in coronary artery disease (CAD) over the past 25 years. Numerous new hypotheses and innovative drugs have been proposed, some successful, others failing, but overall, patient care has progressively improved. The following developments have been pivotal in this success: the recognition of the etiological role of intravascular thrombus formation and, subsequently, of inflammation in destabilizing plaques; better outcomes using antithrombotic therapy in these syndromes, as well as timely reperfusion in ST segment elevation myocardial infarction (STEMI); regression of atherosclerosis with lifestyle adjustments and appropriate drug therapy; and immediate relief of severe obstruction with percutaneous revascularization procedures (percutaneous coronary intervention [PCI]). However, ACS are still challenging because the prevalence, morbidity and mortality of these syndromes remain high. Furthermore, their management requires highly specialized care with a need for transfer for coronary angiography with a view to revascularization.

By having a rich background in epidemiological sciences, molecular biology and genetics, clinical trial design, guideline recommendations, quality controls, and rapidly evolving diagnostic and therapeutic procedures, there is a realistic hope for

Relever les nouveaux défis du syndrome coronarien aigu

Le syndrome coronarien aigu est une entité clinique bien établie qui est souvent utilisée comme diagnostic provisoire dans la foulée des directives de pratique thérapeutiques et diagnostiques élaborées à ce jour. Par contre, ce syndrome reste un défi, compte tenu de sa prévalence et de la morbidité et de la mortalité élevées qui y sont associées. En outre, cette entité est lourde pour le système de soins de santé puisqu'une stratégie thérapeutique efficace précoce est recommandée chez la plupart des patients qui en sont atteints. Pour relever ces défis, il faut aller au-delà des algorithmes diagnostiques et thérapeutiques actuels et établir un schéma plus adéquat de stratification du risque qui tienne compte des facteurs spécifiques à chaque patient et du risque associé à la maladie; dans cet ordre d'idée, il faut réintégrer le syndrome coronarien aigu dans la perspective plus globale de la coronaropathie, et envisager un traitement antithrombotique plus efficace, qui n'aggrave pas davantage le risque hémorragique, des médicaments qui contrôlent les stimuli thrombogènes et des interventions de pharmacothérapie et/ou de revascularisation ciblées en fonction de physiopathologies individuelles plus spécifiquement identifiées au moyen de marqueurs sanguins et de techniques d'imagerie plus récentes.

new breakthroughs in the near future that will lead to more comprehensive control of the disease. Achieving this control requires the recognition of the opportunities that emerge around us for coping with needs that are as yet unmet and/or unrecognized, and also by reintegrating ACS into the broad spectrum of CAD in general. The present article offers some thoughts in that direction by focusing on risk stratification, pathophysiology, recent trials, and novel diagnostic and therapeutic strategies.

RISK STRATIFICATION: BEYOND THE TRADITIONAL RISK MARKERS

The INTERHEART study (1) identified cigarette smoking and an abnormal ratio of blood lipids (apolipoprotein B to apolipoprotein A1) as the two most important risk factors for heart attacks, accounting for two-thirds of the risk worldwide in a study group of 15,152 individuals with a first heart attack and 14,820 matched controls with no heart disease. Additional risk factors in the study were high blood pressure, diabetes, abdominal obesity, stress, a lack of daily consumption of fruits and vegetables, and a lack of daily exercise, whereas regular consumption of small amounts of alcohol was modestly protective. Altogether, these nine factors predicted more than 90% of the risk of a heart attack worldwide (1).

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Figure 1) Schematic representation of coronary artery disease at various stages with corresponding mechanisms, prognoses and therapies. ACEIs Angiotension-converting enzyme inhibitors; ARBs Angiotensin II receptor blockers; ASA Acetylsalicylic acid; Ca²⁺ ant Calcium antagonists; GP Glycoprotein; IV Intravenous; LMWH Low-molecular-weight heparin; NSTEMI Non-ST segment elevation myocardial infarction; STEMI ST segment elevation myocardial infarction; UA Unstable angina; UFH Unfractionated heparin

These epidemiological data on atherosclerosis emphasize the worldwide magnitude of the problem and the need for a cohesive multidisciplinary effort in society toward the control of risk factors. For medical doctors, the effort starts with the physician-patient partnership.

However, additional issues are present in ACS that need to be better understood and addressed. These issues include the immediate pathophysiological mechanisms that result in plaque destabilization, the reasons why the atherosclerotic process turns excessively inflammatory and thrombogenic in some patients, and why the impaired prognosis can perpetuate long past the acute phase.

The fundamentals for the risk stratification algorithms formulated by the American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines for the management of unstable angina/non-STEMI (UA/NSTEMI) ACS rely on markers of ischemia and its severity. These markers essentially are pain, elevations in troponin T or I, or creatine kinase-MB levels, and ST segment shifts. The troponins are sensitive markers of cell necrosis caused by a severe obstruction and/or distal microembolization of thrombotic material from the culprit lesion and, therefore, indirectly of an intracoronary thrombus. ST segment depression suggests ischemia and, when the changes are dynamic and associated with symptoms, a rapidly progressive stenosis that impedes blood flow. These markers are now routinely used.

The time may have come, however, for other markers that pertain to the activity of the atherosclerotic process to be added to risk stratification schemes. Many of these markers have been very well validated, such as older age, an inflammation state, diabetes and renal failure. Their integration into the framework of ACS could help to improve patient care and bridge ACS with other forms of CAD.

In the multicentre, prospective Canadian ACS Registry that enrolled more than 4500 patients hospitalized for STEMI

or UA/NSTEMI across Canada, each age increment (from younger than 65 years, to between 65 and 75 years, to 75 years or older) predicted a 1.87-fold increase in the odds of death at one year ($P < 0.001$) (2). Decreases in creatinine clearances of 90 mL/min or greater, between 60 mL/min and 89 mL/min, between 30 mL/min and 59 mL/min, and less than 30 mL/min were associated with one-year mortality rates of 2.8%, 6.4%, 14.5% and 40.9%, respectively (3). Diabetes also predicted the one-year mortality after adjustment for other validated prognosticators ($OR = 1.47$; $P = 0.002$). Noteworthy, each one of these three high-risk conditions was associated with significantly less use of cardiac catheterization and PCI in-hospital, and of guideline-recommended medications in-hospital at discharge and after one year.

PATHOPHYSIOLOGY

The culprit lesion(s) and the disease

Pathology and angiographic studies have linked the mechanisms of ACS to rupture of a plaque triggering the formation of an intravascular thrombus, the so-called culprit lesion. Such a culprit lesion is indeed most often found at angiography in ACS patients. Cardiologists and invasive cardiologists subsequently extended this concept to include detection of plaques prone to rupture, with a view of intervening on these plaques to prevent the occurrence of ACS. Promising results have been obtained along this line, with plaque characterization by nuclear magnetic resonance and other methods (4). Although attractive, the concept of prophylactic PCI has some limitations. First, most plaque ruptures develop on plaques of only moderate severity, and second, the culprit lesion in many patients may not be unique, but represents a more diffuse pan-coronary disease and, in some cases, a diffuse vascular disease. Thus, the total number of plaques in coronary arteries, whatever their severity, is a strong predictor of accelerated progression of the disease and of the subsequent prognosis. Figure 1 illustrates the spectrum of the disease from the 'cold' stable fibrotic plaque that can long remain unchanging to the 'warm' unstable plaque that is prone to rupture; a gradient in the intensity of inflammation exists between these two extremes, as well as a large overlap in clinical manifestations. Blood and cell inflammation markers, and eventually the blood proteomic profile, may become most useful to identify these patients with lesions and disease at risk.

Thrombus formation

Role of coagulation factors: Tissue factor (TF) expressed by the diseased endothelium and by monocytes within the plaque is the main trigger for intracoronary thrombus formation (Figure 2). TF can also be found in the circulating blood where it is expressed by monocytes and by microparticles released from activated monocytes, and may play a role in the formation of thrombi at a distance from the culprit lesion. When exposed to circulating blood, TF forms a complex with factor VII (TF-FVIIa). This complex activates coagulation factors IX and X. Activated factor X (FXa), while generating a small amount of thrombin from prothrombin, forms a binary complex with the TF pathway inhibitor. This binary complex forms a quaternary complex with TF-FVIIa to become inhibitory to TF-FVIIa itself, thus preventing new FXa formation (Figure 2). Relatively strong thrombogenic stimulation is required to overcome this inhibitory pathway to TF-FVIIa and

allow the generation of more thrombin. Once formed, however, one molecule of thrombin can cleave numerous fibrinogen molecules, while amplifying its own generation by activating factors V and VIII. Thrombin also activates factor XI on the platelet surface to promote the generation of activated factor IX, which is also a potent platelet agonist. The platelet effects of thrombin are mainly mediated through specific protease-activated receptors (PARs); in this, thrombin cleaves the receptor to expose a new amino terminus that acts as a tethered ligand to initiate transmembrane signalling. Four PAR receptors have been identified. PAR-1 is the main receptor on human platelets with also some role for PAR-4 and glycoprotein (GP) Ib.

Role of platelets: The activation of platelets results in a number of changes that profoundly modify their behaviour. The membrane is polarized into a procoagulant surface, facilitating the assembly of the coagulation complexes on their surface. Intracellular signalling occurs and results in an increase in intracellular Ca^{2+} content and the secretion of numerous active compounds, including P-selectin, procoagulant and proaggregant factors, proinflammatory cytokines such as interleukin (IL)-1 beta, chemokines such as CD40 ligand and RANTES (regulated on activation, normal T cell expressed and secreted), and growth factors such as transforming growth factor-beta and platelet factor 4. P-selectin binds glycoprotein ligand-1 on neutrophils and monocytes to facilitate their activation, rolling, and adhesion to the endothelium. Cytokines mediate interactions between inflammation and thrombosis, and growth factors mediate the rapid progression of atherosclerosis. Platelet activation is also associated with the activation of the GPIIb/IIIa receptors, making them competent to bind fibrinogen. Fibrinogen is a heterodimeric molecule that cross links platelets, resulting in platelet aggregate formation and the platelet clot.

TREATMENT

The goal for the treatment of CAD is to prevent acute ischemic events and vascular death, with specific targets set at various stages of the disease, from a predisease state with risk factors present to a disease state that progresses from an asymptomatic phase to stable manifestations and to unstable states including ACS and STEMI (Figure 1). Treatment usually becomes more intensive as the manifestations of the disease become more severe and/or begin to have an impact on prognosis. This is evaluated by the clinical evolution and, as needed, by provocative testing, left ventricular function studies, biological markers and various imaging methods. Symptoms should not be overlooked because they are useful markers of an increased risk. In the REduction of Atherothrombosis for Continued Health (REACH) Registry (5), symptoms as such were associated with a twofold to threefold increase in the risk of a major outcome event compared with no symptoms. New drugs are usually added to previous therapies. Thus, both antithrombotic drugs and risk factor control are intensified when an ACS develops.

Primary prevention

Primary prevention essentially implies the control of risk factors by lifestyle adjustments and drugs as needed. Statin therapy is indicated in selected individuals to prevent acute events, death and progression of atherosclerosis, and acetylsalicylic acid therapy is indicated to prevent acute thrombotic events.

Figure 2 Schematic representation of the mechanisms regulating the initial steps in intravascular coagulation. Tissue factor (TF), when expressed by endothelial cells, monocytes (mono)/macrophages, and their microparticles, binds factor VII (FVII) in the circulation (TF-FVIIa). Activated factor X (FXa) converts prothrombin (factor II) to thrombin (activated factor II [IIa]) and also binds the TF pathway inhibitor (TFPI). The active binary complexes are TF-FVIIa and TFPI-FXa, and they combine into a quaternary complex to inhibit TF-FVIIa

A recent meta-analysis (6) of six primary prevention trials (three trials involving men only, one involving women only and two involving men and women) reported on sex-specific benefits of acetylsalicylic acid compared with placebo. Among 44,114 men, acetylsalicylic acid reduced the odds of a cardiovascular event by 14% ($P=0.01$) and of myocardial infarction (MI) by 32% ($P=0.001$), but had no significant benefit on the rates of stroke and cardiovascular mortality; in contrast, among 51,342 women, acetylsalicylic acid reduced cardiovascular events by 12% ($P=0.03$) and stroke by 17% ($P=0.008$), but had no significant impact on the rates of MI or cardiovascular mortality. In the women-only trial, however, women aged 65 years or older had relative risk reductions of major cardiovascular events by 26% ($P=0.008$), of ischemic stroke by 30% ($P=0.05$) and of MI by 34% ($P=0.04$) (7).

The addition of clopidogrel to acetylsalicylic acid in a recent trial (8) added no benefit over acetylsalicylic acid alone in primary prevention in high-risk individuals, but was associated with an excess of ischemic events, deaths and serious bleeding.

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program based the recommendations for statin therapy on patient risk category and low density lipoprotein cholesterol (LDL-C) levels after therapeutic lifestyle adjustment. Numerous placebo-controlled clinical trials have shown the efficacy of LDL lowering in reducing the risk for CAD in primary prevention for persons with LDL-C levels greater than 3.4 mmol/L. Expert recommendations for statin therapy based on recent trials have suggested their use in the following patients: in high-risk CAD patients or those with the CAD risk equivalent (10-year risk greater than 20%) who have LDL-C levels of 2.59 mmol/L or greater, with any lower levels also being an option for therapy; in moderately high-risk patients (two or more risk factors, 10-year risk of 10% to 20%) who have levels of 3.36 mmol/L or greater, with levels of 2.59 mmol/L to 3.36 mmol/L being optional; in moderate-risk patients (two or more risk factors, 10-year risk of less than

10%) who have levels of 4.1 mmol/L or greater; and in lower-risk patients (zero to one risk factor) who have levels of 4.14 mmol/L or greater. Target LDL-C levels for these subgroups are less than 2.6 mmol/L (less than 1.81 mmol/L optional), less than 3.36 mmol/L, less than 3.36 mmol/L and less than 4.1 mmol/L, respectively, with the advice of reducing basal LDL-C levels by 40% to 50% (9). Furthermore, specific considerations are suggested for diabetic patients and patients with hypertension with low or borderline cholesterol values in whom clinical trials have shown a marked benefit of taking a low-dose statin (10,11).

A 'polypill' containing low doses of a statin, three blood pressure lowering drugs, folic acid and acetylsalicylic acid has been suggested for a potential reduction of cardiovascular events in society in general by more than 80% (12). Two recent randomized trials did not support a benefit from folic acid; one trial looked at the prevention of cardiovascular events among 5522 patients aged 55 years or older with vascular disease or diabetes (13), and the other looked at the progression of atherosclerosis and the occurrence of cardiovascular events in patients with chronic renal failure (14).

ACS are classified as UA, NSTEMI and STEMI, each condition currently calling for a specific management strategy (Figure 1). Percutaneous intervention procedures can also be considered an ACS based on the endothelial damage created and the risk of acute thrombosis. These ACS situations are all indications for the aggressive control of risk factors; the Pravastatin or Atorvastatin Evaluation and Infection Trial – Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) (15) findings made a strong case for achieving LDL-C levels of less than 1.81 mmol/L.

STEMI mandates immediate reperfusion therapy with thrombolysis or primary PCI; the choice being largely influenced by the timely availability of a catheterization laboratory. Antiplatelet and anticoagulant therapy is required in various combinations in all ACS patients. Options for antiplatelet therapy are acetylsalicylic acid, the thienopyridines (ticlopidine and clopidogrel), dipyridamole, intravenous GPIIb/IIIa antagonists (abciximab, eptifibatide and tirofiban), and cilostazol in some countries but not in Canada.

The anticoagulants used in ACS are unfractionated heparin (UFH), low-molecular-weight heparins – mainly enoxaparin – fondaparinux and bivalirudin. Data from large trials are available for UFH, enoxaparin and fondaparinux. Bivalirudin was mainly studied in the context of angioplasty in stable patients and, more recently, in ACS patients (16).

UFH and enoxaparin

UFH and enoxaparin share similar indications in ACS, with the former being a good choice for short-term use, such as patients with planned early angiography or coronary artery bypass grafting, and the latter for more prolonged medical therapy. The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction (ExTRACT-TIMI 25) trial (17) documented a superiority of enoxaparin over UFH in 20,506 STEMI patients managed with fibrinolysis, with the primary efficacy end point of death or nonfatal MI through 30 days being reduced by 17% (9.9% versus 12%, respectively, $P<0.001$). Contrasting with these benefits in patients with STEMI managed with thrombolysis, no benefit of enoxaparin was observed among the 10,027 UA/NSTEMI patients

managed with an early invasive strategy in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial (18).

Fondaparinux

Fondaparinux was compared with enoxaparin in 20,078 UA/NSTEMI patients in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial (19), and with UFH or no anticoagulants in 12,092 STEMI patients in the OASIS-6 trial (20). The former trial documented the equivalence of the two drugs at nine days on the primary efficacy end point of death, MI or refractory ischemia, and on individual components of this end point. Major and minor bleeding, however, were reduced in the fondaparinux group by 48% (2.2% with fondaparinux versus 4.1% with enoxaparin) and 66% (1.1% with fondaparinux versus 3.2% with enoxaparin), respectively. Patients who had major bleeding during hospitalization fared significantly worse than those who did not at the 30-day follow-up ($P<0.001$), with higher rates of death (13.2% versus 2.8%), reinfarction (11.9% versus 3.6%) and stroke (3.5% versus 0.7%); similar results were seen at 180 days. With minor bleeding, the 30-day mortality rates were also higher (6.9% versus 2.8%). In the OASIS-6 trial (20), fondaparinux was globally useful, but results varied between the various subgroups: compared with fibrinolysis – mainly streptokinase – without anticoagulation, fondaparinux was clearly better than fibrinolysis; compared with no fibrinolysis but with heparin, fondaparinux was also slightly better; and compared with PCI, it was not better.

Thienopyridines

Thienopyridines, particularly clopidogrel, have emerged in recent years as very effective drugs. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) secondary prevention trial (21), which included patients with symptomatic peripheral vascular disease, or a recent stroke or MI, clopidogrel was marginally superior when directly compared with acetylsalicylic acid. Subsequent trials showed that the combination of clopidogrel and acetylsalicylic acid was better than acetylsalicylic acid alone in trials of UA/NSTEMI (22), PCI (23,24) and STEMI (25,26) patients, whereas clopidogrel alone was as effective but safer than the combination in patients with strokes (27). More recently, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (8) showed no superiority of the combination over acetylsalicylic acid alone in primary and secondary prevention; there was a 12% relative risk reduction ($P=0.046$) in secondary prevention but a trend toward more ischemic events in primary prevention and significantly more deaths and bleeding. Contrasting with the CAPRIE trial (21), which enrolled patients early after an acute event, the CHARISMA trial (8) enrolled patients late after the event. The concept of clopidogrel resistance or nonresponsiveness has been developed based on inadequate ex vivo inhibition of ADP-induced platelet aggregation in a significant number of patients. The clinical significance of this laboratory finding remains to be validated (28).

GPIIb/IIIa antagonists

The role of GPIIb/IIIa antagonists has been challenged in recent years in view of the impressive success achieved with a

combination of acetylsalicylic acid and clopidogrel in ACS and PCI patients, and by the results of two randomized placebo-controlled trials that failed to show a benefit of abciximab in low-risk patients undergoing PCI who were pretreated with acetylsalicylic acid and loading doses of clopidogrel (29,30). Recently, however, the same group of investigators confirmed a benefit from abciximab in patients with UA/NSTEMI who were pretreated with a combination of acetylsalicylic acid and clopidogrel (31). The trial enrolled 2022 ACS patients with accelerating, prolonged or recurrent rest angina within the 48 h that preceded the medical consultation and who had elevated troponin T levels or ST segment depression or transient ST segment elevation, or new (or presumed new) bundle branch block. Once PCI was decided on, abciximab or placebo was administered before crossing the lesion with the guidewire. The primary end point of death, MI, or urgent target vessel revascularization after 30 days had a relative reduction of 25% with abciximab compared with placebo (8.9% versus 11.9%, respectively, $P=0.03$). Noteworthy, the event rate was 4.6% in the two groups of patients without elevated troponin levels, and risk reduction was 29% ($P=0.02$) in patients with elevated troponin levels.

Phosphodiesterase inhibitors

A new formulation of dipyridamole made acidic to promote its absorption was shown to be as useful as acetylsalicylic acid for the secondary prevention of stroke and transient ischemic attack (32), and the benefit of each drug was additive in the group of patients who received the combination in this trial. The potential benefit of this new formulation has not yet been tested in ACS patients. Cilostazol is a potent inhibitor of phosphodiesterase-3 that also directly inhibits smooth muscle proliferation and enhances re-endothelialization; small, randomized studies have suggested that the drug was as useful as the thienopyridines in preventing acute stent thrombosis, with the added benefit of preventing restenosis (33,34). Additional trials with cilostazol are mandated.

NEW PERSPECTIVES IN ANTITHROMBOTIC THERAPY

The success of antithrombotic therapy has been an incentive for further development in the field, resulting in an increasing number of new molecules reaching clinical development.

Anticoagulants

The anticoagulants under development target both the upstream and downstream coagulation cascade. FVIIa and the complex TF-FVIIa, which initiate coagulation, can be blocked by inactivated recombinant FVIIa, active site-blocked FVIIa, the recombinant nematode anticoagulant protein c2 (which acts as a TF pathway inhibitor by binding FX and FXa to inhibit the complex TF-FVIIa), and sunol-CH36, which is a chimeric monoclonal antibody to TF that prevents the binding of FX to the complex TF-FVIIa (Figure 2) (35). An inhibitor of factor IX is also under investigation, as well as new orally and parenterally active inhibitors of FXa (eg, otamixaban, apixaban and DX-9065a) and thrombin (eg, dabigatran etexilate).

Antiplatelet drugs

As the potential and limitations of GPIIb/IIIa antagonists became better recognized and the success of the combination of clopidogrel and acetylsalicylic acid emerged, antiplatelet

therapy also shifted to proximal inhibition, with the goal of preventing activation and secretion. Indeed, although useful when administered intravenously in the context of ACS and PCI, GPIIb/IIIa antagonists administered orally in the context of secondary prevention can increase mortality. This paradoxical thrombogenic situation is likely related, in part, to an outside-to-inside platelet signalling and platelet activation produced by drug occupancy of the inactivated receptor; this activation is associated with the release of various compounds promoting thrombus formation, an inflammatory response and the progression of CAD.

There are many possible approaches to platelet inhibition – from blocking various agonists to interfering with intracellular signalling, membrane and shape changes, and the release of various secretion products and their extra-platelet effects.

Trials with ADP receptor blockade are currently underway with the following agents: prasugrel, a thienopyridine that blocks the ADP P2Y₁₂ receptor somewhat more rapidly and reproducibly than does clopidogrel; cangrelor, an ATP analogue administered intravenously that possesses a short half-life of 5 min to 9 min; AZD6140, a nonthienopyridine orally active agent that inhibits the P2Y₁₂ receptor directly, reversibly and with a favourable dose-response up to near complete inhibition of ADP-induced platelet aggregation. Furthermore, full aggregation to ADP requires the participation of the P2Y₁ receptor, which initiates aggregation through mobilization of calcium stores, and of the P2Y₁₂ receptor coupled to adenylyl cyclase inhibition for stabilization of aggregates and prevention of disaggregation. Studies in experimental thrombosis and in P2Y₁ knockout mice suggest that the P2Y₁ receptor could be a potential therapeutic target.

Thrombin receptor inhibitors

The platelet and cell effects of thrombin have received less attention than its effect on the coagulation system. However, thrombin is a very potent platelet agonist *in vivo* and may play a role in arterial thrombosis. Controversial effects of UFH on platelet function have been reported. In a study from our laboratory (36), UFH administered to patients was associated with hyperexpression of P-selectin and GPIIb/IIIa receptor activation in response to ADP and to the thrombin receptor agonist peptide; enoxaparin produced similar effects but of lesser magnitude, whereas argatroban, a direct thrombin inhibitor, had no detectable effects.

Orally active inhibitors of the thrombin receptor PAR-1 with a favourable pharmacokinetic profile are currently being tested clinically in patients undergoing PCI. Such agents will help to better define the roles of thrombin and PAR inhibition in platelets.

Inflammation-thrombosis axis

The inflammation-thrombosis axis is an attractive but only superficially explored therapeutic target. The interactions between inflammation and thrombosis are bidirectional and complex. Inflammatory cytokines, mainly IL-6, stimulate TF expression by the endothelium and monocytes. Vice versa, the coagulation proteases upregulate inflammation responses and cytokine release through activation of the PAR receptors that are located on multiple cell lines, including platelets, endothelial cells, monocytes, neutrophils, fibroblasts and smooth muscle cells. Platelet activation is associated with the release of procoagulant factors and various proinflammatory cytokines,

and with the formation of neutrophil- and monocyte-platelet aggregates that bridge inflammation and thrombosis.

There are multiple potential therapeutic targets on this axis. One such target is immune modulation therapy aiming to create a balance between the proinflammatory cytokines (eg, tumour necrosis factor- α , IL-1 and IL-6) and the anti-inflammatory cytokines (eg, IL-4 and IL-10). Another target is the thrombin-thrombomodulin-protein C axis, which activates protein C to limit thrombogenesis by shutting down activated factor V and activated factor VIII regeneration by thrombin, and by promoting clot breakdown by inhibiting plasminogen activator inhibitor-1. Thrombomodulin and activated protein C receptor are impaired in damaged endothelial plaques. Better insight into the molecular mechanisms for the close relation between inflammation and coagulation may lead to the identification of new therapeutic targets. It can be hypothesized that the simultaneous modulation of coagulation and inflammation, rather than specific therapies aimed at one of these systems, could more successfully control the underlying pathophysiological mechanisms.

Whereas many of the beneficial pleiotropic effects of statins are attributed to anti-inflammatory effects, subgroup analyses of large primary and secondary clinical trials have suggested that patients with elevated C-reactive protein could benefit from statin therapy independently of LDL-C levels. A large prospective study is currently testing the hypothesis that statin therapy may prevent cardiovascular events in patients with elevated C-reactive protein, no documented CAD and LDL-C levels within an acceptable range.

SUMMARY AND HYPOTHESES

Because many of the trials discussed in the present article compared treatment strategies in addition to specific drugs, the data allow clinically relevant observations and the formulation of new hypotheses.

A first observation pertains to different durations of administration of the study drugs and of comparator in many trials. Thus, almost all trials that showed a superiority of enoxaparin over UFH compared a 48 h treatment course of UFH with enoxaparin administered for the full hospital stay. The survival curves in these trials usually diverged after 12 h to 36 h of treatment. In the ExTRACT-TIMI 25 trial (17), an excess event rate was seen after the early discontinuation of UFH, suggesting a rebound phenomenon. In the SYNERGY trial (18), which showed similar efficacy of enoxaparin and UFH, PCI was performed promptly within 24 h in most patients in the two groups. The OASIS-5 trial (19) showed a similar early benefit at nine days of fondaparinux and enoxaparin, with the two drugs being administered for an average of more than five days.

Based on these results, one could speculate that the mechanisms of benefit of treatment may relate not only to drug effect but also to the modalities of application. Thus, the low-molecular-weight heparins produce more reproducible anticoagulation, which could result in better plaque stabilization after a few days, with the prevention of recurrent events and of the rebound phenomenon, which is frequently observed following the early discontinuation of heparin (37). It can also be speculated that prolonged use of an anticoagulant after an acute event could add on benefit. New orally active inhibitors of FXa and thrombin are now being developed to answer this question and others.

A second observation pertains to the excess bleeding commonly observed with enoxaparin compared with UFH and fondaparinux. Similar excess bleeding was seen in the ExTRACT-TIMI 25 trial (17), although the doses of enoxaparin were reduced in patients with a creatinine clearance of less than 30 mL/min and in patients aged 75 years or older. On the other hand, the OASIS program used low doses of fondaparinux – lower than the ones approved for the prevention and treatment of venous thromboembolic disease – without apparent compromises on efficacy results. Could this suggest that the doses of anticoagulants and enoxaparin could be further reduced without compromising on efficacy?

Data are emerging that could challenge the common paradigm that more effective antithrombotic therapy begets a higher risk of bleeding. Indeed, fondaparinux during the hospitalization phase proved as effective as enoxaparin in the OASIS-5 trial (19), but was associated with 50% less major bleeding and 66% less minor bleeding. Drugs aiming for more potent antithrombotic effects but lesser antihemostatic effects to promote efficacy while reducing the risk of bleeding are now in an early stage of clinical investigation.

Another challenging observation is the relationship between bleeding and subsequent events. The OASIS-5 trial (19) crystallized many previous observations on the close interactions that exist between risk of the disease and risk of bleeding. Indeed, most fatalities and cardiovascular events in the trial occurred in patients with early bleedings, independently of treatment with enoxaparin and fondaparinux, and of other clinical characteristics predictive of bleeding. Furthermore, almost all the difference in mortality between the groups at the end of the study could be attributed to the lower rate of bleeding with fondaparinux. The reasons for the putative association between bleeding and subsequent mortality are not well known, but deserve considerable attention in view of the clinical consequences. These reasons could be multifactorial, such as patient characteristics, common pathophysiologies, adverse effects of anemia and/or blood transfusions, or changes in antithrombotic therapy precipitated by bleeding resulting in a thrombotic state.

While bringing an end to a series of positive large clinical trials with clopidogrel, the CHARISMA trial (8) helped define the lower boundaries of the drug's benefits, and reinforced the previous positive results observed with the drug. Altogether, the trials with clopidogrel have shown risk reductions that parallel patient risk, that is, risks and benefits were highest during the acute phase of UA/NSTEMI, STEMI and PCI, moderate in patients with such recent events, lower in patients with remote cardiovascular events, and absent in patients with risk factors but no evidence of the disease.

The indications for GPIIb/IIIa therapy have also been clarified following the results of the Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment (ISAR-REACT) 2 trial (31). Whereas the efficacy of abciximab was recently questioned in elective PCI in the presence of clopidogrel and acetylsalicylic acid, the drug dramatically reduced event rates in patients with UA/NSTEMI. Noteworthy, the benefit was confined to patients with elevated troponin levels and, therefore, with an intracoronary thrombus. These results support the hypothesis that blocking the GPIIb/IIIa receptors is useful when the receptors are activated, but less so when they are not.

Finally, new frontiers in risk stratification are being defined that integrate the markers of ischemia in UA/NSTEMI with the markers of active atherosclerosis, such as diabetes, renal failure and a subclinical inflammatory state. The emergence of ACS as a specific clinical, prognostic and pathophysiological

entity in the past 20 years helped provide new dimensions to CAD in general. Strong with this knowledge, the reintegration of ACS within the large spectrum of CAD with common investigative tools and research facilities can only profit to a more global perspective on the disease and its control.

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