Treatment strategies and risk stratification in non ST elevation acute coronary syndromes

Windhausen, A.

Citation for published version (APA):
Chapter 1

General introduction
Acute coronary syndromes (ACS)

In this chapter a general overview is given of the pathophysiology, diagnosis and treatment of acute coronary syndromes, in particular acute coronary syndromes without ST-segment elevation on the electrocardiogram. At the end of this chapter, the rationale and design of the ICTUS trial is briefly discussed.

ACS describes the spectrum of clinical manifestations which follow disruption of a coronary arterial plaque, complicated by thrombosis, embolization and varying degrees of obstruction to myocardial perfusion. The clinical features depend upon extent and severity of myocardial ischaemia. In the clinical setting the term ‘acute coronary syndrome’ is used as an initial working diagnosis. According to the ECG and biomarker results, the diagnosis is later refined. The therapeutic management is guided by the final diagnosis and risk assessment.

Pathophysiology

The most common cause of ACS is plaque rupture or erosion with superimposed (non)-occlusive thrombus. Persistent or transient thrombotic occlusion at the site of plaque rupture or erosion may lead to episodes of myocardial ischemia, which may lead to irreversible myocardial damage.

Coronary atherosclerotic plaques are very heterogeneous, structurally as well as biologically, and even neighboring plaques in the same artery may differ markedly. During a lifetime, none or only few coronary plaques will give rise to a clinically significant intracoronary thrombosis. These rare but dangerous thrombosis-prone plaques are called vulnerable. One of the important future challenges is to identify the thrombosis-prone plaques, treat them, prevent thrombosis and thus avoid ACS.

Disruption of a formed plaque and subsequent thrombus formation is a complex pathologic process. The presence of large, eccentric lipid pools and infiltration of foam cells are the characteristics of the lipid core most frequently associated with fissured or ruptured plaques. The majority of these lesions rupture at the sites of greatest mechanical stress, notably the junction of the plaque cap and the adjacent normal intima or the shoulder regions of the lipid pool. In contrast, smooth muscle cell-mediated healing and repair processes stabilize plaques, protecting them against rupture. Therefore, plaque size or stenosis severity
reveals nothing, or only a little, about a plaque’s vulnerability.\textsuperscript{4,5} Many rupture-prone plaques are invisible angiographically, because of compensatory vascular remodeling, and they appear to be highly thrombogenic after rupture, probably because of a high content of tissue factor.\textsuperscript{5}

Plaque rupture often exposes the subendothelial matrix (e.g., collagen and tissue factor) to circulating blood. Platelets initiate thrombosis at the site of a ruptured plaque: the first step is platelet adhesion via the glycoprotein Ib receptor in conjunction with Von Willebrand factor. This is followed by platelet activation, which leads to a shape change in the platelet, degranulation of the alpha and dense granules, and expression of GP IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is platelet aggregation, in which fibrinogen (or Von Willebrand factor) binds to the activated GP IIb/IIIa receptors of two platelets.

Simultaneously with formation of the platelet plug, the plasma coagulation system is activated. Tissue factor triggers most coronary artery thrombosis. Ultimately, factor X is activated (to factor Xa), which leads to generation of thrombin (factor IIa), which plays a central role in arterial thrombosis.\textsuperscript{7}

![Figure 1. Spectrum of Acute Coronary Syndromes](image-url)
Diagnosis and risk stratification of ACS

Diagnosis and risk stratification in patients with ACS are closely linked (Figure 1). The leading complaint of patients with ACS is usually chest pain which initiates a diagnostic cascade. The clinical presentation of patients with ACS encompasses a large variety of symptoms. The cardinal symptom is the ischemic chest pain which is typically described by the patient as burning, tightness, or heaviness. Patients often have associated symptoms of nausea and fatigue. However, the assessment of clinical symptoms alone is insufficient for risk stratification as symptoms may be difficult to assess objectively and can easily be subject to misinterpretation.

Physical examination of patients with chest pain includes chest examination, auscultation, and measurement of heart rate and blood pressure. The major purpose of the examination is to exclude non-cardiac causes of chest pain, non-ischemic cardiac disorders and to look for signs of potential hemodynamic instability and left ventricular dysfunction. In patients with myocardial infarctions particular attention has to be drawn to systolic murmurs indicative of mitral regurgitation or ventricular septal defects.

The 12-lead electrocardiogram (ECG) segregates patients into those presenting with ST-segment elevation (approximately one third), and those presenting without ST-segment elevation (approximately two-third). Patients with ST segment elevation are likely to have acute, total occlusion of a coronary artery which will eventually lead to extensive myocardial ischemia and transmural myocardial infarction. These patients should be considered for immediate percutaneous coronary intervention in order to open the occluded coronary artery and restore perfusion. In patients without ST segment elevation (nSTE-ACS), severe myocardial ischemia will result in subendocardial myocardial infarction which can be detected by measuring concentration of markers of myocardial injury such as troponin T and CK-MB in a blood sample. Elevated concentration of these sensitive markers of myocardial necrosis is regarded as indicative of myocardial cell necrosis and fulfills the definition of non ST elevation myocardial infarction (NSTEMI). If no rise in markers is detected, the term unstable angina is used and non-cardiac differential diagnoses must be considered.
At presentation, NSTE-ACS patients can be assigned to the high-risk or to the low-risk category based on the combination of clinical history, symptoms, ECG, and biomarkers. Troponin T elevations are associated with increased risk. In addition, dynamic ST-segment depression, critical arrhythmias (ventricular tachycardia, ventricular fibrillation), or haemodynamic instability (symptoms of shock) are also linked to increased risk. Furthermore, the presence of diabetes is linked to a high likelihood of significant coronary artery disease and this alone places the patient in the high-risk group.

The long-term risk of mortality is related to the established risk factors, biochemical markers of inflammation (C-reactive protein), neurohormonal activation (NT-proBNP) and markers of renal function. From imaging modalities the extent of coronary artery disease (main stem lesion) and reduced left ventricular function are predictors of future outcome.

The therapeutic management is guided by the final diagnosis and risk assessment. At this stage, risk assessment encompasses the risk for ischemic complications, the risk for bleeding complications and the risk for complications related to invasive procedures.

**Treatment of nSTE-ACS patients**

The management of nSTE-ACS patients includes four therapeutic tools: antiplatelet agents, anticoagulants, anti-ischemic agents and coronary revascularization.

**Antiplatelet and anticoagulation therapy**

Antiplatelet and anticoagulation therapy is the cornerstone medial therapy for nSTE-ACS patients. The most important antiplatelet agents are aspirin, clopidogrel and GP IIb/IIIa receptor antagonists.

Aspirin decreases overall aggregation at the site of the thrombus by blocking the synthesis of thromboxane A2 due to inhibition of cyclooxygenase 1. This inhibition of cyclooxygenase 1 is permanent; thus the antiplatelet effects last for the lifetime of the platelets, approximately 7 to 10 days. Since the 1980s, several trials have demonstrated clear beneficial effects of aspirin in nSTE-ACS patients, with a more than 50 percent reduction in the risk of death or myocardial infarction.8-10
Clopidogrel inhibits platelet aggregation by inhibiting adenosine diphosphate (ADP) action on platelet receptors. The CURE trial demonstrated the benefit of adding clopidogrel to the regimen of treatment for nSTE-ACS patients who are receiving aspirin and other medications. Treatment with clopidogrel reduced the risk of myocardial infarction and recurrent ischemia, with a trend toward lower rates of stroke and death from cardiovascular causes. Clopidogrel was approved for the ACS indication in 2002 after publication of the CURE trial data.\textsuperscript{11}

The GP IIb/IIIa receptor blockers inhibit the final common pathway of platelet aggregation, the fibrinogen-mediated cross linkage of platelets. Several randomized trials have shown that GP IIb/IIIa inhibitors reduce the incidence of PCI related MI by 30-50\%.\textsuperscript{12-14} However, the GUSTO IV ACS study conclusively demonstrated that immediate medical treatment with a GP IIb/IIIa inhibitor in addition to aspirin and heparin was not beneficial in the context of a non-invasive strategy in non-ST-elevation acute coronary syndrome.\textsuperscript{15} In addition, a meta-analysis has shown no benefit of GP IIb/IIIa inhibitors outside the setting of PCI.\textsuperscript{10} The usefulness of treatment with GP IIb/IIIa inhibitors seems thus to be limited to the setting of PCI.

With respect to anticoagulation, there were traditionally two options: unfractionated heparin (UFH) or low molecular weight heparin (LMWH), but new treatment options have emerged. In aspirin-treated patients with acute coronary syndrome without ST elevation, short-term unfractionated heparin or LMWH halves the risk of myocardial infarction or death. There seems to be no clinically significant difference in efficacy or safety between LMWH and unfractionated heparin.\textsuperscript{17, 18}

More recently, Fondaparinux was compared to LMWH (enoxaparin) in nSTE-ACS patients. Fondaparinux is a synthetic pentasaccharide which is an indirect Xa inhibitor. By 30 days, mortality was significantly lower in the fondaparinux arm (2.9 percent versus 3.5 percent, \(p = 0.02\)). However, in the subset of patients undergoing PCI, fondaparinux was associated with more than a threefold increased risk of catheter-related thrombi, something also observed in patients with STEMI treated with fondaparinux.\textsuperscript{19, 20}

**Anti–ischemic therapy**

Meta-analysis and registry data have shown that long-term treatment with beta-blockers in nSTE-ACS patients may lead to a significant risk reduction for death. Therefore, beta-blocker therapy should be initiated in all patients and maintained indefinitely in the case of reduced LV function, with or without symptoms of heart failure, unless contraindications exist.\textsuperscript{21}
The use of an oral ACE inhibitor should also be initiated as soon as possible. Meta-analyses of major trials carried out with the main objective of demonstrating the anti-atherogenic effect of ACE inhibitors have shown a significant reduction in mortality, non-fatal myocardial infarction and stroke in patients with atherosclerosis.\textsuperscript{22}

Long-term statin therapy improves outcome for all forms of CAD (coronary artery disease), after ACS or in patients with chronic manifestations of CAD. The rationale behind the prompt initiation of statin therapy after NSTE-ACS includes the possibility of plaque stabilization, anti-inflammatory effects, and restoration of endothelial function.

The potential benefit of intensive lipid-lowering therapy compared with moderate lipid-lowering therapy among a wide spectrum of NSTE-ACS patients was assessed in PROVE-IT. This study showed improved outcome in patients randomized to the intensive lipid-lowering therapy.\textsuperscript{23, 24}

**Coronary angiography and revascularization**

NSTE-ACS patients often undergo coronary angiography to assess the coronary anatomy. When coronary revascularization is indicated, the choice is between percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG).

The use of PCI to treat CAD has expanded dramatically over the past three decades. In the absence of left main or diffuse multivessel CAD, PCI is nowadays often the preferred method of revascularization. In the early eighties PCI was performed using balloon angioplasty. This technique had important limitations such as abrupt closure of the treated vessel (requiring emergency CABG) which occurred in 3 to 5 percent of patients. Restenosis of the treated segment resulted in symptom recurrence in 30 percent of patients within 6 to 9 months after angioplasty. In the late 1980s coronary stents were designed to scaffold the inner arterial wall to prevent early and late vascular remodeling. With routine use of stents, angiographic success rates are high, generally more than 95 percent, although the presence of a superimposed thrombus can increase the risk of acute complications such as abrupt closure or distal embolisation in nSTEMI patients (as compared to patients with stable angina). Therefore, the use of aspirin, clopidogrel, antithrombotics (heparin of LMWH) and GP IIb/IIIa in these patients is mandatory. CABG is recommended for patients with disease of the left main coronary artery and multivessel disease and impaired left ventricular function.\textsuperscript{25}
Invasive versus selective invasive treatment strategy

Randomized trials prior to the ICTUS

In five large, randomized trials, a routine, early invasive strategy (early angiography followed by revascularization, depending on angiographic findings) was compared with a ‘conservative’ strategy (angiography and subsequent revascularization only if medical therapy failed or substantial residual ischemia was documented). The TIMI IIIb trial showed no apparent benefit for a routine early revascularization and the VANQWISH data suggested that an early invasive approach might even be harmful.\textsuperscript{26, 27}

An early invasive strategy was shown to be beneficial in the FRISC II, TACTICS–TIMI 18, and RITA-3 studies, especially in subgroups of patients at high risk, such as those presenting with an elevated cardiac troponin level.\textsuperscript{28–30} As a result, 2002 guidelines of the American College of Cardiology–American Heart Association and the European Society of Cardiology recommend an early invasive approach in high-risk nSTE-ACS patients.\textsuperscript{31, 32}

Despite these recommendations, the available evidence did not show that an early invasive strategy reduced mortality. A reduction in mortality was shown in the FRISC II study at two years, but was not seen in any of the other studies. In addition, in the FRISC II trial, an early hazard for MI (mainly attributable to the incidence of PCI related MI) was observed. Importantly, the reduction in the incidence of myocardial infarction associated with an early invasive strategy in these studies depended on the definition of myocardial infarction. Moreover, recent advances in medical therapy, such as the early use of clopidogrel and intensive lipid-lowering therapy, have been shown to improve the prognosis in patients with acute coronary syndromes but were not used during the five earlier major strategy trials in nSTE-ACS.\textsuperscript{11, 24}
The Invasive versus Conservative Treatment in Unstable coronary Syndromes (the ICTUS trial)

The ICTUS trial was an investigator initiated, randomized multicenter trial, and was started in the Netherlands in 2001. Between July 2001, and August 2003, a total of 1200 patients were enrolled from 42 Dutch hospitals, 12 of which were high-volume centers with percutaneous intervention and on-site cardiac surgery. The ICTUS trial compared an early invasive treatment strategy aimed at coronary angiography and revascularization within 24-48 hrs, with a ‘selective invasive’ (conservative) treatment strategy that included the use of aspirin, low molecular weight heparin, clopidogrel, intensive lipid-lowering therapy and abciximab accompanying all PCI procedures, in nSTE-ACS patients with an abnormal cTnT and either evidence of ischemia on the electrocardiogram or a documented history of coronary artery disease. ICTUS applied current ESC/ACC redefined definition of MI and incorporated serial CK-MB sampling at admission, in the event of a recurrent acute coronary syndrome and after every PCI.33
OUTLINE OF THE THESIS

Part 1 (chapters 2 - 5): the short-term and long-term results of the ICTUS trial

The ICTUS trial compared an early invasive with a selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome (nSTE-ACS) with an elevated troponin T. In the first part of this thesis, in chapter 2, the main results of the ICTUS trial after one year follow-up are presented. In chapters 3 and 4 the long-term outcome of the ICTUS trial is described.

In chapter 5, the data from the ICTUS trial is analysed as if the data had been obtained by means of an observational study because in several post-hoc analyses from observational studies, revascularization was associated with substantial reduction in mortality in nSTE-ACS patients. In chapter 5 the association between actual in-hospital revascularization and long-term outcome is investigated in patients with nSTE-ACS included in the ICTUS trial.

Part 2 (chapters 6 - 9): additional risk stratification

Patients presenting with non-ST-elevation acute coronary syndrome represent a heterogeneous population in terms of short-term and long-term prognosis. Accordingly, risk stratification plays a central role in the evaluation and management of patients with this condition. In the second part of this thesis we investigated several factors for additional risk stratification and addressed the question whether additional risk stratification with biomarkers (NT-proBNP, cystatin C) or evidence of ischemia on the 12 lead electrocardiogram can identify patients that may benefit most from an early invasive treatment strategy. In chapter 6, we assess the prognostic value of ST segment deviation on the admission electrocardiogram. In chapter 7, the value of NT-proBNP (a marker for ventricular dysfunction) is described. In chapter 8, the value of additional risk stratification with cystatin C (a marker of renal function) is assessed.

In chapter 9, we examine the benefits and risks of an invasive strategy in women vs. in men with nSTE-ACS by means of a collaborative meta-analysis.

This thesis ends with a summarizing chapter (chapter 10) in which the results of the ICTUS trial, its impact and the effect of additional risk stratification are briefly discussed. Finally, this chapter concludes with recommendations for clinical practice and future research.
REFERENCES


