Invasive and pharmacological treatment of acute coronary syndrome

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Chapter 1

Introduction and outline
ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) is a collective term for a spectrum of acute clinical presentations due to a decreased supply of blood to the myocardium, predominantly caused by coronary artery disease (CAD).\(^1\) CAD refers to atherogenesis of the coronary arteries caused by atherosclerosis, a chronic inflammatory disease driven by accumulation of extracellular lipids in the intimal layer of the arterial vessel wall.\(^2\) The accumulation of lipid pools, known as atherosclerotic plaques, results in a gradual luminal narrowing of the coronary arteries due to intimal thickening (Figure 1).\(^3\) Besides, a lipid rich plaque can further progress into vulnerable thin-cap fibroatheroma.\(^4\)\(^-\)\(^6\) ACS and CAD are a major causes of mortality and morbidity worldwide. In the Netherlands, an estimated 750,000 people are known with CAD and more than 34,000 ACS patients were hospitalized for ACS in 2017.\(^7\),\(^8\)

Figure 1. Progression of atheromatous plaque from initial lesion to complex and ruptured plaque

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Typically, ACS is caused by a sudden rupture or erosion of the fibrous cap overlying a vulnerable atherosclerotic plaque located in the coronary arterial wall. Subsequently, local inflammation and platelet aggregation at the site of the disrupted plaque causes superimposed thrombus formation leading to complete
or partial occlusion of a coronary artery. The blood flow in the occluded artery is then limited causing a decrease in the supply of oxygen and other nutrients to the downstream myocardium leading to ischemia. Myocardial ischemia presents as angina pectoris, which encompasses symptoms of chest pain, dyspnoea and nausea.

The first step to differentiate among patients with angina suspected for ACS is based on the presence of persistent ST-segment elevation on the 12-lead electrocardiogram (ECG), as is displayed in Figure 2. These signs indicate transmural ischemia caused by a complete occlusion of a coronary artery and is referred to as ST-elevation myocardial infarction (STEMI). In ACS patients without persistent ST-segment elevations (NSTE-ACS) ischemia is generally caused by a partial occlusion or distal embolization of thrombus. Laboratory measurement of high-sensitivity cardiac troponin (hs-cTn) in the blood is used to detect myocardial necrosis and makes a further distinction among NSTE-ACS patients. Elevated levels or a rise-and-fall pattern of hs-cTn are indicative of non-ST-segment elevation myocardial infarction (NSTEMI), whereas normal levels of hs-cTn (≤ 99th percentile of the upper reference limit) indicate absence of myocardial necrosis and is referred to as unstable angina pectoris (UAP).

**Figure 2.** Differentiation of acute coronary syndrome based on electrography and cardiac troponin levels

| Ischaemic symptoms | Working diagnosis | Acute coronary syndrome | Electrocardiogram | No ST-segment elevation | ST-segment elevation | Biomarkers | Normal cardiac troponin levels | Rise or fall of cardiac troponin levels | Final diagnosis | Unstable angina pectoris | Non-ST-segment elevation myocardial infarction | ST-segment elevation myocardial infarction |
GUIDELINE RECOMMENDED THERAPIES

During the last 3 decades the treatment of ACS has strongly improved outcomes. Treatment strategies specific for STEMI or NSTE-ACS differ. However, the two main concepts of invasive and pharmacological treatment are similar for the ACS subcategories.

Invasive therapy

Invasive treatment entails coronary angiography to evaluate the coronary anatomy and if indicated, subsequent coronary revascularisation can be performed. Revascularisation can be performed in two ways, 1) percutaneous coronary intervention with optional (drug-eluting) stent placement, or 2) coronary artery bypass grafting (CABG) in patients with severe CAD, i.e. three-vessel or left main disease, or if the coronary anatomy is unsuitable for PCI (Figure 3).

Figure 3. Schematic illustration of percutaneous coronary intervention and coronary artery bypass grafting for the treatment of coronary artery disease

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In STEMI patients timely reperfusion by primary PCI (emergent coronary angiography with subsequent PCI) of the occluded infarct-related artery improves clinical outcomes. Because ischemic time is strongly correlated with myocardial salvage, reperfusion preferably by primary PCI, should be performed within 12 hours after symptom onset and within 2 hours after STEMI diagnosis is confirmed. Therefore, it is recommended to immediately transfer patients to a PCI-capable hospital as soon as the diagnosis STEMI is confirmed. Primary PCI is the main reperfusion therapy used in STEMI patients living in developed countries.
Although, primary PCI is known to be superior over a pharmacoinvasive strategy with administration of intravenous fibrinolysis, fibrinolysis is still frequently used in more geographically remote and less developed areas.\textsuperscript{18, 19}

Contrary to STEMI, where the focus lays on expeditious PCI to restore blood flow, the performance and timing of an invasive strategy with coronary angiography and revascularization in NSTE-ACS is guided by risk stratification based on clinical presentation, comorbidities, and diagnostic findings.\textsuperscript{14} There are two treatment strategies that have been extensively studied, an early invasive and a selective invasive strategy. A routine early invasive strategy entails invasive coronary angiography, usually performed within the first 24 hours of hospital admission, with subsequent revascularization performed based on the angiographic findings. In contrast, a selective invasive or ischemia-driven strategy, consists of initial optimal antithrombotic and antianginal management with coronary angiography only performed in case of persistent or recurrent ischemia despite optimal pharmacological therapy or ischemia inducible by pre-discharge non-invasive stress testing. In the ICTUS trial there was no benefit of an early invasive strategy over a selective invasive strategy in reducing death or myocardial infarction at 1, 3 and 5 year follow-up.\textsuperscript{20-22}

In contrast to the findings in the ICTUS trials, the current European guidelines recommend early invasive strategy within 24 hours, in NSTE-ACS with a GRACE risk score >140, ST-segment deviation, and patients with elevated cardiac troponin levels, e.i. NSTEMI.\textsuperscript{14} These recommendations are largely based on findings from various meta-analyses based on multiple individual randomized trials such as FRISC-II, RITA-3, and TIMACS.\textsuperscript{23-27} However, a more recent meta-analysis of 8 randomized trials could not demonstrate a mortality benefit of an early invasive strategy.\textsuperscript{28}

Long-term follow-up of these trials is important to appreciate the long-term impact of these strategies. In RITA-3 there was no mortality benefit of a routine early invasive strategy at 10-year follow-up.\textsuperscript{29} The 15-year follow-up study of FRISC-II showed that an (early) invasive strategy postponed death or MI by 18 months and rehospitalisation for ischemic heart disease by 37 months.\textsuperscript{30} The 10-year results of the ICTUS trial are presented in this thesis.
Pharmacological therapy
Management of ACS patients with pharmacological treatment can be divided into antithrombotic, anti-ischemic or anti-hypertensive, and lipid lowering therapies.

Antithrombotic therapy can be initiated if ACS is the working diagnosis and usually consists of loading doses of aspirin and a P2Y12 inhibitor. Aspirin prevents the aggregation of platelets by acetylation of the COX-1 enzyme and limiting the formation of thromboxane A2 in platelets. Several studies have shown a reduction in adverse events with the administration of aspirin in ACS patients.\textsuperscript{31-33}

P2Y12 inhibitors selectively affect the activation of adenosine diphosphate (ADP) on thrombocyte receptors. Clopidogrel was the first available P2Y12 inhibitor in the early two-thousands. The CURE and CURRENT-OASIS-7 trials showed a benefit of clopidogrel plus aspirin, also known as dual antiplatelet therapy (DAPT), over aspirin alone in the reduction of events in ACS patients and those treated with PCI.\textsuperscript{34, 35} Clopidogrel is a prodrug which becomes active after metabolisation by cytochrome P450 (CYP2C19). Up to 14% of the patients may experience therapy resistance to clopidogrel associated with a genotype variation in the metabolisation of CYP2C19.\textsuperscript{36} More recently the novel P2Y12 inhibitors ticagrelor and prasugrel have shown to be beneficial over a dual antiplatelet therapy (DAPT) regimen with clopidogrel in ACS patients.\textsuperscript{37, 38} Both ticagrelor and prasugrel are the preferred P2Y12 inhibitors, due to improved potency and faster P2Y12 inhibition compared to clopidogrel.\textsuperscript{13, 14} Notably, prasugrel is contraindicated in the elderly (≥75 years), patients with lower body weight (<60 kg), and those with prior cerebrovascular accidents. In ACS patients who underwent PCI DAPT is recommended for a duration of 6-12 months.

In patients at a high risk of bleeding treated with DAPT (prior gastrointestinal bleeding or peptic ulcer, elderly, (novel) oral anticoagulants users, chronic use of non-steroidal anti-inflammatory drugs or steroids, and Helicobacter pylori infection) gastric protection with a proton pump inhibitor is recommended.\textsuperscript{39} This includes patients treated with DAPT or a single platelet inhibitor in combination with a vitamin K antagonist or novel oral anticoagulation therapy.

Beta-adrenergic blockings agents, known as beta-blockers, lower the heart rate and myocardial oxygen consumption. Beta-blocker therapy is indicated in all ACS patients with reduced left ventricular ejection fraction (LVEF), unless contraindicated.\textsuperscript{14, 20} Most studies demonstrating a benefit of beta-blocker therapy in ACS patients were performed in the pre-PCI era. Benefit of oral beta-blockers
in the PCI era remains less well established in patients with preserved ejection fractions. Furthermore, early intravenous beta-blocker administration has shown to reduce ventricular arrhythmias in STEMI patients treated with fibrinolysis. However, data on early administration of intravenous beta-blockers in the setting of primary PCI remains conflicting. Results from a meta-analysis of studies on early intravenous beta-blockers are discussed in the second part of thesis.

Angiotensin converting enzyme (ACE) inhibitors prevent the conversion of angiotensin I into angiotensin II. This leads to a decrease in cardiac output and lower blood pressure, due to a reduction of renin secretion and activity of the renin-angiotensin-aldosterone system. ACE inhibitor use reduces mortality, MI, and heart failure in ACS patients with reduced LVEF, diabetes mellitus or anterior STEMI and should be initiated within the first 24 hours after hospitalisation. If ACE inhibitors are not well tolerated, angiotensin receptor blockers (ARB) serve as an alternative. Similar to beta-blockers, the value of long-term ACE inhibitor or ARB use in ACS patients preserved LVEF has not been studied in a randomized trial.

Early and intensive prescription of lipid lowering drugs has proven to be beneficial for secondary prevention in ACS. The most frequently used class of lipid lowering drugs are statins. Statins block the production of LDL cholesterol (LDL-C) by inhibition of HMG CoA reductase in the liver, which leads to a reduction of the LDL-C blood levels. Statin therapy reduces cardiovascular mortality, MI, stroke, and revascularization. Statins are indicated in all ACS patients with the goal to achieve LDL-C levels of <1.8 mmol/L or a 50% reduction in patients with baseline LDL-C levels of 1.8-3.5 mmol/L. If LDL-C reduction cannot be achieved with intensive statin therapy alone or in those intolerant for statins, addition of ezetimibe should be considered.

Optimal medical therapy (OMT) in ACS is a term used for a combination of five aforementioned guideline recommended drugs; aspirin, P2Y12 inhibitors, statins, beta-blockers, and ACE inhibitors or ARBs. The prescription of all five drugs at discharge is referred to as the ‘golden five’ or optimal medical therapy and became a quality indicator of the Safety Management Program (VMS Veiligheidsmanagement Programma) in 2008. We evaluate the prescription of OMT and its relation to outcome in the second part of this thesis.
THESIS OUTLINE

This thesis aims to provide an overview of the development and implementation of invasive and pharmacological treatment strategies provided to ACS patients.

Part A of the thesis provides an overview on various aspects of ACS care in the Netherlands. In Chapter 1 we provide insight into the Dutch primary PCI network and report the impact of the initiation of off-site PCI centres on ambulance driving time in the Netherlands. In Chapter 2 the first results of a national STEMI registry are presented. Chapter 3 describes treatment patterns of angiography and revascularisation from a national registry of NSTE-ACS patients who presented at Dutch non-PCI centres. Besides, we discuss the potential impact of implementing a policy of same-day transfer (<24 hours) to undergo coronary angiography in a PCI centre, as recommended by the European Society of Cardiology, in high-risk NSTE-ACS patients presenting at non-PCI centres.

In Part B we discuss the long-term outcomes of the ICTUS trial. In the ICTUS trial an early invasive treatment strategy was compared to a selective invasive treatment strategy in patients NSTE-ACS and elevated cardiac troponin levels. The 10-year results of the ICTUS trials are presented in Chapter 4. Chapter 5 presents correspondence between our research group and readers of the Journal of the American College of Cardiology. Their letter-to-the-editor and our reply raise the attention on the differences in revascularisation rates between early and selective invasive strategies in the ICTUS trial and the impact on long-term outcome. A subgroup analysis of patients with diabetes mellitus enrolled in the ICTUS trial is presented in Chapter 6.

Part C of this thesis focusses on the pharmacological treatment of ACS patients. Chapter 7 provides a patient-pooled meta-analysis of four randomized studies of STEMI patients treated with early intravenous beta-blocker administration or control. Chapter 8 describes temporal trends in optimal medical therapy use in ACS patients from a large single centre registry. Chapter 9 reports trends and outcomes regarding PPI use in the era of novel P2Y12 inhibitors from the same single centre registry. Guideline adherence of optimal medical therapy prescription is presented in Chapter 10 and based on a combined ACS cohort from two Dutch tertiary heart centres.

Finally, in Chapter 11 we provide a summary of this thesis, as well as a discussion of the results and an appraisal of the future perspectives in the field of ACS.
REFERENCES


