Invasive and pharmacological treatment of acute coronary syndrome

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Chapter 12

Summary and future perspectives
SUMMARY

In this thesis we discuss invasive and pharmacological treatment in patients with acute coronary syndrome (ACS). ACS refers to a spectrum of clinical symptoms caused by a coronary artery occlusion provoked by a rupture or erosion of an atherosclerotic plaque with superimposed thrombus formation. The differentiation of ACS types and subsequent treatment is based on electrocardiographical findings and cardiac troponin assays indicating myocardial ischemia or necrosis. In patients with ST-elevation myocardial infarction (STEMI), caused by an acute total occlusion of a coronary artery, there is a clear benefit of immediate revascularization by primary percutaneous coronary intervention (PCI). In NSTE-ACS, the coronary artery is only partially or intermittently occluded and some patients respond well to initial pharmacological treatment. Additional use and timing of invasive coronary angiography (CAG) and subsequent revascularization in NSTE-ACS is based on risk stratification.

Although the invasive treatment strategies in STEMI and NSTE-ACS differs, the underlying pathophysiological pathway of atherosclerosis does not. Therefore pharmacological treatment of ACS focusses on reducing the progression of atherosclerosis and minimizing the recurrence of atherothrombotic events. The aim is to provide ACS patients with a regimen of secondary preventative medication referred to as ‘optimal medical therapy’ (OMT). OMT consists of aspirin and a P2Y12 inhibitor to inhibit platelet aggregation and thrombus formation, a statin to lower low-density lipoprotein cholesterol (LDL-C) levels associated with the progression of atherosclerosis, and beta-blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs) to attenuate ventricular remodelling.

Chapter 1 provides a general introduction into ACS and provides the outline of this thesis, which consists of three parts. The first part of this thesis provides insight in the current state of ACS care in the Netherlands. The second part describes the long-term outcome of an early or selective invasive treatment strategy in patients with NSTE-ACS and elevated troponin levels. The third and final part of this thesis describes the pharmacological treatment of ACS patients.
Part A: ACS care in the Netherlands
In its’ early days, PCI was only performed in centres with back-up of cardiothoracic surgery (on-site). However, due to further technical advancement PCI can be performed safe with fewer complications. Therefore, there has been an increase in PCI centres without surgical back-up (off-site) during the last 10-15 years. In Chapter 2, we evaluated the impact of the initiation of off-site PCI centres in the Netherlands on ambulance driving time. The addition of off-site PCI centres has significantly reduced the ambulance driving time to a PCI. We demonstrated that all inhabitants of the mainland of the Netherlands reside ≤120 minutes from a PCI centre. This means that every STEMI patient in the Netherlands can be treated in accordance with the European guidelines. It seems unlikely that the addition of new off-site PCI centres will greatly impact the accessibility to PCI care in the Netherlands.

National ACS registries have contributed to the evaluation and improvement of health care systems. To date, a national registry for ACS patients in the Netherlands is lacking. Chapter 3 is the first report of an effort by the National Cardiovascular Database Registry (NCDR) to initiate a national STEMI registry in the Netherlands. Although, only data from four ‘snapshot’ weeks are presented, it demonstrates the feasibility of a national STEMI registry.

Chapter 4 describes the treatment patterns of NSTE-ACS patients who presented at one of 23 voluntarily participating Dutch non-PCI centres. The aim of the registry was to identify patients who are considered high-risk NSTE-ACS (e.i. elevated troponin, dynamic ST- or T-wave changes, and a GRACE risk score >140) and, according to the European guidelines, should be transferred to a PCI centre for CAG. This recommendation is contrary to local practice in the Netherlands, where we found that approximately 50% of the high-risk NSTE-ACS undergo CAG at a non-PCI centre. Moreover, revascularisation was only performed in 55% of these patients and 36% were pharmacologically treated. Based on our analyses it remains unclear whether same-day transfer would be of benefit in all high-risk NSTE-ACS patients.

Part B: Long-term results of the ICTUS trial
There are two predominant treatment strategies for patients with NSTE-ACS, an early invasive and a selective invasive strategy. Both strategies have been extensively studied in numerous randomized controlled trials, one of which was the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndrome) trial, which enrolled patients from 2001 until 2003. In the ICTUS trial,
patients with NSTE-ACS and elevated troponin randomized to an early invasive strategy underwent CAG within 24-48 hours, with subsequent revascularization by PCI or coronary bypass surgery (CABG), if indicated. Patients randomized to a selective invasive strategy only underwent CAG if initial pharmacological treatment with intensive antithrombotic and antianginal therapy failed or patients had inducible ischemia during a non-invasive stress test. Chapter 5 presents the long-term results of the ICTUS trial, in which we could not demonstrate a benefit of an early invasive versus a selective invasive strategy for the composite of 10-year death or spontaneous myocardial infarction (MI). Additionally, no difference in death or spontaneous MI was observed after stratification for baseline risk. The absence of a benefit of an early invasive strategy, in contrast to earlier trials, may be explained by the relatively high cross-over rate to CAG and subsequent revascularization in the selective invasive group. Conversely, one could argue that despite a lower revascularization rate (absolute difference 22%) compared to an early invasive strategy, a selective invasive strategy may still be a reasonable option in selected NTE-ACS patients, which is also highlighted in Chapter 6.

NSTE-ACS patients with diabetes mellitus have a higher risk for recurrent cardiovascular events and represent approximately 20-30% of the NSTE-ACS population. In Chapter 7, we performed a subgroup analysis of NSTE-ACS with diabetes mellitus enrolled in the ICTUS trial. We could not demonstrate a benefit of an early invasive strategy over a selective invasive strategy in NSTE-ACS patients with diabetes mellitus. We did observe a 2-fold increase of 10-year death of spontaneous MI in patients with diabetes mellitus compared to non-diabetic patients, regardless of in-hospital treatment (medical therapy, PCI, CABG). These findings illustrate the ongoing adverse impact of diabetes mellitus on patients with ACS.

Part C: Pharmacological treatment of ACS patients
Beta-blockers have been a cornerstone therapy for ACS ever since their benefit on mortality was demonstrated during the pre-reperfusion era, in the 1980s. The administration early of intravenous beta-blockers during the acute phase in STEMI patients before primary PCI has been studied in several trials, however results remained inconsistent. In Chapter 8, we performed a meta-analysis of randomized clinical trials that assessed the safety and clinical efficacy of early intravenous beta-blockers versus control. We pooled patient-level data from four trial (BEAT-AMI, EARLY-BAMI, Hanada et al. , and METOCARD-CNIC) and found that early intravenous beta-blocker administration was safe, but did not result in a benefit in the composite of 1-year death or MI compared to control. The larger
trials included in this meta-analysis (EARLY-BAMI and METOCARD-CNIC) were only designed to detect a difference in infarct size between the treatment arms, which could not be demonstrated in the meta-analysis. Given the similar results of cardiac necrosis markers in both treatment arms, the small but significant increase in left ventricular ejection fraction on CMR at 6 months with beta-blockers might be a spurious finding. Therefore, a trial that assesses the effect on left ventricular function might still needed to determine the role of early intravenous beta-blockers in STEMI patients.

Two chapters in Part C of this thesis describe the use of secondary preventative medication recorded in a registry from the Isala Hospital in Zwolle, the Netherlands. We describe temporal trends and patterns in OMT prescription in ACS patients in Chapter 9. At discharge 43.7% of the patients were on OMT, this later decrease to 25.5% at 1-year. There were no changes in the percentage of OMT prescription during the 9-year study period running from 2006 until 2014. Besides, OMT prescription was significantly lower among NSTEMI patients. We observed an association of OMT prescription at discharge and a reduction in 1-mortality. However, OMT users were younger and had fewer comorbidities and despite extensive adjustment, residual confounding could still be present.

In Chapter 10 we evaluated to effect of proton pump inhibitors (PPI) on cardiovascular and bleeding events after ACS. PPI prescription more than doubled from 34.7% in 2010 to 88.7% in 2014. PPI use at discharge was associated with a reduction in the composite of 30-days death, MI, or stroke, but was not associated with a reduction in gastrointestinal bleeding at 30-days. The uptake of PPIs coincided with the introduction of novel P2Y12 inhibitors, but also high-sensitivity troponin in daily clinical practice. Therefore, PPI prescription in this study could rather indicate improved therapies or selection of lower risk patients, than being the cause of improved outcome.

Chapter 11 evaluates the prescription of OMT in a pilot registry performed at the Academic Medical Center in Amsterdam and the Isala Hospital in Zwolle, both in the Netherlands. Discharge OMT prescription was 43.2%, increased to 60.1% at 1 month, and decreased to 28.7% at 1 year. OMT prescription was lower in NSTEMI patients and decreased with increasing age. These results correspond with our findings in Chapter 6 and other local registries. The most often discontinued drugs during follow-up were P2Y12 inhibitors and ACEi/ARB. The most reported reasons for drug discontinuation were statin-related myalgia and myopathy.
CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Dutch national ACS registry
During the last 20-30 years outcomes after ACS have improved dramatically due to development of invasive and pharmacological treatments.\(^1\)\(^2\) This thesis evaluated the use of these treatments that have only just become commonplace in the recent decades. We showed that ACS care in the Netherlands is easily accessible nationwide. The National Institute for Public Health and the Environment (RIVM) reports the 30-day mortality after ACS in The Netherlands is 8.2%, which is on par with rates observed in Norway (7.7%), Denmark (7.7%), and Sweden (7.8%).\(^3\)

However, in contrast to the Scandinavian countries the development of a fully operational national ACS registry, that can be used for benchmarking, observational studies, and pragmatic registry-based randomized trials, remains challenging.\(^4\) In this thesis we demonstrated that running short-term temporary registries of Dutch STEMI and NSTE-ACS patients is feasible. Several Dutch hospitals have initiated local and regional registries, including studies in this thesis (Chapters 9-11). This shows that ACS registration about to start in the Netherlands.\(^5\)\(^-\)\(^9\)

A key next step would be to solidify these local and regional initiatives and unite them under the umbrella of a national ACS registry governed by the Netherlands Heart Registry. We should take benefit from the example of the Danish Heart Registry, which oversees its’ regional branches of the Western and Eastern Denmark Heart Registries.\(^10\)

The current biggest obstacle towards a national ACS registry, with complete and valid data collection, remains financial. A first study using national claims and pharmacy data from the Dutch Health Insurance companies showed promising results from highly accurate data.\(^5\)\(^11\) However, it remains costly for researchers to gain access to these data, as they are legally owned by the health insurance companies. Besides, the ideal registry should record detailed information on considerations, procedures and medication during hospitalisation and follow-up. Not all these variables are included in the health insurance database and some need to be recorded and collected separately. Therefore, the success and accuracy of registry data can only be ensured if hospitals allocate time and funding for trained personnel to maintain their ACS registries.
Furthermore, due to strict Dutch privacy laws, the exchange of medical information between health care providers remains complicated. In the Scandinavian countries it is permitted by law to use the personal identification number (BSN, Burgerservicenummer) for the exchange of medical information. This has been one of the contributing factors of the success of their national registries. Unfortunately, in 2011 the Senate of the Netherlands rejected a draft law that would introduce a Dutch national electronic medical record (EMR) by enabling the use of the BSN for information exchange, over safety and privacy concerns. In the meantime all Dutch hospitals have introduced their own EMRs and have prioritized the security of patient data. Moreover, patient privacy should be better guaranteed since the introduction of the European General Data Protection Regulation (GDPR) in 2018. In accordance with these regulations, registry studies may only operate if patients are provided with informed consent and are offered the possibility to opt-out. Hopefully, these measures will contribute to build the infrastructure for the national registries of the future, without compromising patient privacy.

There lays a potential in so-called Registration of Source (Registratie aan de Bron). This initiative from the Netherlands Federation of University Medical Centres aims to make use of data from electronic medical records for monitoring quality of care and outcome. Matching these data with other readily available data from ambulance services, procedural databases from PCI and non-PCI centres, general physicians, pharmacies, health insurers, and The National Health Care Institute could contribute to building a national ACS registry.

**NSTE-ACS**

The results of the ICTUS trial have contributed to the foundation on which the current NSTE-ACS care in the Netherlands is built upon. In this thesis we studied the 10-year results of ICTUS and could not demonstrate a benefit of an early invasive strategy over a selective invasive strategy. Based on ICTUS, Dutch cardiologist are comfortable adhering to a selective invasive strategy, which can be regarded as a viable option in selected patients. However, in reality currently >80% of the high-risk NSTE-ACS patients will undergo CAG during admission to identify a culprit lesion and potentially revascularise if indicated.

To make effective use of resources and staff, ideally all NSTE-ACS patients with an indication for PCI or CABG should be able to undergo CAG at the same hospital where revascularisation is performed. However, we do not have this centralized approach for organizing NTE-ACS care in the Netherlands. According to the National Health Care Institute (Zorginstituut Nederland), approximately 50% of
the Dutch NTE-ACS patients present at non-PCI centres. There the attending physician makes a clinical assessment to determine whether CAG should take place in a PCI or non-PCI centre. In the latter situation, there is a low threshold for referral to a PCI centre if revascularisation is expected. In this thesis we observed that only 55% of the NSTE-ACS patients presenting at non-PCI centres needed additional revascularisation, demonstrating that CAG at non-PCI centres may also serve as a form of gatekeeping.

Recently the VERDICT trial, a contemporary clinical trial from Denmark, aimed to identify high-risk NSTE-ACS patients with imminent or established vessel closure whom may benefit from a very early invasive with CAG <12 hours over a delayed invasive strategy with CAG <48-72 hours. All patients presenting at non-PCI centres were transported to a PCI centre to undergo CAG. Even though the median difference between the timing of CAG was 57 hours (4.7 versus 61.6 hours), there was no difference in 5-year death, MI, or hospital admission for refractory angina, or heart failure. Only patients with a GRACE risk score >140 had an observed benefit of a very early invasive strategy. However, the authors do not specify which component of the composite endpoint contributed to the benefit of a very early strategy in this patients group.

These results suggest that in a contemporary setting NSTE-ACS patients with elevated troponin but with a GRACE risk score ≤140 benefit equally well from delayed CAG. Besides, the revascularisation rate in VERDICT (56%) was similar to our observation in Chapter 4 (55%). This observation calls for better selection of NSTE-ACS patients with an indication for revascularization.

Computed tomography coronary angiography (CTCA) may be a way to exclude patients without obstructive coronary artery disease or identify patients who need revascularisation. All patients in VERDICT underwent CTCA prior to CAG, but these results have not been published yet. We are awaiting the CTCA results from VERDICT and together with results from the ongoing RAPID-CTCA trial, may gain further insight whether CTCA in addition to standard care may be a helpful tool for patients selection in NSTE-ACS.

Medication
In recent years development of new pharmacological therapies in ACS has increased the variety drug combinations physicians can choose from. The list of developments includes guided-de-escalation or prolonged duration of dual-antiplatelet therapy, (low-dose) novel oral coagulants, ezetimibe, PCSK9...
inhibitors, and possibly anti-inflammatory drugs. \textsuperscript{17-25} Contrary, pragmatic randomized trials are studying the relevance of current therapies established in the pre-PCI era. No less than 5 trials are currently re-evaluating the role of beta-blockers in ACS patients with preserved left ventricular ejection fraction.\textsuperscript{26-28} The challenge for the future will be to choose the right regimen of drugs for the right patient. Physicians should be considering various factors including atherosclerotic, bleeding, and inflammatory risk. An easy to use decision making tool that helps to match the right regimen to a patient's risk profile will therefore be welcome.

Finally, I must note that the most important aspect of ACS care, and health care in general, has hardly been discussed in this thesis. I believe pills and stents are only part of the solution. We as health care providers should repeatedly bring up the importance of a healthy lifestyle (a healthy diet, daily physical activity, and smoking cessation) to the attention of our patients.\textsuperscript{29, 30} Together with our patients we need to determine how they can adjust their lifestyle and which support can be offered to them make improvements. Hopefully, further initiatives that support health-conscious actions and discourage unhealthy behaviour can contribute to improve the well-being of society.
REFERENCES


