On secondary prevention after acute coronary syndrome
-what, when, and who

Daniel Huber

Department of Public Health and Clinical Medicine
Umeå 2019
“It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.”

Sherlock Holmes
-A Scandal in Bohemia
Original papers

The following papers are the basis for this thesis:


IV. Huber D, Wikén C, Henriksson R, Mooe T. *Statin treatment after acute coronary syndrome: Adherence and reasons for non-adherence in a randomized controlled intervention trial*. Submitted

In the dissertation, these papers are referred to by their roman numerals.

The original papers are reproduced by permission by respective publisher in this thesis.
# Table of Contents

## Abstract

Background ........................................................................................................ iii
Aims .................................................................................................................. iii
Methods .......................................................................................................... iii
Results ............................................................................................................. iv
Conclusion ...................................................................................................... v

## Abbreviations and acronyms

Enkel sammanfattning på svenska ................................................................. ix

## Introduction

Atherosclerosis and acute coronary syndrome ............................................. 1

- Atherosclerosis ......................................................................................... 1
- Acute coronary syndrome, or ACS .......................................................... 2
- Epidemiology ............................................................................................ 3
- Risk factors ............................................................................................... 3
- Initial treatment and secondary prevention ............................................. 4
- Secondary prevention in clinical practice ............................................... 5
- Low-density lipoprotein cholesterol, or LDL-C ...................................... 6
- Blood pressure, or BP ............................................................................... 6

Adherence and persistence ........................................................................ 7
Nurse-based telemedicine ........................................................................... 10
Aims .............................................................................................................. 11

## Materials and Methods

Setting ........................................................................................................... 12
The NAILED study ....................................................................................... 12

- Participants ............................................................................................... 13
- Outcomes and targets ............................................................................... 13
- Intervention .............................................................................................. 14
- Control ..................................................................................................... 14

Study design ................................................................................................. 15

- Study I ..................................................................................................... 15
- Study II .................................................................................................... 16
- Study III .................................................................................................. 17
- Study IV .................................................................................................. 17

Data acquisition: ......................................................................................... 18
Statistical methods ...................................................................................... 18
Results .................................................................................................................. 21
Feasibility of a telephone-based, secondary preventive intervention programme –
inclusion, exclusion, declines, and their rates and reasons (Study I) ...................... 21
  Exclusion ........................................................................................................... 23
  Declining ......................................................................................................... 23
  Mortality .......................................................................................................... 24
Adaptability of a telephone-based intervention programme – guideline change in
target for LDL-C (Study II) .................................................................................. 26
Efficacy of a telephone-based interventional programme – 12-month outcomes for
LDL-C and BP (Study III) .................................................................................... 29
  LDL-C .............................................................................................................. 31
  BP ..................................................................................................................... 31
Barriers to intervention – statin adherence over time (Study IV) ......................... 33
Analysis .............................................................................................................. 40
Discussion ......................................................................................................... 41
  Patient population ............................................................................................ 41
  Feasibility of a nurse-based secondary prevention programme ......................... 42
  Guideline perseverance .................................................................................... 43
  Risk factor control .......................................................................................... 44
  Adherence to treatment .................................................................................... 46
  Key methodological features and study limitations ............................................ 50
    Case validity .................................................................................................. 50
    Measurement errors ....................................................................................... 50
    Missing data ................................................................................................ 50
    Sample size .................................................................................................. 51
    Survival analysis and competing risks ............................................................ 51
    The methodology used to study adherence ..................................................... 51
    Considerations in the NAILED study design ................................................. 52
    Generalizability ............................................................................................ 52
  Implications and future research .................................................................... 53
Conclusions ....................................................................................................... 55
Acknowledgements .......................................................................................... 56
References .......................................................................................................... 57
Abstract

Background
Cardiovascular disease, of which coronary heart disease constitutes the lion’s share, is the leading cause of premature morbidity and mortality worldwide. Management of the condition has evolved rapidly in recent decades, and mortality has more than halved in the western world. Because of intense research, solid evidence supports effective and inexpensive means of preventing disease progression. However, secondary prevention still yields disappointingly low success in meeting guideline-recommended risk factor targets. It is therefore vital to develop more effective risk factor management.

Aims
We aimed to assess the feasibility of a nurse-led, telephone-based, secondary preventive intervention in an unselected population with acute coronary syndrome (ACS). Furthermore, we sought to evaluate the flexibility of the intervention to adapt to a change in guidelines. We also aimed to evaluate whether the intervention was more effective than usual care at improving risk factor levels for blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) 12 months after discharge. Finally, we aimed to measure whether the intervention improved long-term adherence to statins.

Methods
All papers are based on the Nurse-based Age-independent Intervention to Limit Evolution of Disease after ACS (NAILED-ACS) trial. The NAILED trail has two arms, one after stroke/transient ischemic attack (NAILED-Stroke) and one after ACS (NAILED-ACS). All studies are based on NAILED-ACS aside from study II which includes both arms. The trial was an open, 1:1 randomized, controlled, parallel group trial that compared nurse-led telephone follow-up with medical titration (intervention) to a control group with follow-up by a general practitioner (control). All patients admitted to Östersund Hospital for ACS during 2010–2014 were eligible if available for preventive management by telephone. A baseline assessment was made at 1 month after discharge and thereafter every 12 months for at least 3 years.

Feasibility was assessed among patients admitted until 31 January 2013, and predictors of exclusion and non-participation were identified. The performance of the intervention in implementing a guideline change was evaluated in patients with diabetes with both ACS and stroke as inclusion events after a change in LDL-C target from <2.5 mmol/L to <1.8 mmol/L. LDL-C levels were compared
between intervention and control patients before and after the guideline changed. Reasons for not reaching the target level were recorded. The outcomes of the intervention on BP and LDL-C were studied in patients admitted until 31 December 2013. We measured proportions reaching targets and levels of LDL-C and BP during the first 12 months of follow-up, with comparisons between the intervention and control groups. Adherence to statin treatment was measured in the entire study cohort, with at least 36 months of follow-up, with classification of reasons and analysis of predictors for both a first and a permanent discontinuation.

Results
Of 907 screened patients with ACS in the first study, 72.9% were included, and 11% declined participation. Among the 16.1% who were excluded, the predominant reasons were participation in other trial, dementia, and advanced disease. Non-included patients were significantly older, with more comorbidities, decreased functional capability, and lower level of education compared to included. Excluded and declining patients also had a reduced one-year survival in comparison with included.

Before the guideline changed, 96% of the 101 patients in the intervention group reached LDL-C <2.5 mmol/L compared to 70% of the 100 control patients (p<0.001). One year after target reduction to <1.8 mmol/L, the same proportions were 65% and 36%, respectively (p<0.001). The predominant reason for non-attainment of target in the intervention group was full-dose treatment; for the control group, it was that no medication adjustment was made.

After medical titration, at 1 month (baseline), 94.1% in the intervention group achieved target for LDL-C (<2.5 mmol/L) compared to 68.4% in the control group. Mean LDL-C was 0.38 mmol/L lower in the intervention group (p<0.05 for both). At the 12-month assessment, 77.7% of the intervention group attained the LDL-C target compared to 63.2% of the control group, and mean LDL-C was 0.3 mmol/L lower among intervention patients (p<0.05 for both). In the intervention group, 91.9% achieved targets for systolic BP and 96.2% for diastolic BP after baseline titration compared to 65.6% and 82.0%, respectively, in the control group (p<0.05 for both). In the intervention group, 91.9% reached the target for systolic BP and 88.1% for diastolic BP, compared to 63.7% and 82.8%, respectively, in the control group (p=0.125 and <0.05). Mean systolic BP was 7 mmHg lower and mean diastolic BP 4 mmHg lower in the intervention group after 1-month titration compared to controls. At 12 months, the mean systolic BP was 1.5 mmHg lower and mean diastolic BP 2.1 mmHg lower in the intervention group.
In our assessment of adherence to statin treatment, 89.3% in the intervention group and 81.7% in the control group were adherent to treatment during a mean follow-up of 3.9 years (p<0.001). In the intervention group, 27.8% discontinued at least once during the period, compared to 20.8% in the control group (p<0.05). The main reason for a first discontinuation was avoidable in both groups: side-effects without a compelling association with treatment. The main reason for permanent discontinuation was predominantly non-avoidable in the intervention group (advanced disease and dementia) but avoidable in the control group (side-effects without a compelling association with treatment). Predictors for increased risk for discontinuation were female sex, and for a first event, inclusion in the intervention group. Predictors for reduced risk of non-adherence were ST elevation myocardial infarction as an including event, and for permanent discontinuation, inclusion in the intervention group.

**Conclusion**

A nurse-led telephone-based method for secondary prevention can encompass a large proportion of an ordinary ACS cohort. Compared to usual care, it is more adaptable to changes in treatment guidelines and leads to better achievement of major risk factor targets as well as improved medication adherence.
# Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AP</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin II receptor blockers</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>CCU</td>
<td>Coronary care units</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CHOICE</td>
<td>Choice of Health Options In prevention of Cardiovascular Events</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CR</td>
<td>Cardiac rehabilitation</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EUROASPIRE</td>
<td>European Action on Secondary Prevention by Intervention to Reduce Events</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin scale</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>n</td>
<td>Number of valid cases</td>
</tr>
<tr>
<td>NAILED</td>
<td>Nurse-based Age-independent Intervention to Limit Evolution of Disease</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RESPONSE</td>
<td>Randomized evaluation of secondary prevention by outpatient nurse specialists</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>SEPHIA</td>
<td>Secondary Prevention after Heart Intensive Care Admission</td>
</tr>
<tr>
<td>SMCs</td>
<td>Smooth Muscle Cells</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
</tr>
<tr>
<td>SWEDHEART</td>
<td>Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>UA</td>
<td>Unstable angina pectoris</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Enkel sammanfattning på svenska

Bakgrund

Hjärt-kärlsjukdomar är idag den största orsaken till nedsättning av livskvalitet och förtidig död i världen. Detta till trots att utveckling av behandling och förbättringar i livsstilsrelaterade faktorer har halverat dödligheten under de senaste decennierna i västvärlden.


Syfte

Vi vill specifikt undersöka om en sjuksköterskeledd telefonbaserad uppföljning efter hjärtinfarkt med individuell medicinjustering:

- Är tillämpbar i den normala patientgruppen med hjärtinfarkt.
- Är i jämförelse med dagens vård mer följsamt till vetenskaplig utveckling.
- Uppnår bättre resultat under de första 12 månaderna än sedvanlig uppföljning avseende behandling av blodfettsrubbning (LDL kolesterol) samt blodtryck.
- Ökar följsamheten till statiner, den vanligaste behandlingen av blodfettsrubbning.
Metod
Avhandlingen baseras på den randomiserad kontrollerade studien NAILED (Nurse-based Age independent Intervention to Limit evolution of Disease) som har två armar: en med akut koronart syndrom (hjärtinfarkt och instabil kärlkramp) samt en med stroke och TIA (transient ischemisk attack). Alla ingående delarbeten förutom studie II fokuserar på patienter med akut koronart syndrom

NAILED-ACS

Intervention
I interventionsgruppen skedde utefter behov efter svar på mätvärdena en medicinjustering för att uppnå måltvärdena på blodtryck (<140/90 mmHg) samt LDL-kolesterol (<2,5mmol/L). Justeringen utvärderades efter 4 veckor med nya mätningar och om fortsatt behov upprepades denna rutin tills målvärde uppnåtts eller en bedömning om att målet var ouppnåeligt. Patienterna fick även råd om livsstilsförändringar.

Kontroll
I kontrollgruppen skedde ingen justering eller rådgivning, och resultaten av mätningarna skickades till patientens ordinarie vårdcentral och eventuell vidare justering skötes därför frän enligt gällande rutin.
Studie I
I den första studien undersökte vi hur stor andel av patientgruppen som kunde och ville delta i studieupplägget. Vi undersökte vilka faktorer som bidrog till deltagande eller icke-deltagande.

Studie II
Under 2013 genomförde primärvården i länet en justering av målvärdet för LDL-kolesterol hos diabetiker från <2,5 mmol/L till <1,8 mmol/L för att följa nationella riktlinjer. Vi antog samma målvärde i studien, och undersökte vad som hände med behandlingen i de två grupperna under det följande året. I denna studie inkluderade vi patienter med både akut koronart syndrom och stroke/TIA.

Studie III
Vi undersökte resultatet av interventionen i jämförelse med kontrollgruppen med avseende på LDL-kolesterol och blodtryck under det första årets uppföljning.

Studie IV
I fjärde studien undersökte vi andelen som avslutat behandling med statiner under minst 3 år av uppföljning. Vi tog reda på orsaker till avslut och vilka individfaktorer som ökar risken för avslut av behandling.

Resultat
Av 907 bedömda patienter kunde 72,9% inkluderas, 11% avstod deltagande och 16,1% exkluderas. Den vanligaste orsaken till exklusion var deltagande i annan studie följt av demens eller annan svår sjuklighet. Icke-deltagande patienter (exkluderade och de som avstod) var i allmänhet äldre, med mer samsjuklighet samt lägre utbildningsnivå jämfört med deltagande patienter. Detta avspeglades även i en ökad risk för död i gruppen av icke-inkluderade patienter.

Före förändringen av riktlinjerna för LDL-kolesterol uppnådde 96% av de 101 diabetikerna i interventionsgruppen målnivån på <2,5 mmol/L. Samma andel i kontrollgruppen var 70% av 100 patienter. Ett år efter målnivåjustering till <1,8 mmol/L uppnådde 65% av diabetikerna i interventionsgruppen och 36% i kontrollgruppen den nya målnivån. Den vanligaste orsaken till att inte uppnå den nya målnivån var i interventionsgruppen fulldos behandling och i kontrollgruppen att ingen läkemedelsjustering hade utförts.

Efter den medicinska justeringen 1 månad efter utskrivning uppnådde 94,1% i interventionsgruppen målvärdet för LDL-kolesterol (<2,5 mmol/L), jämfört med 68,4% i kontrollgruppen. Vid 12-månaderskontrollen uppnådde 77,7% i interventionsgruppen samma målvärde jämfört med 63,2% i kontrollgruppen. Vid 1 månadskontrollen var LDL-kolesterol i medel 0,38 mmol/L lägre i
interventionsgruppen och vid 12 månadens kontrollen 0,3 mmol/L lägre jämfört med kontroller. Gällande blodtryck efter justeringen vid 1 månad uppnådde i interventionsgruppen 91,9% målvärdet för systoliskt blodtryck och 96,2% målvärdet för diastoliskt blodtryck jämfört med kontrollgruppen där 65,6% uppnådde målet för systoliskt samt 82,0% för diastoliskt blodtryck. Vid 12-månaderskontrollen uppnådde i interventionsgruppen 68,9% målvärdet för systoliskt och 88,1% för diastoliskt blodtryck. Motsvarande uppfyllelse i kontrollgruppen var 63,7% för systoliskt och 82,8% för diastoliskt blodtryck. Medelblodtryck var efter medicinjustering vid 1 månad 7 mmHg systoliskt och 4 mmHg diastoliskt lägre i interventionsgruppen jämfört med kontrollgruppen. Vid 12 månader var medelblodtrycket i interventionsgruppen lägre jämfört med kontroller med 1,5 mmHg systoliskt och 2,1 mmHg diastoliskt.

Vid bedömning av följsamhet till statinbehandling var 89,3% i interventionsgruppen och 81,7% i kontrollgruppen följsamma efter i medel 3,9 års uppföljning. I interventionsgruppen avslutade 27,8% sin behandling någon gång under studietiden och motsvarande siffra i kontrollgruppen 20,8%. Den vanligaste anledningen till ett första avslut var i båge grupperna undvikbar (biverkan utan tydlig relation till medicinering). Den vanligaste anledningen till ett permanent avslut var i interventionsgruppen oundvikbar (avancerad sjukdom inklusive demens) och i kontrollgruppen fortsatt undvikbar (biverkan utan relation till medicinering). Kvinnor löpte en ökad risk för behandlingsavslut och s.k. ST-höjningsinfarkt vid vårdtillfället minskade risken. Att vara deltagare i interventionsgruppen ökade risken för ett första behandlingsavslut men minskade risken för att permanent avslut.

**Slutsatser**

En sköterskeledd telefonbaserad metod för sekundär prevention efter akut koronart syndrom kan innefatta en stor andel av en normal hjärtinfarktspopulation. Jämfört med nuvarande rutin leder metoden till ökad följsamhet vid förändringar i rutiner samt bättre måluppfyllelse av de viktigaste riskfaktorerna högt blodtryck och blodfettsrubbning. Metoden leder även till ökad följsamhet till statinbehandling och minskad risk för undvikbara avslut av densamma.
Introduction

Atherosclerosis and acute coronary syndrome

Atherosclerosis
Atherosclerosis is a systemic inflammatory vascular disease that can affect the arteries in almost all systemic organs. The inflammatory process begins in early adulthood and progresses without symptoms at various rates but most commonly over decades. The disease is driven by risk factors (i.e., familial predisposition, physical inactivity, obesity, smoking, dyslipidaemia, and high blood pressure [BP]), but these are not always present.

The normal arterial wall consists of three layers. The innermost of these, the tunica intima, has a single layer of endothelial cells towards the arterial lumen, which ensures passage of nutrients as well as protecting the blood from exposure to thrombogenic stimuli. The intima also contains smooth muscle cells (SMCs). The second layer, the tunica media, consists of extracellular matrix such as collagen in which SMCs are embedded. The third and outermost layer, the tunica adventitia, mainly consists of mast cells, microvessels, and nerve endings.

The most widely accepted notion is that intimal endothelial cells subjected to irritative stimuli such as shear stress, dyslipidaemia, hypertension, or a pro-inflammatory environment express surface adhesion molecules for inflammatory cells. In this process, the endothelial cell membrane becomes permeable to these inflammatory cells, which are mainly mononuclear phagocytes and also T cells that transmigrate into the intima. The monocytes differentiate into macrophages, which in turn engulf cholesterol containing low-density lipoprotein (LDL-C) from the blood, forming a nascent atheroma or “fatty streak” within the intima. Lipid-containing macrophages differentiate into “foam cells”, which attract SMCs and initiate production of extracellular matrix. A plaque with a fibrous cap is formed and foam cells start to die in a more or less organized manner. The lipid-rich residues from foam cells and cholesterol crystals often reside in the central part of the plaque, forming a soft necrotic core with inflammation-mediated formation of a disarrayed microvascular structure. The plaque formation extends the diameter of the vessel wall both inwards and outwards, sometimes obstructing the blood flow in the arterial lumen. (1)

Today, three known mechanisms underlie the pathogenesis of acute coronary syndrome (ACS):
1. *Plaque erosion* is a disruption in the endothelial cell layer that induces thrombus formation within the vessel lumen. However, the fibrous cap overlying the plaque is not disrupted, and the plaque generally lacks a necrotic core. The plaque is associated with minimal or no active inflammation. The mechanism behind the erosion is poorly understood. (2)

2. In *plaque rupture*, the most common reason for thrombus formation (about 70%), the fibrous cap over the plaque develops fissures, exposing the lipid-rich matrix and allowing pro-inflammatory as well as thrombogenic mediators into the arterial lumen. This process initiates thrombus formation within the vessel lumen, which partly or totally obstructs the blood flow. The rupture can be mediated by an inflammatory process, occurring by microvascular bleeding within the core or associated with hardened calcium nodules within the vessel wall. (3)

3. In the third case, no apparent thrombus can be found at invasive investigation or autopsy.

**Acute coronary syndrome, or ACS**

Injury to the myocardium encompasses a wide variety of underlying and precipitating factors, one of which is ACS. ACS is characterized by an insufficiency between the supply and demand of blood in cardiac myocytes because of reduced blood flow in the coronary arteries. The syndrome covers acute myocardial infarction (MI) and unstable angina (UA). (4)

This dissertation is based on the Nurse-based Age-independent Intervention to Limit Evolution of Disease after ACS (NAILED-ACS) study, in which we used the third universal definition of myocardial infarction: *clinical signs and symptoms of myocardial ischaemia with evidence of myocardial necrosis*. (5) This evidence comprises a rise or fall in myocardial-specific biomarkers (e.g., cardiac troponins), MI-specific electrocardiography (ECG) changes, or radiological evidence of imminent loss of viable myocardium or incessant coronary thrombus. Type 1 MI is defined as *an event related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus and myocyte necrosis*. It can further be clinically subclassified into non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), based on associated ECG changes.

ACS also encompasses UA, which is characterized by symptoms consistent with myocardial ischaemia but without elevation in biomarkers for myocardial injury. (5) In the NAILED-ACS, we also required changes on the ECG suggestive of ischaemia for the diagnosis of UA.
Of note, there is a wide range of underlying causes for coronary obstruction, presenting from gradual evolution of symptoms to MI or death as a first symptom. An initial plaque with luminal obtrusion might lead to ischaemic symptoms without myocardial necrosis in the context of increased oxygen demand (stable angina). With increasing obstruction, the symptoms might appear without any evident context of increased demand (unstable angina). In the event of plaque erosion or rupture, a thrombus might partially or totally occlude the coronary lumen, leading to myocardial necrosis (NSTEMI or STEMI). This occlusion may also be temporary or permanent, depending on endogenous thrombolysis.

**Epidemiology**

Cardiovascular disease (CVD) is the most common cause of death globally, accounting for a third of all deaths and 45% of deaths from non-communicable disease. This rate is more than twice that caused by cancer. (6) In the PURE study, the authors found that even though the risk for MI was most profound in high-income countries and least in low-income countries, mortality rates were inversely related with highest mortality in low- and middle-income countries, constituting 80% of all deaths due to CVD. (7) The total cost related to CVD in the EU was estimated in 2009 as €106 billion, constituting 9% of total health expenditures, and the estimated global total cost for society was $863 billion.(8, 9) Because of this large mortality burden, global inequality, and cost, the World Health Organization (WHO) began an initiative to reduce mortality from non-communicable disease globally by 25% by 2025. (9)

According to the report from the Swedish National Board of Health and Welfare statistics (10) , approximately 340/100 000 inhabitants or 26 400 Swedes experienced an MI during 2017. Despite an increase in mean age in the population, the incidence of MI has been steadily decreasing in recent decades, by almost 50% in western countries. More men than women have MIs, although the sex differences are narrowing, according to the Swedish statistics. The incidence increases with age and with a lower level of education. Also, mortality due to MI has more than halved during the same period, at 82 deaths per 100 000 in 2016. The decline in mortality is an effect of both the reduced incidence of MI and an increase in survival among those who experience it. In cause of death registries, about one-quarter of patients die from any cause within the first month after the MI and one-third within the first year after an ACS. (10) (11)
**Risk factors**

Risk factors for developing atherosclerosis are complex and well-studied, elucidated by both interventional and observational research. Despite prominent key candidates, findings show a clustering of factors that have a cumulative influence on the risk profile. (8) In a study of 2369 patients treated for MI, 93% had ≥1 risk factor, 72% ≥2 risk factors, and 40% ≥3. (12) The INTERHEART study was a worldwide case–control study that aimed to establish the effect of modifiable risk factors on ACS and whether their contribution varied by geographic region. These authors found that nine risk factors (abnormal lipids: odds ratio [OR] 3.8; smoking: OR 2.9; history of hypertension: OR 2.5; diabetes: OR 3.0; abdominal obesity: OR 2.2; psychosocial factors: OR 2.5; physical activity: OR 0.7; daily consumption of vegetables/fruit: OR 0.7; and moderate alcohol intake: OR 0.8) could account for 90% of the increased risk in men and 94% in women, irrespective of age and region of the world. (13) Individual factors also contribute differently in short-term and the life-time risk, as well as in primary and secondary prevention. These distinctions indicate that the importance of treatment intensity of individual risk factors might vary in younger age compared to established disease in the elderly. (8) In the Framingham heart study, age, dyslipidaemia, elevated BP, smoking, and diabetes were the most crucial determinants, and factors for modification. (14)

In an attempt to explain the decline in coronary heart disease (CHD) incidence in recent decades in the western world, Björck et al found that 36% of the reduction was attributable to advancements in treatment and 55% to decreases in risk factor contribution in Sweden. The primary factors were a decrease in serum cholesterol levels because of changed dietary habits and a decline in smoking prevalence. This pattern is in contrast to a contemporary increase in prevalence of both obesity and diabetes during the period. (15)

**Initial treatment and secondary prevention**

In recent decades, the initial management of ACS has changed substantially, and the benefits of early reperfusion of the coronary arteries to reduce further damage and death have played a major role. Percutaneous coronary intervention (PCI) with balloon angioplasty and placement of a metal stent to protect the integrity of the vessel lumen is now the gold standard in most cases of lumen obstruction. This procedure is not only especially crucial in context of clinical evidence of occlusion (i.e., STEMI) but also recommended early in the event of intermittent obstruction (NSTEMI and UA). If time from onset of symptoms to revascularization cannot be minimized, fibrinolytic therapy is recommended followed by PCI. In circumstances with a more high-risk coronary disease and under relatively stable clinical circumstances, the indication is for surgical revascularization with coronary artery bypass grafting (CABG).
Simultaneously, medical treatment is initiated to decrease the acute burden of cardiac stress, stabilize the thrombogenic situation, and commence secondary prevention. Antithrombotic treatment after stent placement is usually a combination of acetylsalicylic acid (ASA) and a P2Y12 inhibitor. Other guideline-recommended cardioprotective treatments initiated during post-MI care are usually a hypertensive agent such as an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (ARB) together with beta-receptor blockade and a lipid-lowering HMG-CoA reductase inhibitor (i.e., statin). (16)

When CVD is established, all patients are regarded as high-risk for recurrent events and thus as candidates for intense secondary prevention. (8) In the Global Registry for Acute Coronary Events (GRACE), 3.6% of STEMI patients suffered a new MI within 2 years, as did 5.6% of NSTEMI patients and 3.9% of those with UA. (17) In a retrospective Swedish registry study by Jernberg et al, 10% of the cohort suffered a new MI during the first year after discharge for the index MI, and another 8% during the subsequent 2-4 years. (18)

Secondary prevention programmes, i.e., interventions to reduce the risk for further events when disease is established, reduce risk for hospital readmission and recurrent MI. (19) Secondary prevention in CVD is generally aimed at modifying all possible risk factors. Motivational counselling and training (i.e., cardiac rehabilitation [CR]) is recommended to address behavioural aspects such as sedentary lifestyle, overweight, dietary habits, and smoking cessation. Meta-analyses of organizational strategies to conduct cardiac rehabilitation could not establish superiority of any of the usual components, such as exercise or comprehensive risk factor education. (20) (21) Medical treatment is crucial for elevated BP, dyslipidaemia, and disturbance in glucose regulation. Medical treatment of risk factors alone is perceived to reduce the risk of MI by 20%–88% (22, 23)

**Secondary prevention in clinical practice**

The major cardiovascular societies have issued guidelines on evidence-based risk factor evaluation and targets as well as the most effective means to conduct a secondary preventive program (8, 24) But participation in a secondary preventive program remains disappointingly rare. Studies show that among MI patients, only 14%–35% participate in such a programme and that 70% of suitable patients do not receive dedicated intervention to reduce their risk profile. (25)

In the EUROASPIRE surveys of a cross-sectional European ACS cohort, the number of patients on recommended medication at discharge increased incrementally over time and is now at 80%. Still, 12 months after discharge, few had reached adequate risk factor control. Of patients, 59.9% were physically
inactive, 58.2% had central obesity, and 42.7% had a BP and 80.5% LDL-C above target. (26)

These data imply that the search for more effective means to conduct secondary preventive intervention must continue. Such a programme must be easily accessible in all aspects of society and have a patient-centred approach. It is also important that a resource effective programme is adaptive to current evidence and guidelines. (25, 27) Guidelines acknowledge the advantages for home-based rehabilitation and use of telemedical methods to increase programme participation. (8, 28)

**Low-density lipoprotein cholesterol, or LDL-C**
Total cholesterol in serum mainly consists of LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Although HDL-C seems to counteract the atherosclerotic process, LDL-C is causally related to atherosclerotic disease progression. (1)

The mainstay of treatment for high LDL-C in high-risk individuals are HMG-CoA reductase inhibitors (collectively called statins), which reduce cholesterol biosynthesis and modulate lipid metabolism. (29) Statins, one of the most researched areas in modern cardiovascular medicine, have been proven effective in reducing both LDL-C levels and cardiovascular morbidity and mortality. With every 1 mmol/L reduction of LDL-C, recurrent cardiovascular morbidity and mortality decreases by 20%. The benefit continues, according to current evidence, without a lower limit in LDL-C (30, 31) (32), regardless of age (33).

**Blood pressure, or BP**
Elevated BP is the most prominent risk factor for premature mortality, leading globally to 9 million deaths yearly and still increasing in incidence. (34) Hypertension is widely prevalent in society, with more than one-third of adults affected. The risk for CVD mortality shows an incremental increase from BP levels as low as systolic BP (SBP) 115 mmHg and diastolic BP (DBP) 75 mmHg. The absolute risks from elevation in BP are age-related, but in adults ages 40–69 years, the risk for CVD death doubles with each SBP increase of 20 mmHg. (35) The age-related relative risk from hypertension is fairly constant, even though the absolute risk is more limited in the young and in the very elderly. But both the HYVET and SPRINT trials showed beneficial risk reduction from treatment in the very elderly. (36, 37) As with LDL-C, meta analyses show a proportional relationship between BP-lowering and reduction on morbidity and mortality irrespective of pre-treatment values. (38) (39) There is through some evidence for a J-shaped relation between risk and BP treatment, with a reduced or even inversed benefit/harm ratio in the low BPs especially for diabetics. (40) The nadir
for the risk related to BP is therefore still highly debated. (41) (42) (43) But guidelines support, and evidence is fairly consistent with, a BP target of <140/90 mmHg. (8)

Initial treatment of elevated BP includes lifestyle interventions consistent with reduced salt intake, increased physical activity, weight control, reduced alcohol intake, and smoking cessation. In the group with high risk for atherosclerotic events, simultaneous initiation of anti-hypertensive drug treatment is recommended. A large number of randomized trials have now established that the main benefits are due to absolute BP reduction and do not depend on the type of agent used. (38) There might be some minor benefits in regard to different settings and co-morbidities with some drugs, but the main type recommended are thiazide diuretics, ACEIs or ARBs, β-blockers, and calcium-channel antagonists. (8)

**Adherence and persistence**

In the effort to reduce the burden of CVD, we now have the knowledge and inexpensive, effective drugs to achieve evidence-based risk factor targets. Intervention is of utmost importance, but without the patient incentive to adhere to treatment plan, efforts are futile.

In spite of the high prevalence of modifiable risk factors in the MI setting, the Study of Patient Information after percutaneous Coronary Intervention (SPICI) trial of patients who had undergone PCI found that non-modifiable risk factors (age and sex) were believed to contribute more to coronary disease than modifiable factors. Two-thirds of the patients also perceived that they were cured, and 38% felt that there was no need for them to change their habits. Only 27% acknowledged the persistent risk and need for further interventions. (44) These findings point to a pedagogical problem in communicating the lifelong risk factor reduction that must be achieved.

A patient’s non-adherence to treatment can manifest in multiple ways and thus provides a complex situation to study. Patients may refuse to initiate treatment or will temporarily or permanently discontinue it, change their dosage, or alter the dosing interval. These disruptions may be intentional or unintentional, and patient ability to correct estimate drug behaviour varies.

Studies using electronic monitoring for treatment of chronic disease show that patients claiming adherence show six categories of behaviours in equal distribution: strict adherence; taking virtually all doses, but with some timing irregularities; omitting an occasional single day’s dose with some inconsistency in timing; taking drug holidays (≥3 days off drug) 3-4 times a year and
occasionally missing a dose; taking at least monthly drug holidays and having frequent dose omissions; and taking few or no doses while giving an impression of good or perfect adherence. (45).

Long-term adherence to therapies for chronic illness are continuously at rates below 50%. (46) (47) Haynes et al conclude in their meta-analysis that:

“Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment”.

The WHO addressed the problem of poor adherence in 2003 to shift the focus from patient-related factors and place the “blame” on the health provider–patient relationship and cooperation. (48) The semantics of the patient’s relation to treatment are somewhat confusing in the literature. The WHO advocated replacing the previously used “compliance” with “adherence” to stress the agreement between provider and patient. WHO defined adherence as: “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider”.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) then defined adherence as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen”. ISPOR also defined persistence as “the duration of time from initiation to discontinuation of therapy”. (49) This means that neither adherence nor persistence alone completely encompasses the full complexity of patient behaviour towards treatment.

Methods for measurements of adherence can be sorted into direct and indirect methods. Direct methods could be drug measurement in blood or urine and indirect methods include patient self-report, pill counts, or time to refill. They all have different advantages and disadvantages, and none is considered the gold standard, although some may be preferred under certain clinical or research conditions. (50)

There are many aspects involved in what contributes to patient adherence, related to the patient, the patient–prescriber relationship, and the patient–healthcare system relationship. Claxton et al found that the number of doses was inversely correlated with adherence. (51) Studies of predictors for non-adherence have additionally highlighted:
• Presence of psychological problems, particularly depression;
• Presence of cognitive impairment;
• Treatment of asymptomatic disease;
• Inadequate follow-up or discharge planning;
• Side-effects of medication;
• Patient lack of belief in benefit from treatment;
• Patient lack of insight into the illness;
• Poor provider–patient relationship;
• Presence of barriers to care or medications;
• Missed appointments;
• Complexity of treatment; and
• Cost of medication, co-payment, or both. (50)

Persistence or adherence rates are usually higher in randomized controlled trials (RCTs) than in observational studies, and the latter are generally seen to concur better with the real-world setting. (52) In a meta-analysis of statin adherence in both primary and secondary preventive settings, rates were 49% in observational studies and 90.3% in RCTs. (53) In the EUROASPIRE survey, the proportion of participants adherent to statins increased over time from 18.5% in the first survey to 85.7% in the fourth study at 6 months after discharge. (54, 55) (26) In a study over a longer term, Perrault et al found in a secondary preventive cohort that persistence to statins dropped from 71% in the first 6 months to 45% after 3 years. (56) The main hindrance was polypharmacy and an increasing number of prescribing physicians.

Naturally, there are different consequences for non-adherence, depending on the treatment to which it refers and whether it is intended for an acute or chronic condition. Non-adherence to anticoagulation in thromboembolic disease or antibiotics could have more direct consequences than lack of adherence to antihypertensive treatment or statins. Adherence is usually lower in treating chronic conditions or in prevention compared to acute or more symptomatic conditions. (48) A high level of adherence to statins (>80%) reduces both cardiovascular events and mortality, and the same applies to duration of time under treatment. (57, 58) (30, 47)

In their review, Osterberg et al suggested four categories of methods for enhancing adherence: patient education, improved dosing schedules, increased opportunity to contact the clinic, and improved patient–prescriber relations. They concluded that a multifactorial approach must be used, incorporating behavioural intervention, reinforcements, education, and convenience of care. They also stress involvement of other medical staff besides physicians and avoiding a paternalistic attitude. (50)
Nurse-based telemedicine

To address the problem with low target achievement and participation in secondary preventive programmes, guidelines recommend using new and multidisciplinary approaches. (59) (8) As stated in the adherence section, the critical issues for the patient are an individualized and flexible approach, high availability, and a bilaterally trusting relationship. Such a programme must be easily accessible disregarding distance to health care and involve as large proportion of patients as possible. It must also be resource effective and preferably involve other healthcare professionals besides physicians. (59)

Meta-analyses of changes in organizational approach (i.e., education of the patient/physician, scheduled appointments) have not identified an effect on risk factor management. (60) (61) One exception is telephone-based follow-up conducted by nurses, which has shown a beneficial increase in both participation rates and risk factor control compared to usual care. (62) (63) (64). Home-based cardiac rehabilitation (CR) in comparison with hospital-based rehabilitation has been proven to be non-inferior and have increased feasibility. (65) In a meta-analysis of nurse-coordinated care, nurse-managed medical adjustments were successful in reducing SBP and LDL-C and also prevalence of smoking. But the analysis was hindered by the heterogeneity of multifaceted studies with a lack of focus and different outcomes, precluding adequate conclusions. Factors for success that the authors identified were nurse-mediated medical adjustments according to predefined algorithms, goal-oriented tailored behavioural consultations, and frequent follow-up. (66)

Most studies of telemedical intervention programmes are restricted by small study populations, extensive selection criteria, single target intervention, and short duration. These factors create circumstances that are not easily generalized to the ordinary clinical setting, which often involves multi-morbidity and an elderly population. Studies are needed on unselected cohorts with longer durations and multifactorial interventions in lifestyle and strict risk factor control.
Aims

1. To analyse the feasibility of a nurse-led, telephone-based secondary preventive programme after ACS in a community-based cohort

2. To analyse the performance of such an intervention in adapting to new guidelines in comparison with usual care

3. To measure the effect of the intervention at the group level on LDL-C and sitting BP during the first 12 months of the NAILED-ACS trial

4. To measure long-term adherence to statins in the NAILED-ACS trial together with rates, reasons, and predictors for discontinuation
Materials and Methods

This dissertation is based on the “Nurse-based Age-independent Intervention to Limit Evolution of Disease” study (or NAILED), conducted in the county of Jämtland-Härjedalen, Sweden.

Setting

Sweden has a publicly financed healthcare system, which includes coverage of both in-hospital and outpatient care as well as subsidies for medication. The patient co-finances a small part of the healthcare costs, and subsidies for medication increase with a maximum threshold for full coverage.

The county of Jämtland-Härjedalen is a vast rural inland area (49,341 km²) in mid-Sweden. The region is sparsely populated with about 130,000 inhabitants and an average age slightly above the mean in Sweden (mean 43 y vs. 41 y). About a third of the population lives in the regional capital Östersund. The region has one secondary care provider in Östersund Hospital, with the only means for inpatient care and a coronary care unit (CCU), where all cases of suspected ACS are referred. Since March 2015, the hospital has been equipped with a 24-7 catheter laboratory for interventional cardiology. Before this, and for those requiring thoracic surgery, patients in need of intervention were referred to the tertiary care centre at Umeå University Hospital. The primary care providers (Hälsocentraler) are interspersed throughout the region at 28 locations [Fig 1].

The NAILED study

The NAILED study is an open, randomized, controlled, parallel group trial. It was initiated in 2010 with two arms, one after ACS and one after stroke and transient ischaemic attack (TIA). This thesis is mainly an evaluation of the ACS arm. In the study, we defined ACS according to the third consensus definition from 2007 as MI type 1 (STEMI, NSTEMI) or UA. We defined UA as symptoms and changes in ECG indicative of ischaemia (i.e., ST depression or T-wave changes) but without measurable biomarkers for myocardial necrosis. Our study nurses are all cardiac nurses with long clinical experience who applied to participate. They received no
formal extra education but were previously trained in motivational interviewing. The study physicians are all practicing at the CCU.

**Participants**
All patients admitted and with evidence of ACS were eligible for inclusion. Patients were identified by the study nurses through daily review of hospital records. An initial 3-month run-in control of our routine to identify patients hospitalized for ACS showed that all eligible patients were identified. During hospitalization, a study nurse assessed patients for inclusion. Our inclusion criteria were ACS and willingness to participate. We limited criteria for exclusion to inability to adhere to our telephone-based study design and participation in another ongoing trial. These criteria include severe or terminal illness not suitable for secondary prevention, and physical or cognitive inability to handle a telephone or to commute to the closest healthcare facility.

After assessment for eligibility, patients were informed about the study, and participants signed an informed consent. We then randomized patients stratified by sex and type of ACS into an intervention or control group in a 1:1 manner by a computerized allocation sequence in blocks of four. The resulting allocation was not blinded to patients, study personnel, or other healthcare providers. All patients, regardless of allocated group, obtained our conventional in-hospital information about ACS, individual risk factor assessment, and an offer of follow-up at the cardiology outpatient clinic. These outpatient visits were usually a nurse visit at 1 month after discharge and a visit to a cardiologist after 3 months. STEMI, high-risk, and younger patients were also offered a visit after 12 months.

**Outcomes and targets**
The primary outcome of the NAILED study was LDL-C at 36 months of follow-up. Secondary outcomes were LDL-C at 12 and 24 months, total cholesterol, standardized sitting systolic and diastolic BP, and the proportion of patients achieving set targets for these measurements at 12, 24, and 36 months of follow-up. Other secondary outcomes were standing BP, rates of smoking, proportion of patients on guideline-recommended preventive drugs, diabetes control measured by glycated haemoglobin (HbA1C), change in body mass index (BMI), and rate of physical activity. Secondary outcomes were assessed in an exploratory analysis.

Measurements were made at each patient’s nearest healthcare provider, and the patient was equipped with a letter of measurement instructions for standardization. LDL-C was analysed at the hospital laboratory and calculated using the Friedwald formula from fasting serum concentration of cholesterol and triglycerides. BP was measured in the right arm, with the patient sitting after 5
minutes of rest and standing after 1 minute. The healthcare provider used manual or automated BP measurement according to their usual routine.

Our initial targets in the study were LDL-C <2.5 mmol/L and a seated BP <140/90 mmHg. As of March 2013, the primary health care in the county changed their target for LDL-C for CVD secondary prevention in diabetic patients to <1.8 mmol/L. The same lower target was adopted for all patients in the local primary healthcare secondary prevention guidelines as of February 2016. Subsequently, we also amended these targets in our study to conform with local guidelines in January 2017.

**Intervention**

The intervention commenced 1 month after discharge for the including event, with telephone contact by the study nurse with patients allocated to intervention. Prior to the call, patients had undergone blood specimen collection and standardized BP measurement. During the call, the nurse interviewed the patient about general well-being, current cardiac symptoms, self-reported adherence to medication, and possible side-effects. The nurse also inquired about healthy living, i.e., diet, exercise, and tobacco abstinence. The patient was informed about the results of blood samples and BP. If indicated to achieve targets, a motivational dialogue was initiated on behavioural changes and medical adherence. If the patient was not within the set limits for LDL-C or BP or had intolerable side-effects, adjustments in medication were made in cooperation with a joint study physician. These adjustments were then re-assessed after 4 weeks with new measurements. If the results were still above set targets, the procedure for titration and re-assessment was reiterated until set targets were met or deemed unachievable. Pharmacotherapy adjustments were made with individual considerations without pre-specified algorithms. This process of interview, assessment, and medication titration was repeated at a 12-month interval until at least 36 months post-discharge or the end of the study. Unscheduled visits could be made upon patient request [Fig 2].

**Control**

Patients allocated to control were telephoned in the same manner 1 month after discharge by a study nurse after undergoing the same measurements of BP and blood specimens at their nearest healthcare provider. They were interviewed about well-being, cardiac symptoms, treatment adherence, side-effects, and healthy living. The study nurse was instructed that no motivational intervention should take place, and no titrations were made. The results of blood samples and BP measurements were forwarded to each patient’s general practitioner (GP). The nurse repeated this procedure at a yearly interval until at least 36 months after discharge or end of study [Fig 2].
Study design

Study I
In the first study, we aimed to analyse the proportion of a community-based cohort that could be included in a nurse-led, telephone-mediated secondary preventive intervention. Our secondary aim was to examine reasons and possible individual characteristics for non-inclusion, i.e., those excluded and those who declined participation. The NAILED-ACS database was the main source of information. We also analysed the 12-month mortality in each group. We based causes of mortality on the Swedish National Cause of Death Registry or, if inconclusive, medical records. We estimated kidney function with glomerular filtration rate (eGFR) calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and patient functional status according to the modified Rankin Scale (mRS).
**Study II**

In the second study, we aimed to investigate the adaptability of our intervention programme to the ever-changing field of medicine. We did this by comparing the performance of the intervention with the performance of routine primary care when implementing a guideline change in LDL-C target in patients with diabetes.

Our primary outcome was the proportion in each group that reached the defined target for LDL-C before and after the guideline change. The median difference in LDL-C before and after the guideline change and in-between group comparison were our secondary outcomes.

The primary care system in Jämtland has a routine for distributing information on medical news and guideline changes through a joint email group. Through this communication, a guideline update was issued on 14 February 2013 regarding patients with diabetes to adapt to national guidelines. These included a new lower LDL-C target for patients with diabetes and established CVD, from <2.5 mmol/L to <1.8 mmol/L. In the NAILED study, we adopted this new target on 24 March the same year to comply with the primary care routine. No other changes were made in terms of assessment intervals in the study. The stated primary care routine for patients with diabetes in our county is to offer yearly visits to their physician. This visit should include risk factor assessment for CVD and adjustment in treatment to reach set targets.

To study the effect of this guideline change, we included all patients in the NAILED database (ACS as well as the stroke/TIA cohort) with diabetes who had had any follow-up before 14 February 2013 and another follow-up between 31 March 2013 and 15 June 2014. As baseline characteristics, we used those most recently reported in the study before the guideline change.

If a patient reached the new LDL-C target at study assessment after 31 March, we reported this as the endpoint LDL-C. If not, we reported the last value after titration as the endpoint value. In the control group, we scrutinized the medical records of those not achieving the new target at their first study follow-up. We performed this step to establish if the primary care physician had taken note of the newly measured LDL-C and if this resulted in an appropriate action. If we found no record within the first month after LDL-C measurement at our study assessment, we used the LDL-C at the first diabetes visit after 31 March. If titration occurred, we used the post-titration measurement. If we found no records on LDL-C or no routine diabetes visits during the set study time, we used the LDL-C at the study follow-up.
Study III
In the third study, we aimed to measure the effect of the intervention on LDL-C and BP during the first 12 months of follow-up. These data comprised the outcome of the initial titration at the first baseline follow-up 1 month after discharge and the 12-month assessment prior to titration. Because no titrations were made in the control group, we used the values at the NAILED 1-month baseline measurement for the control group to compare with the post-titration values of the intervention group. To particularly examine the effect of the intervention, we also analysed data for those who did not reach targets for LDL-C and BP at baseline. In addition, we presented the proportions that reached each target. Targets in the study were LDL-C <2.5 mmol/L, SBP <140 mmHg, and DBP <90 mmHg. As noted in study II, the target for patients with diabetes changed during the studied period. For statistical reasons, we maintained the old, higher target for the whole population in this paper. The NAILED-ACS database was our source of information.

Our primary outcome was mean difference in LDL-C between the intervention and control groups at 12 months after discharge. Mean difference in SBP and DBP at 12 months of follow-up as well as proportions achieving target at each assessment were our secondary outcomes.

Study IV
In the fourth study, we aimed to measure the proportion adherent to statin treatment in both the intervention and control groups over time. Our secondary aim was to quantify termination of statin treatment and the reasons for and predictors of doing so.

At each scheduled assessment, the study nurse verified the patient’s self-reported adherence and present medication. The reported medication was then compared to the corresponding data in the medical record. If the patient had changed or terminated treatment since last follow-up, the nurse addressed the patient with the aim of coming as close as possible to finding the reason why. If the interview proved inconclusive, we scrutinized the joint medical records of in-hospital and primary care to further elucidate the cause. Also, if the LDL-C value differed considerably from previous measurements, the nurse initiated a more in-depth interview.

We recorded every discontinuation with a date and cause estimate. We then classified reasons for discontinuation as:
• Lack of motivation
• Side-effect with a compelling association with medication
• Side-effect without a compelling association with medication
• Intervention by another doctor
• Advanced disease
• Dementia
• Misunderstanding by patient
• “Cost-related”

We defined side-effects with a compelling association with treatment as typical symptoms with statins, which appeared in association with start of treatment or dose escalation and terminated with discontinuation. Our nurses were instructed to also re-challenge the patient in the intervention group with statin treatment to prove re-appearance of symptoms, but not all patients were amenable to this step. This procedure was also not an established primary care routine. Pathological blood samples related to statins regarding liver (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin) or muscles (creatine kinase) were also treated as compelling side-effects. A non-compelling side-effect did not fulfil these criteria.

We classified compelling side-effects, advanced disease, and dementia as non-avoidable causes. The others we categorized as dependent on the healthcare system or patient- and/or doctor-related factors and thus as potentially avoidable. With the term adherence, we refer to the patient’s self-reported intake of prescribed statins at the end of follow-up.

Because we also wanted to relate our findings to the intensity of treatment, we defined a high-intensity LDL-C–lowering regime as those drugs and doses that could potentially lower LDL-C by 50% or more (simvastatin >40 mg, atorvastatin 40–80 mg, or rosvastatin >10 mg). (30)

**Data acquisition:** We used the following inclusion intervals in the NAILED-ACS database:

I: 1 January 2010 – 31 January 2013
II: 1 January 2010 – 14 February 2013, with follow-up until 16 June 2014
III: 1 January 2010 – 31 December 2013, with follow-up until 27 January 2015
IV: 1 January 2010 – 31 December 2014, with follow-up until 31 December 2017
Statistical methods

In the four papers, we treated our data according to an intention-to-treat principle, in which we included patients not adhering to the treatment plan but excluded those lost to follow-up. We applied a level of significance (alpha level) <0.05 and a confidence interval (CI) of 95%. Unless otherwise noted, we made comparisons between groups by the 2-sided independent samples t-test, Fisher’s exact test, or Pearson’s Chi² test, as appropriate. Continuous variables are in general presented as means and categorical variables as percentages. Specific statistical methods for each paper are presented below. We used IBM SPSS Statistics, Armonk, NY: IBM Corp., USA (V22, Studies I and III; V20, Study II; V23, Study IV) for all analyses except for non-proportional hazards in study IV, for which we used SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

I. We compared baseline characteristics between patients who were included, declined, and excluded with univariable t- or Chi² tests. To identify predictors of the decision to decline participation, we set up a multivariable logistic regression model between declining and included patients. Variables in the model were baseline variables with an alpha level <0.1 on univariable comparison. We then performed stepwise exclusion based on level of significance. To evaluate predictors for exclusion, we set up a second multivariable model between included and excluded patients in the same manner. In the multivariable models, we categorized continuous variables. Regardless of significance, we included sex and age in both regression models and presented the results as odds ratios (ORs). We also performed Kaplan–Meier estimations with the log-rank test to compare 1-year cumulative survival between the groups. We used univariate logistic regression to calculate ORs for mortality.

II. In contrast to the above approach, because our data did not fulfil normal distribution, we presented continuous variables as median and percentiles and used the Mann–Whitney U test for group comparison. For group comparison of categorical variables, we used the Pearson’s Chi²-test. To assess the LDL-C change from baseline to last follow-up, we used the Wilcoxon signed-rank test.

III. To exclude any interaction effect of the stratification variables at randomization (sex and type of ACS), we conducted a two-way analysis of variance for the endpoints of LDL-C, SBP, and DBP. In this study, we also performed a post hoc analysis of patients with values above set targets at baseline because we wanted to explore the effect of drug titration.
IV. To illustrate cumulative incidence of discontinuation over time, we used Kaplan–Meier estimates for both the first and permanent events. To assess predictors for discontinuation, we performed multivariable Cox regression, including baseline variables with step-wise exclusion based on level of significance. In the Cox regression model, we verified proportional hazards with Schoenfeld residuals. Because sex showed a non-proportional hazard over time, we included two time-dependent variables, one representing the initial receding risk and one representing the later proportional risk.

Ethics
The regional ethics board in Umeå approved the NAILED study on 28 October 2009 with Dnr 09-142M. All patients in the NAILED trial signed a written informed consent before inclusion and randomized allocation in the study.
Results

Feasibility of a telephone-based, secondary preventive intervention programme – inclusion, exclusion, declines, and their rates and reasons (Study I)

Between 1 January 2010 and 31 January 2013, a total of 961 patients were hospitalized for ACS. Fifty-four patients died during hospitalization. Of the remaining 907 patients, about two-thirds (64.9%) were diagnosed with NSTEMI, one-third (27.8%) with STEMI, and 7.6% with UA. Mean age was 71.3 years (range 32.5-101 years) Of these 907, 661 (73%) were included in the study, 146 (16%) excluded, and 100 (11%) declined participation [Fig 3].

Figure 3 Allocation of for ACS admitted patients and reasons for exclusion.
Table 1 Patient characteristics. *P* values for comparison: i/e, included vs. excluded; i/d, included vs. declined; d/e, declined vs. excluded; smoking – previous or current; hyperlipidaemia – treatment-initiated or untreated total cholesterol >4.5 mmol/L or untreated LDL cholesterol >2.5 mmol/L; only basic education – compulsory school or less; s – significant; ns – nonsignificant. In hyperlipidaemia data were missing in 25.6% of cases and other variables in <3% of cases.

<table>
<thead>
<tr>
<th></th>
<th>Included</th>
<th></th>
<th>Excluded</th>
<th></th>
<th>Declined</th>
<th></th>
<th>p</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% or SD</td>
<td>n</td>
<td>% or SD</td>
<td>n</td>
<td>% or SD</td>
<td>i/e</td>
<td>i/d</td>
<td>d/e</td>
</tr>
<tr>
<td>Participants</td>
<td>661</td>
<td>72.9</td>
<td>146</td>
<td>16.1</td>
<td>100</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>453</td>
<td>68.5</td>
<td>80</td>
<td>54.8</td>
<td>47</td>
<td>53</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Mean age (y±SD)</td>
<td>69.2 ± 1.9</td>
<td>76.3 ± 12.1</td>
<td>77.3 ± 11.7</td>
<td>s</td>
<td>s</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS&gt;3</td>
<td>7</td>
<td>1.1</td>
<td>33</td>
<td>22.6</td>
<td>8</td>
<td>8.0</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>eGFR</td>
<td>78.4</td>
<td>±21.3</td>
<td>68.9</td>
<td>±22.9</td>
<td>70.4</td>
<td>±21.5</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (mean±SD)</td>
<td>27.3</td>
<td>± 4.5</td>
<td>25.8</td>
<td>± 5.2</td>
<td>26.4</td>
<td>± 5</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Only basic education</td>
<td>345</td>
<td>52.2</td>
<td>99</td>
<td>67.8</td>
<td>77</td>
<td>77.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Heredity (first line)</td>
<td>178</td>
<td>27.3</td>
<td>28</td>
<td>21.5</td>
<td>20</td>
<td>21.5</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Prevalent morbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous IHD</td>
<td>156</td>
<td>23.6</td>
<td>51</td>
<td>34.9</td>
<td>34</td>
<td>34.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Current NSTEMI</td>
<td>420</td>
<td>63.5</td>
<td>100</td>
<td>68.5</td>
<td>69</td>
<td>69.0</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Current STEMI</td>
<td>182</td>
<td>27.5</td>
<td>42</td>
<td>28.8</td>
<td>25</td>
<td>25.0</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>48</td>
<td>7.3</td>
<td>26</td>
<td>17.8</td>
<td>15</td>
<td>15.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>PAD</td>
<td>15</td>
<td>2.3</td>
<td>8</td>
<td>5.5</td>
<td>5</td>
<td>5.0</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>CHF</td>
<td>23</td>
<td>3.5</td>
<td>20</td>
<td>13.7</td>
<td>10</td>
<td>10.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>414</td>
<td>62.6</td>
<td>79</td>
<td>54.1</td>
<td>57</td>
<td>57.0</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>AF</td>
<td>95</td>
<td>14.8</td>
<td>42</td>
<td>29.4</td>
<td>26</td>
<td>26.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>463</td>
<td>96.1</td>
<td>110</td>
<td>96.5</td>
<td>80</td>
<td>100</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>354</td>
<td>53.6</td>
<td>95</td>
<td>65.1</td>
<td>67</td>
<td>67.0</td>
<td>s</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>135</td>
<td>20.4</td>
<td>45</td>
<td>30.8</td>
<td>28</td>
<td>28.0</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>
**Exclusion**

The three most prevalent reasons for exclusion were participation in another trial (43/146; 29%), dementia (37/146; 25%), and advanced disease (35/146; 24%). Thus, the excluded group could be reduced to 11% (n=193) of the eligible population without our pre-specified exclusion criterion of participation in another trial [Fig 3].

Compared with the included group, excluded patients were significantly older, with lower BMI and level of independence measured as mRS >3. They were also more likely to be female and have a lower degree of education. Other significant differences were those consistent with multi-morbidity such as a decreased kidney function and higher prevalence of previous CVD [Table 1]. In the multivariate model, age >85 years, mRS >3, and known congestive heart failure were associated with increased risk for exclusion [Fig 4]. Compared to the group that declined participation, the excluded group had a significantly higher proportion of patients with mRS >3 and a nonsignificant trend towards a higher degree of education [Table 1].

**Declining**

Because it is ethically questionable to investigate patient motives, we have no data on subjective causes for declining participation. In the comparison of baseline characteristics with included patients, declining was associated with increased age, reduced level of independence (measured as mRS >3), lower level of education, and female sex [Table 1]. Patients who declined also had more co-morbidities than those who were included, such as decreased kidney function and more pre-existing CVD [Table 1]. In the multivariable model age >85 years, mRS >3, female sex, and lower degree of education were associated with the decision to decline participation [Fig 4].
Figure 4. Forest plot of multivariable association between included patients and (A) patients who declined and (B) patients who were excluded. Age 65 years or younger was used as reference. Age 65-74 yrs, age 75-85 yrs, age 85 yrs+.
**Mortality**

During the first year after discharge, 6.5% (n=43) in the included group, 16% (n=16) in the declining group, and 19.9% (n=29) in the excluded group died. These rates were significantly different between the included group and those who were excluded or declined, but not between the two non-participating groups. However, the Kaplan–Meier estimates revealed a nonsignificant increase in mortality among excluded patients during the first months compared to those who declined. Cardiovascular reasons were a nonsignificantly more common cause of death than noncardiovascular reasons (52.1% vs. 47.5%) [Fig 5].

![Figure 5 Cumulative survival in the three allocated groups; p, participant; np, non-participant; i, included; e, excluded; d, declined; OR, odds ratio.](image)
Adaptability of a telephone-based intervention programme – guideline change in target LDL-C (Study II)

In the NAILED database, 201 patients (101 in the intervention group and 100 in the control group) with diabetes fulfilled our criteria of 1) at least one follow-up before 14 February and 2) one after 31 March 2013 [Fig 6].

In the intervention group, significantly more patients had ACS than stroke compared with the control group. Baseline characteristics also differed between the groups in terms of lower BP and cholesterol values in the intervention group because these were target parameters in the study. Other baseline characteristics were well-matched [Table 2].

Figure 6 Flow chart for study II.
Table 2 Table 3 Baseline characteristics. *, self-reported health between 0–100; ‡, patient included in the study because of ACS or stroke/TIA; §, rosuvastatin, combination of rosvastatin and ezetimibe or gemfibrozil. Values are reported as median (25\textsuperscript{th}–75\textsuperscript{th} percentiles) if not otherwise specified.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>101</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>72 (66-80)</td>
<td>73 (66-79)</td>
<td>0.99</td>
</tr>
<tr>
<td>Women (%)</td>
<td>27.7</td>
<td>30.0</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>4.0</td>
<td>6.0</td>
<td>0.51</td>
</tr>
<tr>
<td>Self-reported health*</td>
<td>70 (50-85)</td>
<td>70 (50-80)</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior cardiovascular disease</td>
<td>38.6</td>
<td>42.0</td>
<td>0.63</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>58 (50-70)</td>
<td>57 (51-65)</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85 (75-97)</td>
<td>86 (76-97)</td>
<td>1.0</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>103 (95-111)</td>
<td>105 (96-112)</td>
<td>0.55</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>128 (120-133)</td>
<td>134 (124-145)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70 (65-80)</td>
<td>76 (70-82)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>3.7 (3.4-4.0)</td>
<td>4.1 (3.6-4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>1.9 (1.5-2.0)</td>
<td>2.1 (1.6-2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.20 (0.98-1.39)</td>
<td>1.18 (0.97-1.48)</td>
<td>0.88</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4 (1.0-1.9)</td>
<td>1.5 (1.2-2.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Study, ACS‡ (%)</td>
<td>64.4</td>
<td>47.0</td>
<td>0.01</td>
</tr>
<tr>
<td>No lipid lowering treatment (%)</td>
<td>9.9</td>
<td>12.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Simvastatin (%)</td>
<td>47.5</td>
<td>54.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Atorvastatin (%)</td>
<td>36.6</td>
<td>32.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Other antilipids§ (%)</td>
<td>5.9</td>
<td>1.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>
At baseline, before the shift in guideline-recommended LDL-C target from <2.5 mmol/L to <1.8 mmol/L, median LDL-C was 1.9 mmol/L in the intervention group and 2.1 mmol/L in the control group (p<0.001). At the end of this study, median LDL-C was 1.7 mmol/L in the intervention group (p for change from baseline<0.05) and 2.0 mmol/L among controls (p for change from baseline=0.77). In the intervention group, 39.6% received medical titration to adhere to the new target, compared to 9.0% in the control group (p<0.001). The proportion adhering to target for LDL-C decreased in both groups after the guideline change and differed significantly between the groups [Fig 7].

![Figure 7 Proportion in each group achieving target LDL-C <2.5 mmol/L and <1.8 mmol/L before and after guideline change.](image)

Figure 7 Proportion in each group achieving target LDL-C <2.5 mmol/L and <1.8 mmol/L before and after guideline change.
The main reason for not achieving the new target in the intervention group was *full-dose treatment* (37.1%) or *no intervention performed* (20%). In the control group, the main reason was *no intervention performed* (76.6%) or *intervention performed but target not reached* (10.9%) [Fig 8].

More patients in the intervention group received high-intensity LDL-C–lowering treatment (61.4%) compared to controls (24.0%), defined as atorvastatin 40–80 mg or rosvastatin >10 mg.

![Figure 8 Reasons for not achieving target after guideline change in each group.](image-url)
Efficacy of a telephone-based interventional programme – 12-month outcomes for LDL-C and BP (Study III)

Of the 1223 patients admitted for ACS during the study period, 841 were included and randomized (424 to intervention, 417 to control). Of these, 768 (91.3%) completed the 12-month follow-up (396 in the intervention group; 372 in the control group) [Fig 9].

Figure 9 Flow chart. * As of 31 March 2013, target value for LDL-C in patients with diabetes was <1.8 mmol/L; ** one patient declined at baseline but re-entered at 12 months. *** One patient submitted LDL-C but not BP.
Only BMI differed among the baseline characteristics [Table 3]. We found no interaction effect by sex or type of ACS on intervention targets (LDL-C and BP).

Table 3 Baseline characteristics by allocation group. Data are given as n (%) unless otherwise noted; eGFR calculated using the CKD-EPI formula

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>396</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>68.8 (11.7)</td>
<td>69.0 (11.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male</td>
<td>273 (68.9%)</td>
<td>258 (69.4%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Event at inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>26 (6.6%)</td>
<td>37 (9.9%)</td>
<td>0.09</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>250 (63.1%)</td>
<td>230 (61.8%)</td>
<td>0.71</td>
</tr>
<tr>
<td>STEMI</td>
<td>120 (30.3%)</td>
<td>105 (28.2%)</td>
<td>0.53</td>
</tr>
<tr>
<td>At discharge for the qualifying event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m² mean (SD)</td>
<td>27.7 (4.5)</td>
<td>27.0 (4.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m² mean (SD)</td>
<td>78.7 (21.3)</td>
<td>78.9 (19.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>mRS &lt;3</td>
<td>386 (95.7%)</td>
<td>364 (97.8%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>83 (21.0%)</td>
<td>68 (18.3%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>37 (9.6%)</td>
<td>27 (7.4%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (0.5%)</td>
<td>5 (1.3%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>29 (7.3%)</td>
<td>25 (6.7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Previous MI</td>
<td>65 (16.4%)</td>
<td>66 (17.7%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous or current smoking</td>
<td>258 (65.2%)</td>
<td>224 (60.2%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**LDL-C**

After initial titration, mean LDL-C was 1.9 mmol/L in the intervention group and 2.3 mmol/L in the control group (mean difference, 0.38 mmol/L; p<0.001 for both). After titration, 94.1% reached the set target in the intervention group. At the 12-month initial assessment, mean LDL-C was 2.1 mmol/L in the intervention group and 2.4 mmol/L among controls (mean difference, 0.27 mmol/L; p<0.001) [Table 4]. The proportion reaching the target at 12 months compared to baseline increased from 68.7% to 77.7% in the intervention group and was significantly larger at last assessment compared with controls. This proportion in the control group decreased from 68.4% to 63.2% between baseline and 12 months [Fig 10].

Of those in the intervention group who were above the set target at baseline, mean LDL-C was 0.4 mmol/L lower at the 12-month follow-up (p<0.001).

**BP**

After initial titration, mean SBP was 124.9 mmHg in the intervention group and 131.8 mmHg in the control group (mean difference, 6.9 mmHg; p<0.001). The proportion of patients who reached the set target after titration was 91.9% in the intervention group. At the 12-month assessment, mean SBP was 131.5 mmHg in the intervention group and 133.0 in the control group (mean difference, 1.5 mmHg; p=0.24) [Table 4].
DBP after initial titration was 73.7 mmHg in the intervention group and 77.7 mmHg in the control group (mean difference, 4.0 mmHg; p<0.001). In the intervention group, 96% reached the set target in the intervention group after titration. At the 12-month assessment, mean DBP was 76.0 mmHg in the intervention group and 78.2 mmHg among controls (mean difference, 2 mmHg; p<0.05) [Table 4]. The proportion reaching the set target at baseline and at 12 months for SBP was constant in the intervention group and decreased in the control group. For DBP, this proportion increased in the intervention group during the period and was constant in the control group [Fig 10].

In the above set targets at baseline, the mean difference at 12 months in SBP was 2 mmHg lower in the intervention group compared to those in the control group (p=0.38). Mean difference in DBP was 7 mmHg lower in the intervention group compared to controls (p<0.001). In terms of medications, only lipid-lowering medication differed at the 12-month assessment [Table 4].

Table 4 Results at baseline (1 month) before and after titration and at 1 year. Crude p values. Data are presented as n (%) unless otherwise noted. s, significant; ns, nonsignificant

<table>
<thead>
<tr>
<th></th>
<th>Baseline – before titration</th>
<th>Baseline – after titration</th>
<th>12 months – before titration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>p</td>
</tr>
<tr>
<td>SBP, mmHg; mean (SD)</td>
<td>131.5 (19.0)</td>
<td>131.8 (18.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>76.9 (10.6)</td>
<td>77.7 (11.2)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-C, mmol/L; mean (SD)</td>
<td>2.16 (0.75)</td>
<td>2.25 (0.87)</td>
<td>ns</td>
</tr>
<tr>
<td>Antilipids, n (%)</td>
<td>365 (92.2)</td>
<td>336 (90.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Beta-blocker, n (%)</td>
<td>359 (90.7)</td>
<td>338 (90.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Alpha-blocker, n (%)</td>
<td>10 (2.5)</td>
<td>9 (2.4)</td>
<td>ns</td>
</tr>
<tr>
<td>ACEI, n (%)</td>
<td>232 (58.6)</td>
<td>230 (61.8)</td>
<td>ns</td>
</tr>
<tr>
<td>ARBs, n (%)</td>
<td>85 (21.5)</td>
<td>67 (18.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>
Figure 10 Proportion (percent) achieving target for SBP, DBP, and LDL-C at each assessment, group-wise.
Barriers to intervention – statin adherence over time (Study IV)

During the study period, 962 ACS patients (486 intervention and 476 control) completed the initial assessment at 1 month [Fig 11]. We found no difference in baseline characteristics [Table 5].

---

**Figure 11 Flowchart study IV. LTFU, lost to follow-up.**
Table 5 Baseline characteristics.  

Former smoker: smoking cessation >6 months; heredity: first-degree relative with CVD; male <55; female <65; statin or ezetimibe; P2Y12 inhibitors: clopidogrel, ticagrelor, prasugrel; anticoagulant: warfarin or non–vitamin-K oral anticoagulant

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>486</td>
<td>476</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, y (mean)</td>
<td>68</td>
<td>69</td>
<td>0.60</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>146 (30)</td>
<td>144 (30)</td>
<td>0.35</td>
</tr>
<tr>
<td>BMI, kg/m² (mean)</td>
<td>27.8</td>
<td>27.4</td>
<td>0.53</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>97 (20)</td>
<td>90 (18.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>211 (43.5)</td>
<td>196 (41.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Heredity, n (%)</td>
<td>136 (28.5)</td>
<td>129 (27.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Basic education, n (%)</td>
<td>224 (46.3)</td>
<td>241 (51.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cholesterol mmol/L, mean (SD)</td>
<td>4.1 (0.91)</td>
<td>4.1 (1)</td>
<td>0.85</td>
</tr>
<tr>
<td>LDL-C mmol/L, mean (SD)</td>
<td>2.18 (0.74)</td>
<td>2.18 (0.85)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**ACS diagnosis, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>152 (31.3)</td>
<td>131 (27.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>295 (60.7)</td>
<td>296 (62.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>UA</td>
<td>39 (8.0)</td>
<td>49 (10.3)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Revascularization, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>261 (53.7)</td>
<td>249 (52.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>CABG</td>
<td>65 (13.4)</td>
<td>59 (12.4)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Co-morbidities, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of MI</td>
<td>79 (16.3)</td>
<td>96 (20.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>History of PCI/CABG</td>
<td>69 (14.2)</td>
<td>89 (18.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>History of ischaemic stroke/TIA</td>
<td>27 (5.6)</td>
<td>30 (7.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>263 (54.1)</td>
<td>267 (56.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>99 (20.4)</td>
<td>96 (20.2)</td>
<td>0.94</td>
</tr>
<tr>
<td>History of hyperlipidaemia</td>
<td>335 (68.9)</td>
<td>335 (70.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>AF</td>
<td>44 (9.0)</td>
<td>40 (8.4)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

**Baseline medication, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering treatment</td>
<td>451 (92.7)</td>
<td>442 (92.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>440 (90.9)</td>
<td>429 (90.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>395 (81.3)</td>
<td>382 (80.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Aspirin</td>
<td>446 (92.1)</td>
<td>446 (93.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>P2Y12-inhibitor</td>
<td>375 (77.2)</td>
<td>372 (78.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>44 (9.0)</td>
<td>33 (6.9)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Of included patients, 89.3% in the intervention group and 81.7% in the control group were adherent to statin treatment over a mean follow-up of 3.9 years (p<0.001). The proportion adherent in each group at each assessment is presented in Fig 12.

![Graph showing adherence over time](image)

*Figure 12 Proportion in each group adherent to statins at each scheduled assessment.*

A larger proportion of patients in the intervention group discontinued medication initially compared to controls (27.8% versus 20.8%, respectively, p<0.05). Of those not on statin treatment at baseline, 92.6% in the intervention group initiated treatment, and of those, 63% persisted until last follow-up. In the control group, 45.7% were initiated, and 28.6% persisted until last follow-up. Kaplan–Meier estimations of first and permanent discontinuation are presented in Fig 13.
In both groups, the most preeminent reasons for a first discontinuation were avoidable causes (*side-effect without a compelling association with treatment* and *lack of motivation*) [Fig 14]. The main reason for permanent discontinuation in the intervention group was primarily non-avoidable (*advanced disease including dementia: 27.5%, n=24*). The most prevalent reasons for permanent discontinuation in the control group were still mainly avoidable (*side-effect without a compelling association with treatment: 32.4%, n=22*) [Fig 15].
Mean LDL-C at last follow-up was 2.00 mmol/L in the intervention group and 2.39 mmol/L in the control group (p<0.001). The majority of patients (69.3%, n=337) in the intervention group were treated with a high-intensity LDL-C-lowering regimen. The proportion in the control group was 44.3% (n=211; p<0.001). In the intervention group, 21.4% (n=104) of patients also had an
additional lipid-lowering medication (mainly ezetimibe), whereas among controls, this proportion was 1.2% (n=10; p<0.001). (Table 6)

Table 6 Type of lipid-lowering treatment at end of follow-up. High intensity lipid-lowering therapy: simvastatin >40 mg, atorvastatin 40–80 mg, or rosuvastatin >10 mg. Low–medium intensity: not fulfilling the above.

<table>
<thead>
<tr>
<th>Lipid-lowering therapy</th>
<th>Intervention</th>
<th>Control</th>
<th>Additional therapy</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>None, n (%)</td>
<td>49 (10.1)</td>
<td>84 (17.6)</td>
<td>382 (78.6)</td>
<td>466 (97.9)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin, n (%)</td>
<td>56 (11.5)</td>
<td>110 (23.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin, n (%)</td>
<td>298 (61.3)</td>
<td>256 (53.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin, n (%)</td>
<td>72 (14.8)</td>
<td>19 (4.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Another statin, n (%)</td>
<td>5 (1)</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe, n (%)</td>
<td>6 (1.2)</td>
<td>3 (0.6)</td>
<td>104 (21.4)</td>
<td>10 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>0</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High intensity, n (%)</td>
<td>337 (69.3)</td>
<td>211 (44.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low–medium intensity, n (%)</td>
<td>94 (19.3)</td>
<td>177 (37.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the regression analysis for predictors for a first discontinuation, allocation to the intervention group led to increased risk (hazard ratio [HR] 1.35, p<0.05), and STEMI as the inclusion event decreased risk (HR 0.74, p<0.05). In the regression analysis for predictors for permanent discontinuation, allocation to the intervention group (HR 0.60, p<0.05) and STEMI as the inclusion event (HR 0.63, p<0.05) both led to decreased risk. Sex showed a non-proportional hazard. After adjustment female sex was associated with an increased risk for both first and permanent discontinuation with a linearly decreasing risk until 1250 days for a first discontinuation and until 900 days for a permanent discontinuation, when the risk was equalized. Mean HR for female sex during the entire period was 1.23 and 1.45 for a first and a permanent discontinuation, respectively.
Analysis

As noted in the introduction, a high proportion of prescriptions at discharge after ACS are in accordance with guideline recommendations for secondary prevention. But further secondary prevention after discharge is halting, and deterioration in patient risk profile is detectable after only 6 months, progressing thereafter.

A nurse-led, telephone-based secondary preventive programme has high outreach success in the general ACS population. Compared to usual care, it also manages to significantly attenuate the deterioration in risk factor control during the initial year after an event and increase adherence to statins over time. In the intervention group, risk factor control improved slightly from discharge to 12 months. Risk factor control was markedly better after the scheduled titration to reach set targets, but much of the improvement did not persist at the first-year follow-up.
Discussion

Patient population
Is the studied population representative of our clinical reality?

We designed the NAILED study to mimic clinical conditions as far as possible. Exclusion criteria in the trial were limited and thus allowed us to include elderly and vulnerable patients with advanced disease. This inclusion is seldom possible in clinical trials, which remain the basis for current evidence. As noted in the introduction, secondary prevention is beneficial in all age groups. (67, 68)

Mean age in our first study without exclusion criteria was 71.3 years with 28.4% >80 years, and mean age just below 70 years in the subsequent studies of randomized patients. In the EUROASPIRE survey, which excluded patients >80 years, mean age was 62 years. The SWEDHEART registry is a quality registry that includes 96% of all CCUs in Sweden. In 2017, the mean age among MI patients in the registry was 71.2 years and 25% were above 80 years. (69) In the National Board of Health and Welfare Registry for MI, patients >80 years constituted 27.5% of the total population.

Prevalent risk factors in SWEDHEART are presented in the subregistry SEPHIA, which includes patients <75 years with a mean coverage of 77% of the target group. In a comparison of present risk factors at randomization among our participants, 20.4% had diabetes compared to 21% in SEPHIA, 23.6% had previous ischaemic heart disease versus 17% in SEPHIA, 62.6% had ongoing or previous smoking versus 63% in SEPHIA, and 53.6% had hypertension versus 51% in SEPHIA. (69)

Comparison with cohorts of previous studies on telephone-mediated prevention programmes is difficult because these cohorts often represent selected population subsets. (62, 70) This selection related to aspects of age, multimorbidity, and the so-called “healthy adherer” (i.e., patients particularly prone to participating in studies more often also adhere to treatment) leads to crucial differences from the ordinary, hospitalized ACS population in “real-life” practice we want to study.

Our catchment area is relatively vast, and it is not uncommon for patients to commute for >3 hours one way to reach our hospital. A third of the population, however, lives in the county capital where the hospital is located. Thus, we claim that our population is representative for the context in Sweden, at least, along with other high-income countries and encompasses both a rural and an urban setting.
Feasibility of a nurse-based telephone conducted secondary prevention programme

How well-suited is the method for our patients?

Almost three-quarters of our cohort hospitalized for ACS could successfully be randomized in the NAILED trial. If we disregard the exclusion criterion of “participation in another trial”, the excluded proportion would decrease from 16% to 11%. The same proportion (11%) declined participation. Our programme yielded higher participation rates than previous studies. In the EUROASPIRE IV study, 50.7% were advised to participate in a secondary prevention programme, and 81.3% of these participated in at least one-half of the sessions, a number that has not changed remarkably over the years. (26) The European Society of Cardiology therefore conducted a nurse-based secondary prevention study (EUROACTION) in both a cohort hospitalized for ACS and a primary care CVD high-risk cohort. (71) Exclusion criteria were age under 50 or above 80 years, severe heart failure, severe physical disability, and dementia. In the ACS subset, 94% were deemed eligible, and 67% were assessed; of the eligible cohort, 54% (860/1589) participated. In the RESPONSE trial, with hospital-based nurse-coordinated secondary prevention of ACS patients ages 18-80 years and excluding multimorbidity, 55% were excluded (30% for not meeting inclusion criteria; 25% declined participation) (72).

In our study, most patients in the excluded group had severe physical or mental disabilities, a population for which the benefit of secondary prevention is questionable. According to evidence, however, the declining group would benefit from further strict risk factor control. Compared to those included, the group that declined participation was significantly older and more likely to be female, with less education and a decreased level of independence. Low education and female sex are well-known risk factors for adverse outcomes in CVD, even though the difference between sexes is gradually decreasing. (10, 69) This inequality emphasizes the need for an effective prevention programme to encompass these particular patient groups. The inequality between the sexes in terms of health care use is a complex and not yet fully elucidated question. Studies have shown sex differences in behaviour to use health care, in how prevalent risk factors influence this use, and in the presentation of manifest disease. There also are inequalities in how the healthcare system responds to these sex differences. (73, 74) One might argue that these differences should not be a problem in highly developed countries where sex differences are a priority on the political agenda, but gender inequalities are also manifest in well-functioning healthcare systems. (75, 76) The WHO issued a position paper highlighting that social structures, such as inequalities in power, money, and resources, and also healthcare structures are more adapted to the health behaviour of men. They stress that gender as a social construct should be seen as a modifiable risk factor. (77)
It is a well-established fact that patients with low socioeconomic status, where level of education constitutes the main portion, have worse outcomes after ACS. This outcome is true even in government-funded healthcare systems with strong egalitarian traditions. (78) Some studies, however, show that telephone-based coaching could reduce these inequalities arising from social class differences. (79, 80)

Our study demonstrated higher participation rates in a relatively unselected ACS cohort than previous studies, leaving out only about a tenth of the population that probably would benefit from intensified secondary prevention. One could speculate that the predisposing factors leading to non-participation also might influence individual engagement and thus the effectiveness of further intervention. It is therefore crucial to identify these individual factors and how to manage them by further research into more subjective reasons for non-participation and non-adherence.

**Guideline perseverance**

*Does the methodology in the programme improve on anything in current clinical practice?*

The world of medicine and health is transforming at a rate surpassing all previous generations. The rise of evidence-based medicine has given us the ability to quickly adapt to more effective treatments and to disavow old beliefs not based on evidence.

In the EUROASPIRE survey of random CVD cohorts across Europe, the use of guideline-recommended drugs at hospital discharge to prevent further disease increased dramatically between the surveys. The overall use of secondary preventive drugs is now high (anti-platelets 94%, beta-blockers 83%, ACEI/ARB 75%, statins 86%). Nevertheless, only half of patients with CVD treated with BP-lowering medication reached the recommended target (<140/90 mmHg), and 21% reached the target for LDL-C (<1.8 mmol/L), with only slight improvements over time. There also were adverse trends in lifestyle, with increasing prevalence of obesity and diabetes and a maintained prevalence of smoking. Furthermore, the proportion on preventive drugs did not increase between studies III and IV. In the primary care arm with high-risk patients but without manifest CVD, even fewer achieved set targets. (81) This investigator group concluded that prescriptions at discharge of evidence-based medicines follow guidelines but that the preventive effect is curtailed because of a lack of further individual titration to meet targets.
We studied the effect of a change in guidelines for patients with diabetes, where the target for LDL-C in those with manifest CVD was lowered from below 2.5 mmol/L to below 1.8 mmol/L. One year after target change, the proportion that achieved the new target had diminished in both groups compared to the previous target (intervention group from 96% to 65%; control group from 70% to 36%). Median LDL-C values before and after the change were 1.9 mmol/L vs. 1.7 mmol/L in the intervention group and in the control group 2.1 mmol/L vs. 2.0 mmol/L respectively. Reasons in the intervention group for not achieving targets were full-dose treatment (37.1%) followed by no adjustments performed for unknown reasons (20%). Main reasons for not attaining target in the control group were no adjustment performed for unknown reasons (76.6%) followed by adjustment performed but target not reached (10.9%).

Even though the amount reaching target decreased in the intervention group, the main reason was full-dose treatment (atorvastatin 80 mg/rosuvastatin 40 mg ± ezetimibe), which warrants the need for more effective treatments. Regarding why 20% (7/35) in the intervention group did not receive adjustment, we have no explanation other than some omission in following protocol. This result illustrates how, even under strict controlled conditions, standardized care is hard to maintain.

Surveys of GP compliance with the guidelines show that most are aware of them but that only one-third to half use them actively. The main barrier for this is time. Additional factors are the perception that there are too many guidelines with unrealistic targets and that clinical judgement is believed to supersede guidelines. With a perception among 80.3% that they treat dyslipidaemia well, only 53.3% knew the guideline-recommended target. Cardiologists working in primary practices tended to be more adherent to guidelines. (82-84) The inability of a healthcare system to act on identified risk factors is called therapeutic inertia. (85) and is a well-established problem. Redon et al, in their study in a primary care setting, identified risk factor values close to normal, and multiple health contacts contributed to lack of titration. (86)

Our study had a structured follow-up schedule, a protocol that called for strictly following guidelines, and ease of access to a physician. These factors proved to reduce the issue of therapeutic inertia and non-adherence to guidelines and also to be more effective in the context of a guideline change.
Risk factor control

Does the intervention lead to an improvement compared to usual practice?

In our study, the majority (91.3%) of included patients were available at the 12-month control. The intervention group had a significantly lower mean LDL-C and a larger proportion reaching the LDL-C target at 12 months compared to controls. In contrast, we could see an improvement in LDL-C control from baseline to the 12-month assessment in the intervention group, even as risk factor control decreased in the control group during the same period.

Regarding BP, the proportion achieving target was larger in the intervention group compared to the control group at 12 months after discharge. The changes in SBP were modest, even though the trends were increased control of SBP in the intervention group and decreased control in the control group. The changes in DBP were more pronounced and significant in regard to the comparison between the intervention and control groups and between 1 and 12 months in the intervention group.

The proportion reaching set targets in our intervention group increased during the first 12 months and were above those in observational studies of ACS. In the EUROASPIRE IV survey, there were large regional differences, but 12 months after discharge, less than two-thirds reached LDL-C <2.5 mmol/L and only two-fifths a BP <140/90. In the same study, the regional values for Sweden were 65.9% achieving the LDL-C target and 62.4% the BP target.

In a meta-analysis of nurse-led secondary prevention programs, factors associated with reduced BP and LDL-C were CR combined with medical titration in a high-intensity strategy with frequent visits at short intervals (>4 face-to-face contacts). (66) The RESPONSE trial evaluated a nurse-led outpatient intervention comprising four visits during the first 6 months and a follow-up at 12 months, aiming at improving both lifestyle factors and optimizing medical titration. The main outcome was Framingham risk score, but at 12 months, 72% achieved an SBP <140 mmHg, 87% DBP <90 mmHg, and 80% LDL-C <2.5 mmol/L. The trial had more extensive exclusion criteria, a mean age of 57 years, and only 20% females (as stated previously, components for reduced adherence) compared to our study. (72) Our design had a simplified protocol with less frequent visits to limit resource use and increase patient convenience in an attempt to expand outreach. This together with a telephone-based methodology to increase feasibility irrespective of distance to health care and individual factors limiting ability to participate showed comparable results.

In our study, the group difference at 12 months was mainly driven by reduced risk factor control in the control group rather than a large absolute improvement in
risk factors in the intervention group. The measurements after baseline titration, however, indicate the potential for large-amplitude risk reduction with intensified titration in our cohort. How to maintain the effect of intensified target control over the period is a critical issue that must be resolved. Most controlled trials of intervention are short and lack data from 12 months and beyond. In the SPRINT trial of an intense SBP treatment target (<120 mmHg) versus an ordinary target (<140 mmHg) of hypertension in patients without diabetes, patients were assessed monthly for the first 3 months and thereafter every 3 months for a planned 5-year period. They maintained the intensified target over a mean 3.2 years when the study was terminated because of a significantly higher rate of composite endpoints in the ordinary target group. (37) Also, in the CHOICE study with an initial 3-month intervention, beneficial improvements in risk factor control after 12 months were maintained after 4 years with reduced BP and cholesterol and an improved coronary risk profile. (87) We will hopefully get indications of whether prolonged intervention with our low-intensity protocol will increase risk factor control beyond the first year in the primary outcome analysis of the NAILED-ACS trial. (88)

**Adherence to treatment**

*Do our patients commit to our intervention?*

The outcome of chronic disease management is largely dependent on patient adherence to prescribed treatment. As noted in the introduction, the vocabulary concerning the patient relationship with treatment is somewhat confusing. In our fourth study, we aimed to study the proportion of patients who stuck with the prescribed treatment at the end of follow-up. We did not analyse how patients executed their prescription in terms of timing of doses, missed doses, drug holidays, and so forth. In this way, we tried to mimic actual clinical conditions. This approach concurs with the WHO definition of adherence, but neither the ISPOR definition of adherence nor persistence is truly applicable in our study.

Previous studies of adherence are of varying quality and present difficulties for drawing generalized conclusions. (89) Observational studies generally show low adherence compared to clinical trials and are perceived to correlate better with clinical reality. In a meta-analysis of statin treatment in both primary and secondary prevention, Lemestra et al found adherence rates of around 49% in observational studies and 90% in controlled trials. (53) Other observational studies report first-year non-adherence of around 20%–50%. (47, 90) (91) Few studies of adherence follow up beyond the first year after the event, but in a database study by Perreault et al of patients in a secondary preventive cohort, statin adherence dropped to 71% during the first 6 months and was further reduced to 45% after 3 years. The greatest discontinuation rate occurred during the first months. (56) In our study, more patients in the intervention group
(89.3%, n=434) adhered to their statin treatment compared to controls (81.7%, n=389) during a mean follow-up of 3.9 years. Thus, we could show adherence rates comparable to those in clinical trials and maintained over a long period of time. Adherence to statins in the intervention group surpassed that of controls in usual care with duration of follow-up. However, the control group also showed surprisingly high adherence over time. As mentioned previously, the EUROASPIRE IV study identified a high level of prescribed guideline-recommended medications at discharge for ACS, (26), similar to our study in which >90% in both groups were discharged with lipid-lowering therapy. Our findings suggest that prescriptions at discharge are maintained in most patients in subsequent years. Thus, among patients not under statin treatment at discharge from the index event, more patients in the intervention group were initiated and adherent at last follow-up compared to the control group.

Snaterse et al showed in a substudy of the RESPONSE trial that a nurse-controlled intervention to reach a set target for LDL-C led to more frequent and intensified management compared to usual care. Compared to 24% treated with usual care, 45% in the intervention group were titrated up or down. (92) We found that the intensity of lipid-lowering treatment in our study was significantly higher in the intervention group compared to the control group, measured as a larger proportion on a high-intensity lipid-lowering regime (69.3% vs. 21.4%) which resulted in a lower mean LDL-C at the last assessment (2.0 mmol/L vs 2.39 mmol/L). High intensity of treatment has previously been shown to increase non-adherence. (93)

Of interest, in our study, the proportion of patients who discontinued a first time was larger in the intervention group (27.8%) compared to controls (20.8%). Re-initiation after a first discontinuation of statin treatment is a common procedure, but unfortunately, re-discontinuations are common. (91) In the USAGE study of Medicare beneficiaries, a third of the patients who discontinued statin treatment did so without first consulting their prescribing physician. A mutually trusting patient–prescriber relationship was seen as one of the most important factors for adherence. (94)

In our study, the most prevalent reasons for a first discontinuation in both groups were deemed avoidable (side-effects without a compelling association with treatment, lack of motivation, and misunderstanding). The most prevalent reason for permanent discontinuation was non-avoidable in the intervention group, with advanced disease including dementia, but in the control group, it was still avoidable with side-effects without a compelling reason for treatment. The statin drug class is the subject of an intense debate about whether it is associated with a high occurrence of adverse events or an unjust nocebo effect, an expression coined to denote the counterpart of a placebo effect. The nocebo effects are
negative expectations of side-effects and effects of treatment. These psychological beliefs are influenced by both patient and physician assumptions, as well as the perception of media and in society. (95) Reported adverse events are mainly muscle symptoms but can include memory impairment, cataract, renal dysfunction, diabetes, and rhabdomyolysis. Although rhabdomyolysis is an established and dangerous side-effect, it is extremely rare and avoidable with regular healthcare contacts. The risk of statin-added insulin resistance in those with a high risk of diabetes is also known, but because these risk factors also cohere with those of CVD, the benefits outweigh the risks with treatment. (96) In a double-blind cross-over extension of the ASCOT-LLA trial with treatment of 10 mg atorvastatin, adverse events were not more common in the statin group compared to placebo. With unblinding, however, the proportion of side-effects increased in the statin group and surpassed those treated with placebo. (97) Other placebo-controlled trials also have shown no increased rates of side-effects with statins. (98) Nevertheless, muscle pain is prevalent and the main cause for discontinuation. (99) These symptoms also are common with increasing age and peripheral atherosclerotic disease, however, so their precipitating cause must be established in each case to avoid unnecessarily withholding the beneficial preventive effects of statins.

In our assessment of reasons for discontinuation, we tried to establish a temporal relationship between treatment and onset of symptoms, as well as symptom regression with dose de-escalation or discontinuation. If symptoms were prevalent before statin initiation or continued after cessation, they were not deemed related to treatment. In the USAGE study, few patients acknowledged that somatic symptoms could have a psychogenic origin. The authors therefore emphasize the importance of a mutually trusting patient–prescriber relationship to minimize the nocebo effect. (99)

Predictors of non-adherence in our study were female sex, and for a first discontinuation, allocation to the intervention group. We also found increased adherence with STEMI as the including event and allocation to the intervention group for longer adherence. In the ACTION trial, female sex, age <65 years, and fewer cardiovascular co-morbidities were associated with non-adherence. (100) Female sex and healthcare inequalities have been discussed previously, but our study cannot answer the question of whether the receding risk with gender over time is an effect of the intervention methodology. Increased adherence with STEMI has also been shown previously and explained by increased use of PCI, treatment at tertiary care centres, a decreased proportion of women participating, and less preceding cardiovascular morbidity compared to NSTEMI. (101)

Our study shows that long-term adherence to prescribed pharmacotherapy at discharge is generally high but that because of therapeutic inertia, medical
adjustments are not made to achieve risk factor targets in usual care. Our intervention with regular contact and individual pharmacotherapy optimization based on blood tests and symptoms comes with increased awareness, and possibly a patient–prescriber nocebo effect leading to increased initial discontinuation in the intervention group. But with continued contacts and adjustments to medication (both up- and down-titration as well as switching between statins), a joint trust and understanding develops regarding symptoms and their cause, as well as of the importance of treatment. The fact that non-avoidable reasons surpassed avoidable ones as the principal argument for discontinuation between first and permanent discontinuations in the intervention group supports this hypothesis. The result is an increased adherence and a more effective treatment. This finding also stresses the importance of the intervention persisting beyond the first year.
Key methodological features and study limitations

Case validity
The county has only one hospital where all patients with suspected ACS are referred. Nevertheless, we cannot rule out that patients living in hospice, for example, were diagnosed with ACS but because of ethical issues subsequently not referred and thus missed. We speculate that these cases are few, however, and because they are not expected to benefit from acute management are not indicated for secondary prevention. Also, patients treated outside the county and not referred before discharge would be missed.

We validated our case-finding method in the NAILED study during a 3-month run-in period with the conclusion that all eligible patients were identified. No further validations were made during the inclusion period. We used the consensus definition of MI type 1 and UA (with the amendment of also using ECG findings for UA) to increase the external validity of the study. Aside from the independent assessments by the discharging physician and study physician, no further ascertainment of the diagnosis was made. A few cases were excluded between discharge and baseline by the study physician because of an ACS that was not MI type 1/UA. These cases included MI with non-obstructive coronary arteries (MINOCA), takotsubo cardiomyopathy, coronary artery dissection, and non-type 1 MI (e.g., heart failure or tachycardia), with no expectation of universal benefit from secondary prevention. We believe that we identified and screened virtually all patients hospitalized with an ACS in our county during the study period, with adequate ascertainment of correct diagnoses.

Measurement errors
For patients in both groups, measurements and blood sample collection were performed at the patient’s closest healthcare provider. Prior to each assessment, participants were given written instructions to bring to the collecting provider. We cannot exclude that some measurements were not in accordance with these instructions or exclude measurement error resulting from incorrect handling or malfunctioning equipment. These errors would be randomly distributed, however, and not expected to compromise our comparison between groups, although intra-individual variability might have been affected to a minor extent. Thus, we consider that our results are not biased by measurement error.

Missing data
A common source for bias in clinical research is missing data, which is not uncommon in a systematic manner. To handle this in statistical analysis, whole cases could be excluded or a variety of imputation methods used. In our study,
the main causes of missing data during follow-up in outcome variables were death and active withdrawal. But the proportions were small and equally distributed between the two groups, so bias from these factors is expected to be minor.

**Sample size**
Sample size in the NAILED trial was calculated to detect a group difference in LDL-C of 0.5 mmol/L and in SBP of 5 mmHg with a two-tailed alpha of 0.05 with 80% power. This resulted in 200 participants in each group. To detect a >10% difference in proportions achieving treatment goals required smaller sample sizes while subgroup analyses required larger main cohorts. In study II, each group had a sample size of 100, and the other studies had >350 participants. The small effect size on SBP in comparison between 1 and 12 months in the intervention group and between groups did not reach significance with the predefined sample size.

**Survival analysis and competing risks**
Survival analysis presumes proportional hazards of the event as well as equal survival probability in event-free cases. If a case is prematurely censored because of another event than the focus of the study, the latter assumption is violated, and the censoring event might be regarded as a competing risk. Because death is an imminent risk in our study cohort, competing risks might also influence our results. Nevertheless, Kaplan–Meier estimation is frequently the method of choice to study incidence of events in cohorts that also have increased risk for death. This approach is used if the objective is to study cumulative incidence of an event given the survival of cases. Thus, the cumulative incidence of the event then depends on the cumulative incidence of death, which must be taken into account in comparison of incidence between cohorts. In our fourth study, the proportion dead was small and equally distributed between the groups. We believe that we have acted in accordance with common epidemiological practice when analysing survival.

**The methodology used to study adherence**
Measurement of adherence is a complex procedure, related methods all have advantages and disadvantages, and no method is considered a gold standard. Direct methods such as observation of intake or measurements of metabolites in blood or urine are expensive and can be distorted by the patient but are indicated in studies of metabolism variations and in clinical trials. Indirect methods include patient self-report, assessing clinical response, performing pill counts, using electronic medication monitors, and tracking rates of refill of prescriptions. These are all simpler approaches than the direct methods but have advantages and disadvantages. Patient self-report is thought to be the most useful in clinical
settings but may be distorted by the patient. Pill counts are objective and quantifiable but can be easily altered by the patient. Rate of prescription refill is easily accessible with electronical records but is not equivalent to ingestion. (50)

In our study, we used patient self-report as the main model for information but added clinical response. If values for LDL-C changed significantly without alteration in treatment or no change occurred with treatment titration, a more conscientious dialogue was initiated. Thus, we cannot fully exclude that some patients more or less deliberately introduced a measurement bias. Such events would, however, be random occurrences in both groups and not influence group comparison.

**Considerations in the NAILED study design**

Blinding of randomization allocation is preferable in all RCTs. In our study, for practical and ethical reasons, information on allocation was open to participants and study staff and also through medical records for other healthcare professionals. This setting may have influenced the secondary prevention strategies provided to the control group.

Our regular measurements of outcome variables were forwarded to each patient’s GP in the control group at an interval determined by the study protocol, which might differ from those provided in usual practice. These regular measurements and interviews may also have influenced patient incentive to adhere to the discharge instructions and medication or to contact their physician for consultation. Such increased awareness would influence the study results by leading to an underestimation of the effect of the intervention. A possible overestimation of the intervention effect could hypothetically be a result if a GP abstained from intervention for a patient in the control group out of concern that the patient was receiving the intervention in the study protocol.

**Generalizability**

In the four papers that support this thesis, we aimed to assess the feasibility, adaptability, and effectiveness of the NAILED protocol in secondary intervention in a fairly unselected ACS cohort. The study is of single-centre design, including only hospitalized patients at the index event and from a defined catchment area.

To what extent our results can be generalized to the total ACS population and under other circumstances can be debated. To increase our external validity, we limited exclusion criteria to the inability to adhere to the study concept, which in turn was designed to include all patients with feasible indications for secondary prevention. The other exclusion criterion, participation in ongoing trials, was included because treatment options might be limited by trial protocol, or not be
common practice. About 5% were excluded because of this criterion according to study I. We argue that patients already willing to participate in RCTs with more limiting exclusion criteria are in better health and more “healthy adherers” than the general ACS population. Therefore, limiting inclusion to this group would provide only an underestimation of the feasibility results. Our cohort concurs well in baseline characteristics with that of the quality registry SWEDHEART in Sweden. (69)

Generalizability also depends on the performance and organization of our primary practice (i.e., usual care), participation rates, and local demographics. The participation rate was high in our study among eligible patients, and the dropout and loss-to-follow-up frequency was low. Even if we cannot ensure equal performance in all primary care practices, our control group performed at least as well as the primary care arm of both EUROASPIRE and SWEDHEART, which are both limited by age restrictions. (102) Thus, we suggest that our study population is generalizable to both rural and urban populations in the western world.

Implications and future research
This thesis provides evidence that secondary prevention after ACS can be enhanced by a simple and systematic nurse-led follow-up. Under a strict guideline-based protocol with assessment and counselling of lifestyle and risk factors, together with individualized titration of pharmacotherapy, a larger proportion of patients adhered to medication and achieved targets regarding BP and LDL-C.

In the present studies, we used only BP, LDL-C, and adherence as outcome variables. The effect the intervention has on other beneficial factors of secondary prevention such as weight-loss, diet, smoking cessation, and exercise also needs to be established because maximized disease reduction is achieved through the combination of increased healthy living and risk factor reduction.

Even though participation rates were high and the intervention easily accessible, a tenth of the ACS population still declined. We also do not know if the studied methodology reduce the inequalities in healthcare due to known individual risks such as female gender and low socioeconomic status. Further studies need to establish in what way we can adapt our secondary prevention to include an even larger proportion of the total ACS population. A qualitative study on subjective reasons for participation and non-participation among patients with a low degree of education and among women might elucidate more modifiable factors to increase participation.
We also discovered the possibilities of risk factor control lost between initial titration and the first-year follow-up. Controlled trials with more intense follow-up show increased maintenance of risk factor reduction. Additional reminders, perhaps using technical tools such as a mobile app, might increase efficacy without requiring much in the way of additional resources. Adherence to medication proved to depend on the duration of follow-up. Even if non-avoidable reasons for discontinuation were dominant at the end of follow-up in the intervention group, there is still room for improvement in reducing avoidable reasons for discontinuation of statins. Thus, we still need to validate the long-term results of our outcome variables in future analyses of the NAILED trial.

Finally, it remains to be established if our results can be translated into a measurable beneficial reduction in cardiovascular events.
Conclusions

In a fairly unselected population of patients discharged after ACS, a nurse-led, telephone-based secondary preventive programme:

- Had a high feasibility, and
- Was easily pursued by patients during the first year in both rural and urban settings.

In comparison with usual practice, the program:

- Showed a more adaptive response to changes in guidelines;
- Led to increased proportions reaching set targets for LDL-C and BP;
- Led to increased adherence to medication over time and reduced avoidable reasons for discontinuation; and
- Led to increased use of high-intensity LDL-C–lowering regimens.
Acknowledgements

Through my journey in this bumpy ride we call science, I´ve had the pleasure of having more or less innocent people trying to keep me on the road. None is forgotten, and I would like to express my sincere gratitude to:

The patients in the NAILED trial, for lending us your time and efforts.

The NAILED study nurses, for your patience with both patients and physicians, advocating the former and challenging the latter. Without your efforts there would be no science.

The Region Jämtland-Härjedalen for funding and encouraging my research.

The faculty of Medicine at Umeå University for making my research possible.

My main supervisor professor Thomas Mooe. For sharing your sincere enthusiasm for science, challenging me, and answering my questions no matter how unsubstantiated or in what hour of the day they arise. Our discussions and your commitment are true inspirations that I will try to bring on the rest of my journey.

My co-supervisor associate Professor Nikolai Stenfors for, with your genuine interest in science, trying to make me see the art at a different angle.

Lars Söderström for your deep and forthright interest in statistics and inspirational discussions.

My co-authors and fellow research colleagues Robin Henriksson, Stina Jakobsson, Christian Wikén, Anna-Lotta Irewall and Joachim Ögren for your cheering support, engaged discussions and your inspirational work. I´m looking forward to our future collaboration.

My parents Rolf and Harriet, and siblings Petra and Erik. For, with love always supporting and never condemning, and laying the ground for my interest in science.

My children Siri, Mira, and Astrid. For always and at all times bringing my attention to what´s most important in life.

And last but certainly not least my wife Malin. For your endless belief, support, and love. I love you to the moon and back.
References


54. Euroaspir I, Group II, European Action on Secondary Prevention by Intervention to Reduce E. Clinical reality of coronary prevention guidelines: a


85. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47(3):345-51.


