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RESIDUAL CARDIOVASCULAR RISK AFTER ISCHEMIC STROKE

Risk factors, medication adherence and risk-benefit considerations

Thesis for the degree of Philosophiae Doctor

Trondheim, March 2022

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
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Risiko for tilbakevendende kardiovaskulære hendelser etter iskemisk hjerneslag

Etter gjennomgått hjerneslag foreligger det en økt risiko for å bli rammet av en ny hjerte-kar hendelse, som et hjerteinfarkt eller et nytt hjerneslag. Likevel er det stor individuell variasjon i risiko for tilbakevendende hendelser. Optimal forebyggende behandling har som mål å redusere denne risikoen. Retningslinjer oppgir anbefalte behandlingsmål for blant annet blodtrykk, kolesterol og medikamentbruk. Få studier har undersøkt hvor godt vi lykkes med den forebyggende behandlingen. Det overordnede målet for denne doktorgradsavhandlingen var derfor å undersøke grad av risikofaktorkontroll, medikamentetterlevelse og hendelsesrater samt å estimere framtidig kardiovaskulær risiko hos pasienter som har gjennomgått iskemisk hjerneslag.

Avhandlingen er en delstudie av Nor-COAST studien som er en prospektiv, multisenter kohortstudie som inkluderte pasienter med hjerneslag i perioden mai 2015 til mars 2017. For å undersøke hvor godt vi lykkes med den forebyggende behandlingen, ble blodtrykk og blodprøver tatt 3 og 18 måneder etter innleggelse, og informasjon om medisinbruk innhentet. Informasjon om tilbakevendende hendelser ble innhentet fra Norsk Hjerneslagregister, Hjerte-karregisteret og Dødsårsaksregisteret. Totalt 664 hjemmeboende pasienter deltok i den **første studien**. Resultatene viste at de fleste fikk foreskrevet flere forebyggende medikamenter ved utreise fra sykehuset, men under halvparten av deltagerne nådde de anbefalte behandlingsmålene for blodtrykk og kolesterol. Deltagerne rapporterte at de i stor grad tok medisinene sine som forskrevet. Alder, kjønn, selvrapportert medikamentetterlevelse og antall medisiner i bruk er av betydning for grad av risikofaktorkontroll. I den **andre studien** undersøkte vi om en risikomodell utviklet for pasienter med karsykdom generelt gir pålitelig og anvendbar informasjon om framtidig risiko hos hjerneslagpasienter. Totalt 465 hjemmeboende pasienter mellom 45 og 80 år deltok. Resultatene viste at modellens anslåtte risiko samsvarte godt med den faktiske risikoen til pasienten. Vi beregnet at vi har mer å gå på når det gjelder den forebyggende behandlingen. Hvis vi optimaliserer blodtrykk og kolesterol, samt oppnår røykeslutt og gir adekvat blodfortynnende behandling, kan risikoen for en ny hendelse reduseres vesentlig. I den **tredje studien** undersøkte vi bruken av kolesterolsenkende legemidler og beregnet nytteverdien ved å intensivere behandlingen i henhold til retningslinjen for 462 pasienter under 80 år. De fleste fikk kolesterolsenkende ved utreise fra sykehuset. Eldre pasienter og kvinner fikk lavere doser, mens pasienter med høyere LDL-kolesterolnivå og iskemisk hjertesykdom fikk høyere dose. Ved 3 måneders oppfølging hadde under halvparten nådd behandlingsmålet for LDL-kolesterol, og vi beregnet at 81% potensielt kunne oppnådd målet med optimalisert forskrivning i henhold til retningslinjen. Absolutt nytteverdi av økt dosering varierer mellom individer, og på gruppenivå beregnet vi median elleve ekstra hjerte-karfrie levemåneder ved å øke den kolesterolsenkende behandlingen hos pasienter som ikke hadde nådd behandlingsmålet.

Avhandlingen viser at det foreligger et potensial for forbedring når det gjelder den forebyggende behandlingen etter iskemisk hjerneslag, men også at årsakene til manglende risikofaktorkontroll er sammensatte. Identifikasjon av pasienter som har høyest risiko for en tilbakevendende hjerte-kar hendelse er viktig, fordi disse vil ha størst nytteverdi av en mer intensiv forebyggende strategi og tettere oppfølging. Modellen vi har benyttet i denne doktorgradsavhandlingen (SMART-REACH modellen) kan være et verdifullt verktøy i klinisk praksis for en mer persontilpasset forebyggende behandling etter iskemisk hjerneslag.

Mari Nordbø Gynnild
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Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i medisin.
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“It's our job to help patients live as long as possible free of complications of cardiovascular disease. Although most patients share that goal, we don't always see the same pathways to get there. I want to believe that if patients knew what I know, they would take their medicine. What I've learned is that if I felt what they feel, I'd understand why they don't.”

L. Rosenbaum (New England Journal of Medicine, 2015)

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Trondheim, November 2021

Mari

LIST OF PAPERS

Paper I

Gynnild MN, Aakerøy R, Spigset O, Askim T, Beyer MK, Ihle-Hansen H, Munthe-Kaas R, Knapskog AB, Lydersen S, Naess H, Røsstad TG, Seljeseth YM, Thingstad P, Saltvedt I, Ellekjaer H. **Vascular risk factor control and adherence to secondary preventive medication after ischaemic stroke**.
J Intern Med. 2021 Mar;289(3):355-368.

Paper II

Gynnild MN, Hageman S, Dorresteijn J, Spigset O, Lydersen S, Wethal T, Saltvedt I, Visseren F, Ellekjaer H. **Risk stratification in patients with ischemic stroke and residual cardiovascular risk with current secondary prevention**.
Clin Epidemiol. 2021 Sep 17;13:813-823.

Paper III

Gynnild MN, Hageman S, Spigset O, Lydersen S, Saltvedt I, Dorresteijn J, Visseren F, Ellekjaer H. **Prescription patterns for lipid-lowering therapy after ischemic stroke and expected benefit from intensification of treatment**

Submitted.

SUMMARY

Although secondary prevention of cardiovascular diseases (CVD) has improved tremendously the last decades, high-risk patients continue to experience (recurrent) CVD events. Optimal secondary prevention aims to reduce this residual risk. Though, studies regarding the adequacy of secondary prevention following ischemic stroke are limited. Therefore, the overall aim of this thesis was to examine residual CVD risk after ischemic stroke by exploring degree of risk factor control, medication adherence, event rates and the distribution of CVD risk to identify patients at especially high risk who benefit the most from more intensive preventive treatment and follow-up.

This thesis was part of the **Nor-COAST study**, a multicenter, prospective cohort study consecutively including patients with acute stroke at five Norwegian stroke units between May 2015 and March 2017. Patients were followed at the outpatient clinics 3 and 18 months poststroke. Information about recurrent CVD events was obtained by linkage to The Norwegian Stroke Registry, The Norwegian Cardiovascular Registry, and The Norwegian Cause of Death Registry.

In **Paper I**, we assessed medication adherence, risk factor control, and factors influencing vascular risk profile 3 and 18 months after hospital discharge for 664 home-dwelling patients. We found that control of vascular risk factors was suboptimal, even though medication adherence was relatively high and persistence to drugs declined only modest during 18 months, especially for lipid-lowering therapy (LLT). Multiple factors interfered with guideline-recommended target attainment for blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), and HbA1c. Older patients had lower odds for BP control, while younger patients and women had lower odds for LDL-C control. Higher self-reported medication adherence was associated with lower LDL-C, while higher statin dose was associated with better LDL-C control.

In **Paper II**, we validated a prognostic model (the SMART-REACH model) aimed at patients with all manifestations of atherosclerotic vascular disease and estimated 10-year and lifetime CVD risk in 465 patients below 80 years. In total, 11.2% had a recurrent CVD event the first two years poststroke (after excluding the events in the subacute phase). The SMART-REACH model generates vascular risk information reasonably well in stroke patients. A substantial variation in estimated future CVD risk was estimated, with corresponding variation in absolute treatment benefit from intensification of secondary prevention. A remaining preventive potential exists and residual risk remains high even after optimization according to current guideline-recommendations.

In **Paper III**, we assessed prescription patterns for LLT and estimated the benefits from guideline-recommended up-titration of LLT for 462 patients below 80 years. At discharge, 92% were prescribed LLT; 99% statin monotherapy. Patients with prestroke dementia and cardioembolic stroke were less likely to receive LLT. Older patients and women were treated with lower doses, while individuals with higher baseline LDL-C, ischemic heart disease, and large artery stroke etiology received higher dose intensity. At 3 months, 45% reached LDL-C ≤1.8 mmol/L. However, we estimated that 81% could theoretically reach this target by optimized prescription of statins and ezetimibe, resulting in a median 11 months (IQR 7 to 17)

of CVD-free life gain for patients with elevated LDL-C, with large interindividual variations in benefit.

Overall, a potential for optimizing risk factors exists, and awareness of groups at risk of undertreatment and objective estimates of the individual patient's benefit from intensification may yield more well-balanced and personalized treatment decisions. The SMART-REACH model can be used to identify patients who will benefit the most from more intensive treatment and follow-up.

SELECTED ABBREVIATIONS

AF	atrial fibrillation
ARR	absolute risk reduction
BMI	body mass index
CAD	coronary artery disease
CeVD	cerebrovascular disease
CI	confidence interval
CVD	cardiovascular disease
DOAC	direct oral anticoagulant
EUROASPIRE	European Action on Secondary Prevention through Intervention to Reduce Events
GDS	Global Deterioration Scale
GFR	glomerular filtration rate
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
$HbA1_c$	haemoglobin $A1_c$
HIS	high-intensity statin
HR	hazard ratio
ICD	International Classification of Diseases and Related Health Problems
LAD	large artery disease
LDL-C	low-density lipoprotein cholesterol
LLT	lipid-lowering therapy
MI	myocardial infarction
MMAS-4	Morisky Medication Adherence Scale 4
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NNT	number needed to treat
Nor-COAST	Norwegian COgnitive Impairment After SToke
NOR-COR	NORwegian CORonary Study
OR	odds ratio
PAD	peripheral artery disease
RCT	randomized controlled trial
REACH	REduction of Atherothrombosis for Continued Health
SMART	Second Manifestation of ARTerial Disease
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SVD	small vessel disease
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WHO	World Health Organization

1 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide (1), with ischemic heart disease being the leading cause and stroke being the second-leading cause (2). However, mortality data underestimate the actual burden of stroke which, in contrast to ischemic heart disease and cancer, is chronic disability rather than death. Globally, stroke is the third-leading cause of death and disability combined, contributing to both loss of life years and loss of quality of life (2).

The incidence of fatal and non-fatal CVD events has decreased over the last decades (1-5). In Norway, mortality from stroke has decreased by 41% in the last ten years, and mortality from myocardial infarction (MI) has decreased by 50% (4). Important explanations are the evolution in treatment in the acute and subacute phases, improved pharmacological prevention, and healthy lifestyle habits (1, 2, 6). In 2018, 8840 stroke events were registered in the Norwegian Stroke Registry, representing a national coverage of 87% (7). A large proportion has minor strokes with a good functional outcome in terms of survival and independence and is home-dwelling after 3 months (8). Increased survival and increasing average life expectancy, in summary, result in a growing prevalence of patients living with established CVD in need of optimal secondary prevention and follow-up to prevent future CVD events (1, 2, 9, 10).

However, studies suggest that implementation of optimal guideline-recommended secondary prevention in clinical practice is inadequate with poor risk factor control and suboptimal medication adherence, in patients with both coronary artery disease (CAD) (11, 12) and ischemic stroke (13, 14). In Norway, one out of four acute strokes is recurrent (8), despite more than 90% of patients being prescribed the guideline-recommended medications at discharge (8). Multiple factors might interfere with both medication adherence (15, 16) and risk factor control, including aspects related to the patient, physician, and health care system (15, 16). Identifying barriers in providing optimal secondary prevention is crucial in helping patients live as long as possible free of complications from (recurrent) CVD events. Identifying individuals at the highest risk of recurrence is essential as they most likely gain the greatest clinical benefit from intensive risk factor control, novel therapies on top of standard treatment, and more intensive and multidisciplinary follow-up.

This thesis aimed to improve knowledge in this field by exploring the degree of risk factor control and adherence to secondary preventive medications early and late after stroke, identifying factors influencing risk factor control, and adding knowledge about the risk of recurrent CVD events with an aim of identifying patients at the highest risk.

2 BACKGROUND

2.1 Ischemic stroke – a heterogeneous disease

The World Health Organization (WHO) defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (17). Ischemic stroke accounts for approximately 86% of stroke cases and is caused by an occlusion of one of the cerebral arteries by a thrombus or thromboembolism, while intracerebral bleeding accounts for 13%; 1% are unspecified (8). While MI and peripheral artery disease (PAD) are caused mainly by atherothrombotic disease, the pathophysiological mechanism of ischemic stroke varies (18). Approximately 25% of all ischemic strokes are due to **large artery atherosclerotic disease** (LAD), 20% are due to **cardioembolic etiology** (i.e., atrial fibrillation (AF) or other cardiac sources), 25% are due to **small vessel disease** (SVD), 5% are due to **rare etiologies** (e.g., arterial dissection, prothrombotic conditions), and the reminding 25% are of **undetermined or multiple possible etiologies** (6). Ischemic stroke etiology is often more heterogeneous among young stroke patients than among older patients (6).

Stroke classification is crucial to determining the optimal secondary preventive strategy (18, 19). The most used classification system is the five main etiologies of the Trial of Org. 10172 in Acute Stroke Treatment (TOAST) classification system (20): LAD, SVD, cardiac embolism, other determined causes, and stroke of undetermined etiology (18). However, TOAST has been criticized for considering only the most likely cause, neglecting the overlap between diseases (18, 21, 22). Several studies have shown associations between SVD, LAD, and cardiac etiology (21-28). A study systematically assessing this issue found considerable overlap (21) and atherosclerosis was present in 90% of all patients, though it was causally related in only 43% (21). Atherosclerosis was present in 92% of patients when cardiac pathology was considered causal (21), harmonizing with other studies showing that AF is common in patients with

atherosclerosis (23, 29). In summary, concurrent etiology is a frequent situation among all stroke subtypes. All identified pathologies should be considered when managing the patient regardless of which is causal for the index stroke (18). In addition, the high prevalence of atherosclerosis highlights the importance of atherosclerotic risk factor control regardless of index stroke etiology.

2.2 Vascular long-term prognosis in individuals with ischemic stroke

The prognosis after stroke in the **early phase** varies according to, e.g., age, stroke severity, infarct location, comorbid conditions, and stroke-related complications (30-36), as well as interventions and rehabilitation. The risk of subsequent cardiovascular events is high in the early phase (32, 33) and associated with characteristics of the index event (6), sympathetic hyperactivity, and immune and inflammatory responses (32). The Norwegian Stroke Registry reports an in-hospital mortality rate of 7.5% (8). The worldwide 30-day mortality rate ranges from 17 to 30% with a declining trend, with large variations between countries (37) and a meta-analysis reported a pooled cumulative risk of recurrent stroke of 3.1% at 30 days (10). The Norwegian Stroke Registry reported a mortality rate of 15.8% after 3 months in 2018 (8). The first 3-4 months are generally considered the subacute phase poststroke, after which a gradual transition to a chronic stable phase occurs (32), when underlying vascular risk factors to a large extent seem to influence **long-term prognosis** (6, 38, 39).

2.2.1 Risk of recurrent stroke

Recurrent ischemic strokes account for 25-30% of all strokes and are often more severe and disabling than the index stroke event (40). A meta-analysis summarizing evidence from 1950 to 2009 reported a pooled recurrence risk of 11.1% (95% CI 9.0 to 13.3) the first year (10), while the risk was 26.4% (95% CI 20.1 to 32.8) and 39.2% (95% CI 27.2 to 51.2) at 5 and 10 years, respectively (10). Another meta-analysis summarizing evidence until 2016 (9) reported an annual risk of recurrent stroke of 4.26% (95% CI 3.43 to 5.09) with no marked variation over time. However, the risk declined significantly with the duration of follow-up (9). In a more recent study including patients with transient ischemic attack (TIA) or minor stroke, the estimated

cumulative event rate of recurrent stroke at 5 years was 9.5% (95% CI 8.5 to 10.5) (41). Also, other, more recent studies show lower cumulative event rates (34, 42, 43). These variations in event rates are presumably explained by differences in case-mix, e.g., time-period, changes in secondary prevention over time, study design, duration of follow-up, age distribution, geographical location, inclusion of TIA, solely ischemic stroke or also intracerebral hemorrhage or inclusion of only first-ever stroke (2, 10, 34, 41, 44, 45). Long-term risk (>10 years) of recurrence remains uncertain because the average follow-up in studies is usually of a shorter time horizon (31, 36, 43, 46). The incidence of dementia following a recurrent stroke is three times higher than that of dementia following first-ever stroke (47). An important component of secondary prevention after stroke is also preventing post-stroke cognitive impairment (6).

2.2.2 Risk of myocardial infarction and vascular death

Patients with TIA or ischemic stroke have a high vascular risk compared to stroke-free individuals (6, 31). Many studies report MI as the leading cause of death in stroke patients (46, 48). A meta-analysis from 2005 reported that the risks of MI and non-stroke vascular death were each approximately 2.2 % per year (46). A meta-analysis from 2016 reported that 3% of ischemic stroke patients have a MI within a year after the index stroke (48). A meta-analysis from 2018 found a 1% risk of MI per year after stroke if no history of CAD was present and 3.6% per year in individuals with CAD (9). Furthermore, while the risk of recurrent stroke declines by time after the index stroke (36), the risk of MI remains relatively stable (9, 30); the risk of a fatal stroke and cardiac death has also been reported as similar (9, 49). Male sex, hypertension, preexisting CAD, and PAD have been associated with increased risk of MI after stroke (9). The risk of MI after stroke have been reported similar across stroke etiology (9).

Mortality risk remains elevated in the years after stroke compared to the matched general population (35, 36, 50). After the first year, when the mortality risk is highest, the risk declines but is two to three times higher than that of the general population (36, 51). In a Norwegian single-center study, a large proportion (69%) of stroke patients died within 10 years of follow-up (33). While the most common causes of death are cardiovascular (51, 52), ischemic stroke patients have a high burden of multimorbidity (35, 53); death due to cancer and other diseases is also common (51).

2.2.3 Large overlap with other cardiovascular entities

Individuals with one CVD manifestation are more likely to have concomitant disease in other vascular areas (21, 22, 48, 54), either silent or manifest. Patients with polyvascular disease are considered at especially high risk of recurrent events (39, 49, 55-58), also despite current secondary prevention (49). Several studies show a significant overlap between cerebrovascular disease (CeVD), CAD, PAD and aortic disease (22, 49, 58-60). For example, many patients with coronary and aortic arch atherosclerosis have co-existing carotid stenosis and intracranial atherosclerosis and vice versa (22, 59, 60). Also, stroke patients without significant intracranial stenoses often have aortic arch and coronary atherosclerosis (22). The prevalence of asymptomatic coronary atherosclerosis in stroke patients ranges from 15% to 80% (48). A recent meta-analysis found that one third of ischemic stroke patients with no cardiac history had more than 50% coronary stenosis (48). Autopsy studies have shown that coronary atherosclerosis and MI are common regardless of the index stroke etiology (54). In summary, there is a strong rationale for a comprehensive, global approach to the prevention of both recurrent stroke and cardiac and other vascular events in patients with ischemic stroke.

2.3 The potential effect of optimal secondary prevention

The INTERSTROKE and INTERHEART studies have shown that the 9 (or 10) common cardiovascular risk factors account for approximately 90% of all strokes and MIs (61, 62) **(Figure 2.1.).** A review of the burden of stroke suggested that attainment of risk factor control could prevent more than three-quarters of the stroke burden worldwide (63). Quantitative modeling estimates that a comprehensive approach including antithrombotic therapy, antihypertensive and lipid-lowering therapy (LLT), smoking cessation, physical activity, and a healthy diet may reduce the risk of recurrent vascular events by 80% (64). Carotid revascularization for patients with significant carotid stenosis and anticoagulation for AF are effective secondary-prevention strategies for selected patients (19).

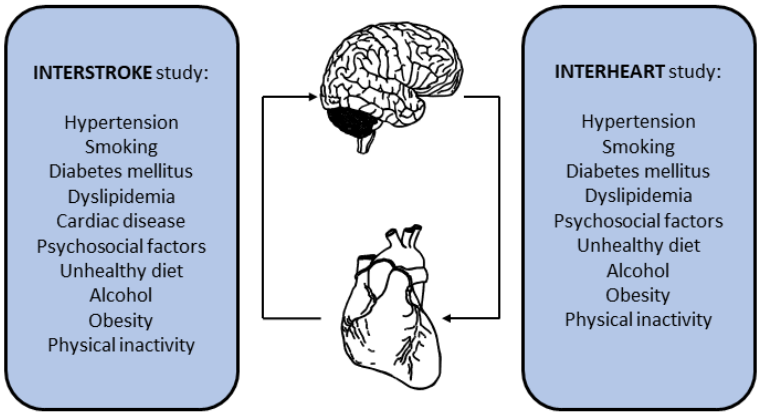

Figure 2.1. Modifiable cardiovascular risk factors in the INTERSTROKE (61) and INTERHEART (62) studies.

2.3.1 Guideline-recommendations for secondary prevention after ischemic stroke

Guidelines aim to assist physicians in choosing the best management strategy for a patient with a given condition by summarizing and evaluating the available evidence in the field (5, 65). Although guidelines aim to facilitate decision-making in clinical practice, the final treatment decision must harmonize with the individual patient's needs and preferences (5, 65, 66). International (5, 66) and Norwegian guidelines (19, 67) give clear recommendations for secondary prevention after stroke. In Norway, there is one guideline for patients with stroke separately (19) published in 2010 (updated in 2017), and one guideline for the prevention of cardiovascular diseases in general (67) covering secondary prevention in the stable phase following CAD, ischemic stroke and PAD published in 2017 (updated in 2018). Treatment recommendations in Norwegian Guidelines (19, 67) are summarized in **Table 2.1.**

Table 2.1 Norwegian guideline-recommendations for secondary prevention after stroke	
	Target and treatment
Antithrombotic therapy	Patients without cardiac etiology (with indication for anticoagulation) are recommended antiplatelet therapy. Clopidogrel or ASA/dipyridamole is suggested over monotherapy with ASA. For patients with atrial fibrillation, DOAC is suggested over warfarin.
Blood pressure control	Target BP <140/90 mmHg achieved by healthy lifestyle and pharmacotherapy with no clear evidence for first choice of type of drug.
Lipid control	LDL-C <2.0 mmol/L or <1.8 mmol/L if high-risk patient[a] achieved with healthy lifestyle and statin at maximally tolerated dose. Ezetimibe should be considered if treatment target is not achieved, PCSK9 inhibitor can be considered if unsatisfying lipid control with standard treatment[b]
Glucose control	HbA1c ≤ 53 mmol/mol (7%) achieved with healthy lifestyle and pharmacotherapy
Smoking cessation	Smoking cessation achieved by motivation, guidance or pharmacotherapy
Physical activity	At least 150 minutes of moderate physical activity or 75 minutes of high activity per week, adapted to the individual patient's functional level and needs
Weight reduction	BMI <25 kg/m^2
Diet	Healthy diet with plant-based food containing unsaturated fats (vegetable oils, nuts), less saturated fat (from meat products), vegetable and fruits, whole-grain products, limited intake of salt and food with high sugar content
Alcohol	≤10 g/d for women, ≤20 g /d for men

[a]The Norwegian CVD prevention guideline (67) recommends LDL-C < 1.8 mmol/L for all patients with established CVD. [b]The Norwegian Stroke Guideline (19) explicitly mentions only statins as recommended drugs; novel lipid-lowering therapies have not been evaluated in the current version of the guideline, and it refers to the Norwegian CVD prevention guideline, which recommends statin as first-line treatment, and ezetimibe if treatment targets are not reached by statin monotherapy or if statin intolerance. Abbreviations: ASA; acetylsalicylic acid (aspirin), DOAC; direct oral anticoagulant; BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; HbA1c, haemoglobin A1c; BMI, body mass index.

2.3.2 Evidence behind guideline-recommendations

2.3.2.1 *Antithrombotic therapy*

Antiplatelet therapy reduces the yearly risk of major CVD events by approximately a quarter in individuals with established CVD (68, 69). A meta-analysis of 16 randomized controlled trials (RCTs) in a secondary preventive setting of acetylsalicylic acid (ASA) versus no ASA (with no other antiplatelet drug in either group) showed an HR of 0.81 (95% CI 0.75 to 0.87) for CVD events, while the HR for recurrent ischemic stroke was 0.78 (95% CI 0.61 to 0.99) (68). The absolute reduction in major CVD events was 6.7% versus 8.2% per year (68). The combination of ASA and dipyridamole has been demonstrated to be more effective than ASA alone (19, 70)

and equivalent to clopidogrel monotherapy (19, 71). In patients with AF, a relative risk reduction of 66% (HR 0.34, 95% CI 0.20-0.57) for recurrent stroke with warfarin compared to placebo has been reported and absolute risk was reduced from 12% to 4% per year (number needed to treat (NNT) 12) (72). Direct oral anticoagulants (DOACs) are preferred over warfarin because of at least non-inferiority in efficacy and safety, and DOACs have fewer interactions, fixed dosing and no need for frequent monitoring with blood tests (19). However, patients' preferences in the choice of drug should be emphasized (19).

2.3.2.2 *Blood pressure lowering therapy*

Hypertension is the most important modifiable risk factor for stroke and TIA and reduces the risk of subsequent vascular events (19, 73). A large meta-analysis from 2016, synthesizing evidence from primary and secondary preventive settings, showed a pooled relative risk reduction for CVD events of 20% (HR 0.80, 95% CI 0.77 to 0.83) per 10 mmHg reduction in systolic BP (74). This proportional risk reduction was broadly similar among patients with and without established CVD. The HR for recurrent stroke was 0.73 (95% CI 0.68 to 0.77) (74). BP lowering to < 130 mmHg systolic was associated with better outcomes (73, 74). The most used treatment target is < 140/90 mmHg; however, the optimal target is unknown (5, 73). Treatment targets of < 130/80 mmHg have been implemented in more recent international guidelines (5, 66, 75). The optimal drug regimen is unknown (5, 19, 67), and comorbidity may guide the choice of drug. Combination therapy was more effective at reducing BP and stroke risk compared to monotherapy in the PROGRESS trial (76). There is clear indication for BP lowering in elderly patients (77). Extensive variation in health status is seen in the elderly (especially those > 75 years), and polypharmacy, interactions, frailty and remaining life expectancy should be taken into account when one considers the optimal treatment target (19, 67).

2.3.2.3 *Lipid-lowering therapy*

A large body of evidence from large RCTs and meta-analyses emphasizes the importance of LDL-C reduction in patients with established atherosclerotic vascular disease (19, 65, 67, 78-

80). The SPARCL trial evaluated the benefits of atorvastatin 80 mg/d in the secondary preventive setting after non-cardioembolic stroke and found that it was associated with a 16% reduction in risk of recurrent stroke (HR 0.84, 95% CI 0.71 to 0.99) and 20% reduction of major CVD events (HR 0.80, 95% CI 0.69 to 0.92) (81). An exploratory analysis of the SPARCL study has also shown that high-dose atorvastatin had a similar relative effect irrespective of ischemic stroke subtype (82); however, this has not been tested in cardioembolic stroke patients per protocol. Although the evidence has historically been less robust in patients with stroke compared to, e.g., CAD, the inverse relationship between LDL-C and stroke has been demonstrated with increasing evidence in both primary and secondary stroke prevention (81, 83). A large meta-analysis synthesizing evidence from both primary and secondary preventive settings showed a 22% relative risk reduction for major CVD events (rate ratio 0.78, 95% CI 0.76 to 0.80) per 1 mmol/L reduction in LDL-C (78). This estimate is largely consistent across several subgroups of patients, including the elderly (84). Average absolute risk reductions are reported between 1 and 3% (NNT 33 to 100) per 1 mmol/L reduction (78, 81, 85). A recent trial supported an LDL-C target of < 1.8 mmol/L in stroke patients with atherosclerotic disease (86), however, the optimal LDL-C target level to reach after stroke (as well as after a coronary event) remains uncertain (65). Evolving evidence in the latest years (after the publication of Norwegian guidelines) indicates that lower treatment targets are more beneficial (83, 85-88).

2.3.2.4 *Diabetes mellitus*

According to the Norwegian guideline for diabetes mellitus (89), the treatment target for HbA1c for most patients should be approximately 53 mmol/mol (7%) to reduce the risk of microvascular complications. HbA1c between 53 and 64 mmol/mol (7 to 8%) can be preferred in patients with long-lasting diabetes, substantial comorbidity, and risk of hypoglycemia (89). There is less evidence of the benefit of intensive glucose control on macrovascular endpoints such as stroke as compared to evidence on microvascular disease. In patients with diabetes mellitus type 2, intensive glucose lowering alone does not lead to reduced stroke risk compared to standard care (90). However, intensive glucose-lowering as part of a multifactorial intervention with BP lowering and lipid-lowering has an impact on reducing the risk of non-fatal stroke (90).

2.3.2.5 *Lifestyle*

Overall, observational studies have shown that **smoking** is associated with increased all-cause mortality (91) and risk of cardiovascular events (92) and that there is a large positive effect of smoking cessation with rapid onset in reducing the risk of CVD (64, 67, 91, 92). Persistent smoking after stroke or TIA is associated with an approximately doubled risk of stroke recurrence, with a demonstrated dose-response relationship (93). One study including 1072 patients with ischemic stroke smoking at the time of index stroke showed that patients who quit smoking had a significant reduction in their 5-year risk of CVD events (HR 0.66, 95% CI 0.48 to 0.90) (94).

An increase in physical activity and a healthy diet has important beneficial effects on CVD morbidity and mortality, pose little or no risk, and the beneficial effects start relatively shortly after initiation (19, 67, 95, 96). Individuals with a **healthy diet** (i.e., high intake of vegetables, fruits, nuts, whole grains, and fish) have lower CVD event rates and dietary intervention improves the prognosis in patients with established CVD (95). Being **overweight** or obese is associated with an increased risk of CVD events (97). There is little robust documentation about the optimal intensity, amount, and type of **physical activity** in secondary stroke prevention and CAD (19, 96). Therefore, recommendations are extrapolated from general knowledge of the importance of physical activity in the primary prevention of CVD (19, 96). High levels of **alcohol consumption** should be avoided (19, 67) and in a recent meta-analysis alcohol consumption was roughly linearly related to a higher risk of stroke (98).

2.4 Adherence to secondary preventive medication – a missing piece in the preventive puzzle?

The WHO defines adherence to long-term therapies as "the extent to which a person's behavior corresponds with *agreed* recommendations from a health care provider" (15). In the literature, different terms – like compliance, persistence, and concordance – describe the adherence phenomenon (99). The main difference between the historical compliance term and adherence is that adherence implies that the patient agrees with the healthcare providers' recommendations and is involved in the decision-making process (100). The term "medication adherence" is preferred to "compliance" because of the judgmental implications associated with being "non-compliant" (16, 101). Non-persistence is used when a medication is prematurely discontinued (100, 101).

From being a slightly neglected aspect of treatment, adherence has, in the last few years, received increasing attention, both because the extent of the problem has been more recognized and because non-adherence is a pervasive phenomenon across therapeutic disciplines (100). Furthermore, non-adherence contributes to the general variation seen in drug responses. In chronic diseases, poor adherence to medications is a common phenomenon and approximately 50% of patients do not take their medications correctly (16). Poor medication adherence has been identified as one of the largest challenges in the secondary prevention of cardiovascular diseases (102) and is a significant barrier to improved patient outcomes (101). It has been suggested that "increasing the effectiveness of adherence interventions may have a far greater impact on health of the population than any improvement in specific medical treatments" (15, 103). Although lifestyle interventions are essential to the prevention of cardiovascular diseases, the focus of this thesis remains on adherence to secondary preventive drugs.

2.4.1 Measuring medication adherence – no gold standard

There is no gold standard for measuring adherence (15, 16). Therefore, the measurements of medication adherence are not uniform across trials, making comparison difficult (101).

Measurement of adherence can be direct or indirect (16, 100). **Direct measures** include observed administration or measuring blood concentrations of drugs or metabolites (16). Direct methods are more accurate, but often more time-consuming and resource-demanding and not necessarily practical in routine clinical care (16, 100, 101). **Indirect measures** include patient self-report (i.e., questionnaires, diaries), pharmacy refill rates, pill counting, monitoring clinical responses, or electronic monitoring systems (16). Indirect methods are often easier to evaluate but often more inaccurate and prone to bias (101). Self-reporting by questionnaires or diaries or monitoring clinical response are relatively easy-to-use-methods, in both research and clinical routine (16). However, patient self-reporting is often prone to recall bias and clinical response is often confounded by factors other than medication adherence (16).

Because all these methods have their specific limitations and pitfalls, a combination of methods might be most feasible (16). However, specific methods might be preferred in certain clinical or research settings (16, 100). Furthermore, there is no consensus on the definition of adequate adherence (16). Adherence can vary from 0% to more than 100%, as some patients might take more drugs than prescribed (16). Adherence is reported mostly as non-adherence versus adherence; however, the cut-off used to define acceptable adherence varies and is also dependent on the drug and disease studied (16). Studies have also shown that most deviations from medication-taking occur as missed doses or delays in the timing of drug intake (16, 99).

2.4.2 Non-adherence and impact on patients' prognosis

Medication non-adherence is associated with adverse outcomes and increased health care costs and hospital admissions (16, 65, 100). A meta-analysis from 2013 estimated that ~9% of all CVD events in Europe are due to poor adherence to CVD medications (102). Studies assessing statin adherence show that patients with high medication adherence have the lowest risk of negative outcomes compared to patients with moderate or poor medication adherence (104, 105). The same relation is shown for stroke patients adherent to antihypertensive agents (106). Patients adherent to placebo also have more favorable outcomes than those non-adherent to placebo (16, 100). This illustrates that optimal drug adherence might be associated with higher adherence to other treatments or health-related

behaviors (e.g., following advice related to a healthy lifestyle, medical visits), a phenomenon often referred to as the "healthy adherer effect" (100).

2.4.3 Non-adherence to cardiovascular medications is highly prevalent

Physicians' ability to identify non-adherence is reported as being poor (16). The prevalence of non-adherence in clinical trials can be notably low compared to real-world adherence rates (16, 65). However, average adherence rates in clinical trials also lie within the range of 43 to 78% among patients treated for chronic conditions (16). A meta-analysis from 2013 found that, on average, about 40% of patients with established CVD are non-adherent to CVD medications (102). A review of non-adherence to secondary preventive drugs in stroke patients showed an overall non-adherence rate of 30.9% (95% CI 26.8 to 35.3%) with considerable heterogeneity in study design, tools measuring adherence, types of drugs included, and follow-up duration (107). Adherence is a dynamic phenomenon and deteriorates with time (16, 108). A study from the Swedish Stroke Registry following patients 14 months poststroke showed that one third of the patients discontinued at least one secondary preventive drug (109). The burden of medication non-adherence is likely to grow in the future due to the ageing of the population and the increasing prevalence of patients taking medication to treat (multiple) chronic conditions (100).

2.4.4 Vascular risk factor control – do we succeed?

For cardiovascular medications like antihypertensives and LLT, medication adherence can be measured indirectly by monitoring clinical response to treatment, i.e., blood pressure and LDL-C serve as surrogate markers of medication adherence (110). Until a few years ago, limited data were available on the attainment of guideline-recommended treatment targets among high-risk patients with established CVD, particularly among patients with stroke. In Europe, the adequacy of risk factor control has been evaluated in five cross-sectional surveys since the mid-1990s (the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) surveys) (11, 111, 112). These surveys show that risk factor

control is suboptimal and has not improved tremendously over time, except from LDL-C levels and statin prescription (111). The surveys have included mainly patients with CAD, but a stroke-specific study module was added to the EUROASPIRE III core survey (14). This study showed that about half of the patients were not achieving guideline-recommended risk factor targets. Norway did not participate in these surveys and, until recently, data from Norway and other comparable countries have been scarce, especially for stroke patients. In 2017, the NORwegian CORonary (NOR-COR) Study reported that most coronary patients had suboptimal risk factor control (12). Overall, there are significant gaps between the evidence and the implementation in clinical practice (113).

2.4.5 Potential factors influencing medication adherence and risk factor control

Multiple factors might interfere with stroke survivors' medication adherence (15, 16, 114) and risk factor control. The WHO has defined five sets of factors determining adherence, referred to as "the five dimensions of adherence" (**Figure 2.2**) (15): socioeconomic factors, factors associated with the health care team or system, disease-related factors, therapy-related factors, and patient-related factors.

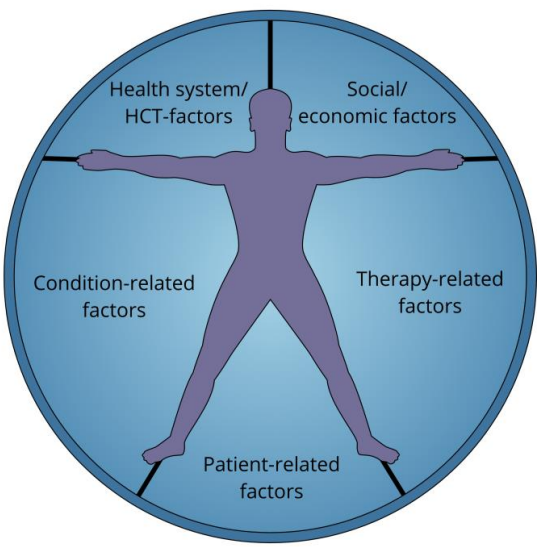

Figure 2.2 The five dimensions of non-adherence. Remade with permission from "Adherence to long-term therapies: evidence for action", WHO, page 27, copyright (2003). Abbreviation: HCT = health care team

Patient-related factors are just one determinant, underlining that medication adherence is not exclusively the patient's responsibility (110). A summary of factors influences peoples' behavior and abilities to adhere to treatment. Awareness of patients at risk of non-optimal adherence may help in tailoring interventions to improve adherence and risk factor control (16). In broader terms, these dimensions can fall into factors related to the **patient, the physician, and the health care systems** (16, 110, 113, 114).

2.4.5.1 *Patient-related factors*

Various patient-related factors – including forgetfulness, previous medication experiences and lack of motivation – may interfere with medication adherence (15, 16, 65, 107, 110, 115). There might be misunderstandings about lifelong treatment due to the chronicity of CVD as a disease (15). Health literacy is crucial; this is the ability to process information about the disease and medications and make appropriate health decisions (65, 110, 115, 116). However, poor knowledge can also be a result of inadequate information (16, 65, 116). Education at hospital discharge is associated with better adherence (107).

Concerns about adverse effects remains a common reason, which can be related to a negative attitude toward taking medications in general (15, 65, 107, 110, 115) and suspicion about over-prescribing or against science and medicine as a whole (15). Perceived adverse effects contribute significantly (65, 101, 110, 114). However, studies also show that poor adherence is less related to the class of drug, which might imply that adverse effects are not the leading cause (117). Medication adherence is also related to symptom severity (15). In asymptomatic conditions like hypertension, adherence is challenging (15, 110, 113) and adherence rates are often better if symptom burden is high (15). Although adherence is often better in secondary preventive settings than in the primary preventive setting (65, 117), adherence typically decreases with time since the index event (65, 108), which might be explained by perceived disease severity.

Age, sex, race, and comorbidity burden have shown conflicting results (15, 16, 107, 114, 118). Low socioeconomic status has been associated with poor adherence (65, 110, 114), but not consistently (16, 110). Lack of social or family support is a predictor of non-adherence (110). Illness-related factors (15) like frailty and disability might influence patients' ability to self-

administer mediations (107), as might anxiety, pain, depression, and drug and alcohol abuse (15, 65, 114, 119). Cognitive impairment, which is common in stroke patients (47), has also been associated with poor adherence (107, 114). In a study involving patients with heart failure (120), both mild cognitive impairment and dementia seemed to be associated with poorer adherence. Although many of these factors might influence medication adherence behavior, they also presumably influence how aggressively physicians treat risk factors. Elderly patients may be especially vulnerable and have many of the factors mentioned above (65, 114).

2.4.5.2 *Physician-related factors*

Prescribing complex medication regimens or making frequent changes in treatment regimens may contribute to poorer adherence (65, 110). Simple dosing helps improve adherence, and an inversely proportional relation is reported between adherence and frequency of dose (16) (121). Polypharmacy has been associated with poorer adherence (15, 110, 114, 122).

Drug(s) and dose intensity prescribed influence BP and LDL-C control (74, 75, 114, 123, 124). **Clinical inertia** is defined as the "failure to initiate or intensify therapy when indicated" (125) and is a multidimensional concept not only related to prescription or up-titration of dose. Clinical inertia may also encompass e.g., a lack of referral to prevention programs, a lack of cardiovascular risk assessment or no adherence monitoring (114, 126). However, there might be several reasons for not intensifying therapy, where good clinical judgment based on a holistic evaluation is important (127). Lack of guideline knowledge or disagreement with guideline recommendations (113) or time constraints due to managing other concurrent diseases might also influence (114, 128). Lack of monitoring has been identified as an important reason for the lack of risk factor control (129). Providing no information or inadequate information about benefits and potential adverse effects of treatment might also contribute to poor adherence (110, 114). A poor therapeutic relationship between the physician and the patient and a lack of involvement in the treatment decision-making process are associated with poor adherence (15, 16, 107, 110). The patient's motivation for adherence is influenced by the perceived cost-benefit ratio of therapy (15). Hence, better communication about the benefits of treatment might help enhance motivation (15, 130, 131). However,

studies have reported that patients remember approximately 50% of what is discussed during a consultation (110).

2.4.5.3 *Health care system-related factors*

The organization of the health care system can create barriers to adherence (15, 16, 114). These factors include inadequate reimbursement of drugs (15) and lack of training of health care providers in managing patients with established CVD and knowledge of adherence (15). Overworked healthcare providers, short consultations, and lack of time to detect non-adherence, educate patients, and provide sufficient follow-up are also important (15, 110). In addition, lack of time might limit the patient's ability to participate in discussions about medication adherence and limit involvement in the treatment decision-making process (110, 114). Studies also show that adherence to treatment increases before and after a visit with a health care provider and declines between; this is often referred to as "white coat adherence" (16, 114, 132, 133). Adherence rates in clinical trials are higher than real-world adherence rates, presumably owing to increased medical attention including frequent follow-up appointments, in addition to the selection of patients (16).

Lack of integrated health information from e.g., hospital medical records and primary care medical records might compromise patient-physician communication and contribute to suboptimal adherence (110). In a study on discharge letters for Norwegian patients with CAD, the authors found sparse information about lifestyle advice and treatment targets (134). In a semi-qualitative explorative interview, the general practitioners (GPs) requested more information about expected follow-up plans, treatment targets and algorithms for up-titration of drugs (134). A Norwegian study reviewing hospital discharge letters for 54 stroke patients also found limited information about treatment targets and plans for follow-up (135).

2.5 Identification of patients at high risk of recurrent cardiovascular events

Estimating an individual's future risk of having a (recurrent) CVD event is a central component of preventing CVD. Guidelines recommend a certain preventive treatment strategy for an individual with a given level of risk (5, 65, 67); the higher the risk, the more intensive the treatment. All individuals with established CVD, including ischemic stroke, TIA, CAD, or PAD, have traditionally been considered at very high risk of CVD events (65, 130). The risk is considered so high that the benefits of standard secondary prevention will (almost) always outweigh the potential harms of treatment.

2.5.1 Risk prediction in secondary preventive settings

For decades, risk stratification has been an important part of the primary prevention of CVD, with multiple existing risk stratification tools like the risk calculators based on the Framingham study (136), SCORE (Systematic Coronary Risk Estimation) (137), or NORRISK2 (138). In guidelines published before the work of this thesis, risk stratification was not considered necessary in secondary preventive settings, but a more individualized approach was acknowledged (65, 130, 139). Emerging studies now show that not all patients with established CVD are at equally high risk of recurrent events (140-142); some have relatively low risk, while some have extremely high risk. This interpersonal variation is usually a result of a combination of several prognostic features like age, genetics, levels of modifiable risk factors, the effectiveness of preventive therapy and competing risks like non-vascular mortality and remaining life expectancy (65, 143, 144).

There has been a debate about which characteristics best discriminate between high-risk and low-risk individuals in a secondary preventive setting (145). Age is a major risk factor for all clinical manifestations of CVD (143, 146). Known risk factors from primary preventive settings like blood pressure, LDL-C, and smoking still influence risk in patients who have already developed symptomatic disease (130, 145, 147, 148). However, other factors might be even more crucial, like years since first CVD event, number of symptomatic arterial disease locations (e.g., CeVD, coronary, and PAD), inflammation, and renal function (39, 55-58, 119, 147-149). Patients with diabetes and CVD have a higher risk (55, 61, 150). Information about carotid

intima-media thickness, carotid stenosis, or reduced ventricular ejection fraction, are also important predictors (147, 151), although not always available. Risk modifiers like psychological distress, ethnicity, and comorbidities are also important (5, 61, 62, 119). Until recently, the definition of very high-risk individuals has remained relatively qualitative, based on the presence or absence of certain comorbidities (57, 67). For example, in the Norwegian guidelines, stroke patients with very high risk are described as patients with e.g., concomitant CAD, PAD, or diabetes (19).

A risk stratification tool or prognostic model is a "mathematical combination of two or more patient or disease characteristics to predict outcome" (6). Several synonymous terms exist in the literature, like *prognostic index, risk score, probability model,* and *clinical prediction rule* (152). To be useful, they must reliably predict clinically relevant outcomes (153). This can be tested by first comparing estimated risk with observed risk in the derivation population (**internal validation**) (6, 154, 155). Next, the estimated risk is preferably compared to the observed risk in population(s) other than that from which the model was derived (**external validation**) (6, 152, 154, 155) – for example, in another geographic region, with a different case-mix, or in patients from a more recent time period (153, 155). The performance in an external population is often less accurate compared to internal validation, and in some cases also insufficient (153-157). Therefore, external validation is crucial before implementing a risk score in clinical practice (152, 155, 157).

2.5.2 Existing risk stratification tools for patients with established CVD

Multiple risk stratification tools have been developed for patients with CAD (158). Some of these have previously been externally validated in stroke patients (159); however, predictive accuracies were interpreted as low. For patients with vascular disease in general (CAD, CeVD, and PAD), two models have been developed to estimate the risk of recurrent CVD events: the 20-month REACH (REduction of Atherothrombosis for Continued Health) model published in 2012 (149) and the 10-year SMART (Second Manifestation of ARTerial Disease) risk score published in 2013 (145). These risk models can be used to estimate patients' **residual CVD risk**, defined as "the risk estimated after initial lifestyle changes and risk factor treatment (5)".

Because age is the most important vascular risk factor, older individuals have an estimated higher CVD risk by most risk models. If risk models are used to select individuals for therapy, this might result in the selection of older individuals (130, 140). However, older individuals and other individuals with high CVD risk also more often have a higher risk of non-vascular mortality, referred to as **competing risk** (130, 155, 160). Yet, most existing risk scores have not taken competing risks and remaining life-expectancy into account (145, 149, 161-165). This might lead to an overestimation of risk as well as the expected treatment effect in older individuals (166), as life expectancy must be sufficient to achieve the benefit. On the other hand, young patients, who often have a lower estimated risk, might miss treatment opportunities (130, 140, 167). Furthermore, as secondary prevention is presumably to be lifelong, it might be more intuitive to estimate lifetime risk. Lifetime prediction models have been published for primary preventive settings (130, 168). In 2018, **the SMART-REACH model** for patients with established CVD was published (140), estimating the 10-year and lifetime risk of CVD, and also taking competing risk into account.

2.5.3 Existing risk stratification tools for stroke patients

Risk stratification tools for stroke patients exist (38, 162-165, 169-172) but they may have some limitations because they are not utilized in clinical care (at least not in Norway). They tend to focus on short-term risk (40, 163, 165, 173, 174) (e.g., 90 days to 1-year risk) and risk of solely a recurrent stroke (174-176). One such example is the Essen Stroke Risk Score (174), which also later has been shown to predict 1-year risk of CVD events; however, AF patients were excluded and discrimination was found to be modest (45, 163). The Essen Stroke Risk Score has also been shown to identify stroke patients with a high risk of MI (177). Some scores focus on stroke patients with a specific underlying etiology like non-cardioembolic stroke (163, 174) or AF (169, 178). For example, the CHA_2DS_2VASc score was originally aimed at patients with AF (169), but can also predict outcomes in ischemic strokes without AF; however, discrimination was interpreted as modest (170, 171, 179). Most models are also derived in clinical trial populations with certain inclusion and exclusion criteria (164, 174), while some are derived in cohorts with solely TIA patients (173, 180). Prognostic models for risk assessment in the longer term (2 to 5 years) have been published for stroke patients and/or TIA patients (38, 175, 180, 181), with vascular events (38, 180), recurrent stroke or death (175), or solely death

(181) as the outcome. These studies suggest that long-term prognosis is more influenced by underlying vascular risk factors than characteristics of the index event in contrast to the short-term prognosis (< 90 days) (6). For example in the Dutch TIA Trial, age, diabetes, claudication, previous peripheral vascular surgery, and pathological Q waves on the electrocardiogram were associated with vascular events and death after a mean of 10.1 years (38). To the best of my knowledge, other risk stratification tools considering long-term total CVD risk in stroke patients are currently not available. Some risk scores from primary preventive settings have been validated in stroke cohorts, though with varying performance (164).

2.5.4 Why risk-stratify patients in the secondary preventive setting?

Due to the large interpersonal variation in the risk of recurrent ischemic events among patients with established CVD (130, 142), the potential benefit from more intensive secondary preventive therapy also varies (141-143, 182). Meta-analyses show broadly consistent relative risk reductions across several subgroups of patients for blood pressure-lowering (73, 74, 183), LDL-C-lowering (78, 79), and antithrombotic therapies (68, 69). This indicates that the individual's baseline cardiovascular risk is a major determinant of the absolute benefit of treatment (74, 77, 130, 144). Therefore, an estimation of average risk also provides the opportunity to translate results from RCTs to estimation of the individual's likely absolute risk reduction with treatment (130, 143, 144).

Both patients (184, 185) and clinicians (6, 185) are often inaccurate in assessing the individual patient's risk without objective risk stratification models, and reliable models can help guide physicians and patients in individualized risk-benefit considerations more objectively and precisely (144). The individual's benefit depends on a complex interplay between several aspects, summarized in **Figure 2.3**.

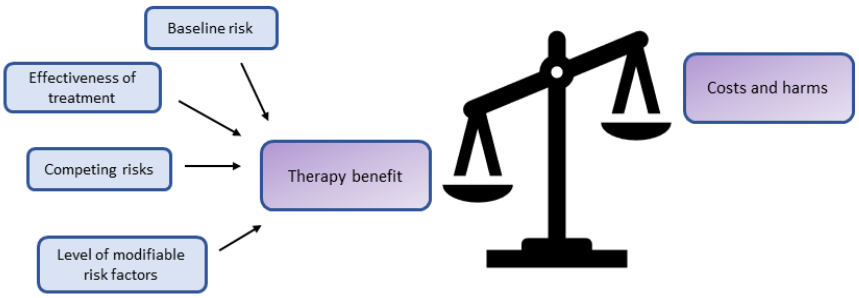

Figure 2.3. Aspects of importance in individualized risk-benefit considerations in the prevention of CVD.

Modified after J.A.N. Dorresteijn, EuroPrevent 2019 (by permission).

It should be acknowledged that all patients with established CVD, in general, require blood pressure and LDL-C management; however, there have been great advances in new treatment options (83, 186) and possible combinations of drugs in the last decade, and an approach toward more stringent treatment targets for LDL-C and BP (65, 75). A more personalized approach in secondary prevention is warranted and risk stratification can be increasingly valuable in clinical decision-making (130). This is especially relevant when considering expensive and potent novel drugs with potentially adverse effects on top of standard treatment (83, 186). For example, PCSK9 inhibitors will not be cost-effective in all patients, at least not with today's reimbursement (187). Risk stratification can also be used to guide the intensification of pharmacotherapy or the use of more stringent treatment targets for LDL-C or BP (65). In situations in which the balance between benefits and harm is marginal, as in patients with high bleeding risk who also require aggressive antithrombotic treatment, risk stratification might be useful (188). Risk stratification can also be relevant to supporting decisions to stop or not intensify treatment if the future expected benefit does not outweigh the disadvantages of that treatment (189). Risk stratification may also be used to select patients with the highest risk who should be prioritized for more intensive short-term and multidisciplinary follow-up, or subspecialist referral (130, 140). Furthermore, individualized communication about the risks and benefits of treatment might positively impact motivation

to adhere to secondary prevention (130, 131, 140). Finally, risk stratification might be useful in selecting relevant patients for therapeutic trials (140).

2.6 Summary of knowledge gaps and motivation for further research

- The provision of secondary prevention across Europe varies, but most of the evidence originates from patients with CAD. Accurate country-specific data for stroke patients are scarce, especially from more recent years. The median duration of hospital stay after stroke is five days (8) and despite the 3-month guideline-recommended outpatient control in specialist health care services (19), no standardized follow-up program is established. The Norwegian Stroke Registry provides information about the hospital stay and functional status at 3-months, but data on the adequacy of secondary prevention, especially in the long-term, is largely unknown.
- Multiple factors might interfere with medication adherence and risk factor control, including factors related to the patient, the physician, and the healthcare systems. Identification of patients at risk of non-optimal prevention is crucial, though few studies have assessed clinical factors influencing risk factor target achievement.
- We lack information about up-to-date CVD event rates for ischemic stroke patients.
- There is a need for better identification of patients at the highest risk of recurrent CVD events because they most likely gain the greatest clinical benefit from a more intensive secondary preventive strategy and follow-up. Currently available risk stratification tools predicting overall cardiovascular risk in stroke patients have some strengths, but also some limitations that restrain their use in clinical care (159, 161). To the best of my knowledge, clinically useful tools for long-term overall CVD risk prediction regardless of underlying etiology of the index ischemic stroke currently do not exist.
- Although CVD risk prediction in ischemic stroke might be challenging due to the etiological heterogeneity, a model aimed at all patients with established vascular disease regardless of anatomical localization might be useful. However, tools like

the SMART-REACH model have been derived and validated in populations dominated by CAD and LAD as stroke etiology (140). It is unknown if this model provides reliable prognostic risk information in an unselected stroke population. External validation is needed before implementation in clinical practice.

- Studies reporting long-term residual cardiovascular risk in patients with ischemic stroke on current guideline-based secondary preventive management are limited.
- Few studies have described the use of LLT in stroke patients and factors influencing dose intensity. Multiple factors may influence prescribing patterns like awareness of an individual patient's risk of CVD events, perceived risk of adverse effects and the expected harm-benefit ratio (65, 190, 191). Whether we utilize the full potential of the effective, safe and low-cost LLTs available is largely unknown.

3 AIMS AND HYPOTHESES

The overall aim of the thesis was to examine residual cardiovascular risk in an ischemic stroke population by exploring the degree of risk factor control, medication adherence and the distribution of CVD risk to identify patients at particularly high risk of recurrent events who benefit most from more intensive preventive treatment and follow-up. More specifically, the aims in the three papers were as follows:

- In **Paper I**, we aimed to examine adherence to secondary preventive drugs and achievement of guideline-recommended risk factor targets at 3 and 18 months poststroke and explore clinical factors associated with the attainment of optimal risk factor control. We hypothesized that medication adherence and risk factor control decline over time and that higher self-reported medication adherence is associated with risk factor control.
- In **Paper II**, we aimed to validate the SMART-REACH model in an ischemic stroke cohort, estimate 10-year and lifetime residual risks of recurrent CVD events, and estimate the theoretical benefit of reaching guideline-recommended risk factor targets. We hypothesized that a model aimed at patients with established vascular disease regardless of anatomical localization can predict future CVD risk in a stroke population and that there is an unutilized potential for standard secondary preventive strategies.

- In **Paper III**, we aimed to address two sets of questions. First, how do current prescription patterns and achieved LDL-C reduction differ in subgroups of stroke patients? Next, what is the expected treatment benefit when theoretically up-titrating LLT according to guideline recommendations? We hypothesized that age, frailty, and cognitive impairment were associated with lower treatment intensity, that prescribing patterns differ in subtypes of ischemic stroke, and that many patients could achieve the current treatment target for LDL-C with statin plus ezetimibe.

4 MATERIAL AND METHODS

4.1 Study design and setting

This study was part of the Nor-COAST (Norwegian COgnitive Impairment After STroke) study, a multicenter, prospective cohort study consecutively including patients with acute stroke in the period from May 2015 to March 2017 at five Norwegian stroke units: St. Olav's Hospital; Oslo University Hospital, Ullevål; Vestre Viken Hospital Trust, Bærum Hospital; Haukeland University Hospital; and Ålesund Hospital (192). Inclusion criteria were hospitalization with acute ischemic or hemorrhagic stroke with less than seven days from symptom debut, Scandinavian speaking, and age > 18 years. Patients with an expected survival of less than three months were excluded.

In total, 1946 patients were potentially eligible for inclusion in the Nor-COAST main study during the 3-year inclusion period (2015-2017), and 815 were included (participation rate 42%) (193). The main reason for non-inclusion was failure to be screened (n=753) due to breaks in inclusion during weekends and holidays. The remaining reasons were declining participation (n=143), early discharge (n=92), and other reasons (i.e., uncertainty regarding diagnosis, inability to follow instructions, other practical reasons) (n=143) (193).

4.2 Study participants

In the current substudy, we excluded patients with intracerebral bleeding (n=78) and patients living in nursing homes at admission (n=8), leaving 729 **home-dwelling patients with ischemic stroke** eligible for analysis. We also excluded patients who died within the first 3 months poststroke (n=28) and patients living in nursing homes 3 months poststroke (n=36). Patients were followed from discharge to 31 December 2018. Within this time range, they had two follow-up appointments at the outpatient clinic approximately 3 months (mean 111 days after admission, SD 37) and 18 months (mean 571 days, SD 71) poststroke. A flowchart of patients included in the three papers is shown in **Figure 4.1**.

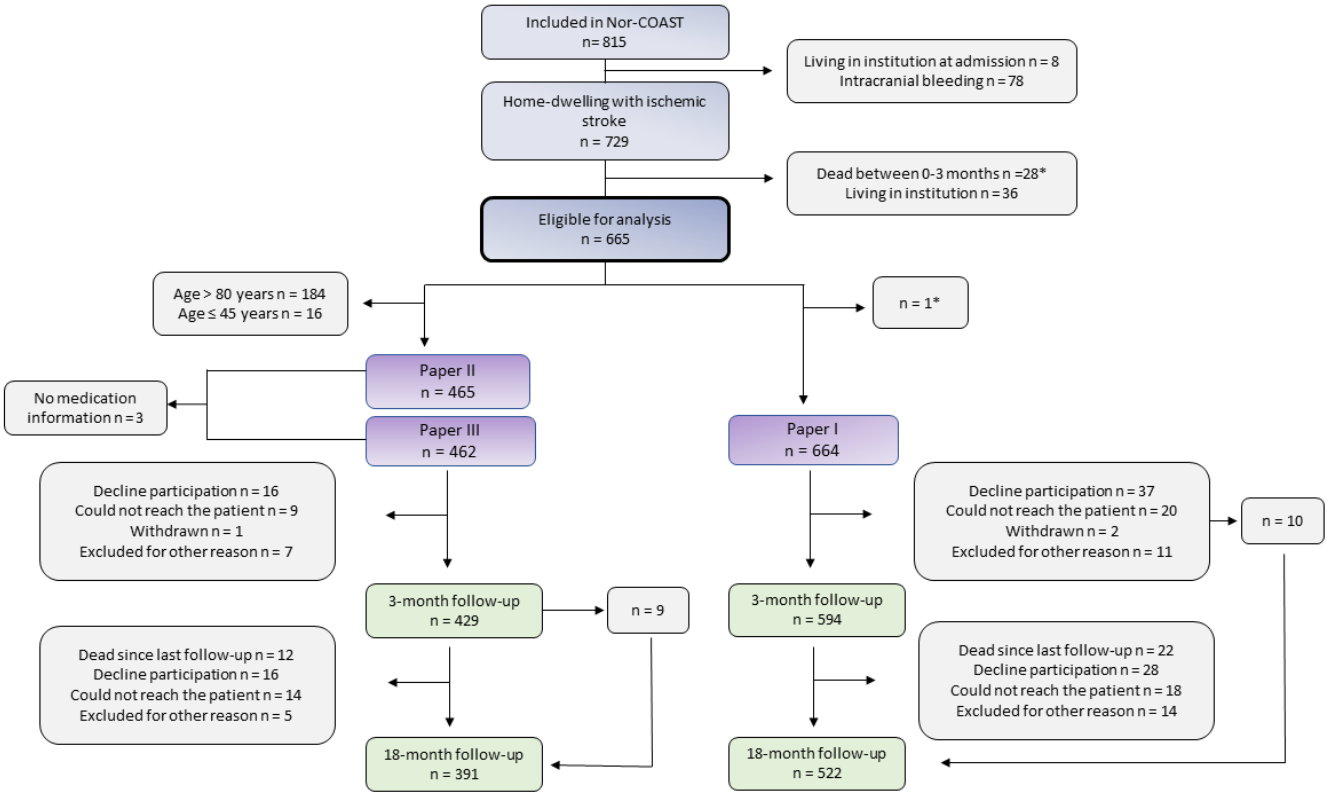

Figure 4.1. Flowchart of inclusion and exclusion of patients in the papers

*One participant was misclassified as dead in the Nor-COAST dataset (not dead according to the Norwegian Causes of Death Registry) and excluded from Paper 1 since this information was not known at the time of the publication.

In Paper I, 664 patients were eligible for analysis at baseline. In Papers II and III, 665 patients were eligible for analysis; however, patients above 80 years (n=184) and ≤45 years (n=16) were excluded because we used a risk prediction model derived and validated in this age group. In addition, 3 patients were excluded in Paper III due to lack of information about medications in use at all time points. This left 465 and 462 patients eligible for analysis in Paper II and III, respectively.

4.3 Data collection and sources

Figure 4.2 shows the timeline of the study, timepoints for the collection of important variables and data sources used in the thesis. Data were collected at the index stay (baseline) and after 3 and 18 months at the outpatient clinics of the respective hospitals by trained study health professionals. Data were systematically registered in a Web Case Report Form (CRF).

4.3.1 Baseline characteristics

Baseline characteristics, including demographic characteristics, prestroke vascular burden, other comorbidity burden, and index stroke characteristics, were based on a review of medical records during the index hospital stay. Prestroke functional and cognitive status was assessed by study nurses' interviews with caregivers. Assessment and definitions of baseline variables used in the current thesis are shown in **Table 4.1.**

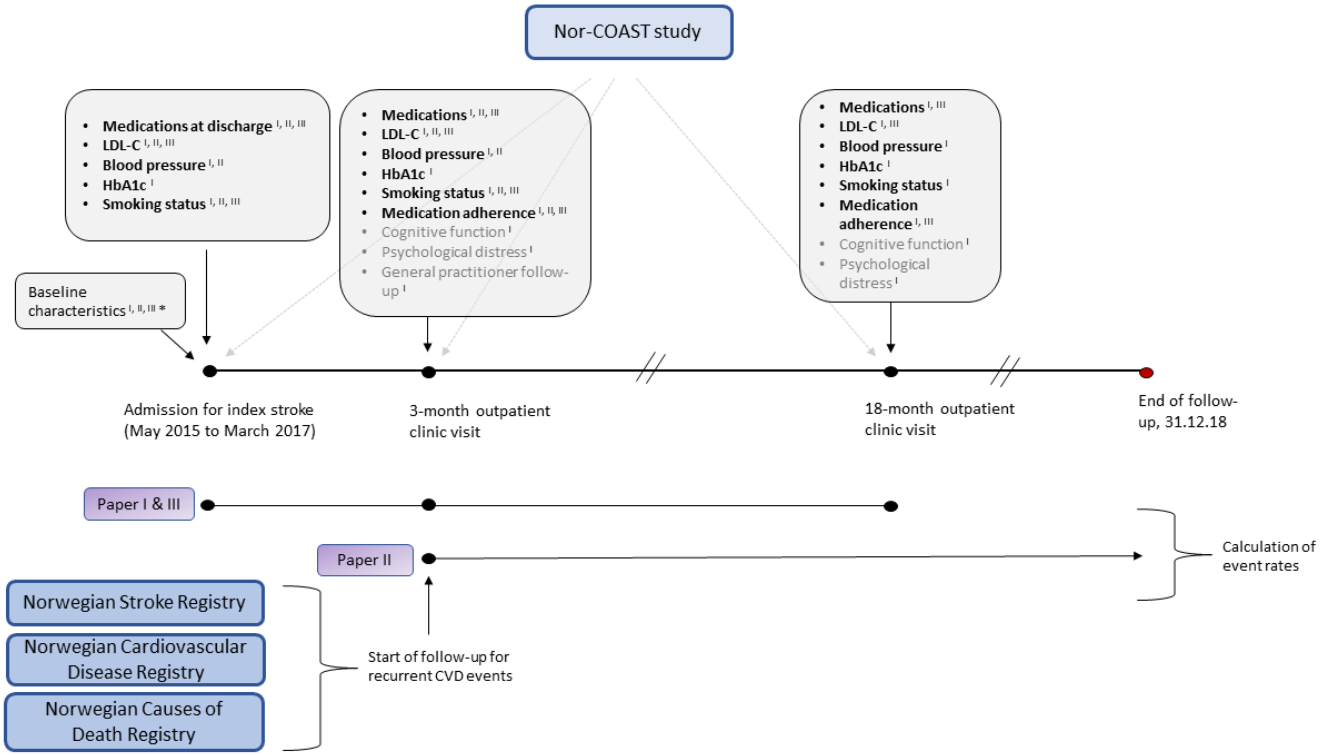

Figure 4.2. Timeline of the study and the data sources used.

[I]Paper I, [II]Paper II [III]Paper III. Abbreviations: LDL-C, low-density lipoprotein; HbA1c, hemoglobin A1c. *As described in section 4.3.1.

Table 4.1. Data collection of baseline variables in the Nor-COAST study	
Variable	**Assessment and definition**
Atrial fibrillation	Self-reported or documented on electrocardiogram or telemetry during admission
Diabetes mellitus	Self-reported (diet regulated) or HbA1c ≥48 mmol/mol or prescribed antidiabetic drugs at admission or discharge
Prestroke hypertension	Self-reported or use of antihypertensive drugs at admission
Prestroke hypercholesterolemia	Use of lipid-lowering therapy at admission
Previous cerebrovascular disease	Previous ischemic stroke, TIA or intracerebral bleeding
Ischemic heart disease/coronary artery disease (CAD)	Previous angina pectoris, myocardial infarction, or coronary revascularization
Peripheral artery disease (PAD)	Symptomatic or documented obstruction of distal arteries of the leg or surgery of the leg or documented surgery of the aorta
Number of vascular areas affected (1, 2, or 3)	One if only stroke (all patients), two if combined with either coronary artery disease or PAD, and three if all three areas were affected
Heart failure	History of heart failure by review of medical records
Estimated glomerular filtration rate (GFR)	Estimated by the CKD-EPI equation (mL/min/1.73 m^2) (194), based on age, sex, and serum creatinine concentration, chronic kidney failure was defined as GFR <60 mL/min/1.73 m^2
Comorbidity burden	Assessed by the Charlson Comorbidity Index (195)
Stroke severity	Assessed by the National Institutes of Health Stroke Scale (NIHSS) at admission and discharge (196)
Ischemic stroke subtype	Assessed by experienced stroke physicians and defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (20)
Functional status	Assessed by the modified Rankin scale (197) and a score ≤2 was defined as independence in daily activities
Cognitive status prestroke	Defined as a score ≥3 on the Global Deterioration Scale (198), which ranges from 1 to 7, where a score of 1 corresponds to normal cognition
Frailty	Assessed by a modified version of the 5-item Fried Criteria (199), based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity, and unintentional weight loss (range 0 to 5), where a score of 0 corresponds to robust and a score ≥3 corresponds to frail
Use of home care services	Information about self-reported use of home care services (yes, no, assisted living facility, institution) was dichotomized (yes or assisted living facility)
Smoking status	Self-reported smoking status (never, current, former, unknown) was dichotomized to current smoking (yes/no)
Body mass index	Calculated as kg divided by height in meters squared
Physically active	Defined as self-reported adherence to physical activity guidelines defined as minimum 75 min per week of high-intensity exercise or minimum 150 min per week of moderate-intensity exercise
Blood pressure	Measured at discharge or day seven
Blood samples	Non-fasting blood samples were taken the first day after admission for baseline measurement of total, LDL and HDL cholesterol (mmol/l), HbA1c (mmol/mol), creatinine (µmol/L), and high-sensitive C-reactive protein (mg/L)
Medications at discharge	Obtained from the discharge summary

4.3.2 The 3- and 18-month follow-up visits

At follow-up, patients completed self-report questionnaires and underwent an interview, clinical examinations, and blood sampling. Patients unable to attend the outpatient clinic were assessed by telephone interview or by proxy information. Trained health professionals obtained information about **medications** in use by interviewing patients and next of kin. If information was missing, we contacted GPs and / or home care services or used the electronic summary care record for safer healthcare in Norway. Non-fasting **blood samples** were drawn from venous blood for the measurement of cholesterol and HbA1c. Blood pressure was measured three times by the same physician with one-minute intervals and the average of the second and third measurements was used in the analysis. Information about **smoking** status at follow-up was retrieved from the self-report questionnaire (never, current, former, unknown) and was dichotomized to current smoking (yes/no). **Cognitive function** was evaluated by the Global Deterioration Scale (GDS) (198), where trained nurses used all available information from a cognitive test battery described elsewhere (200), functional tests, and interviews with the participant/proxy, in addition to an interview with caregivers during the hospital stay. Whether the patients had a **follow-up appointment** at the GP between discharge and three months was retrieved from the self-report questionnaire. **Psychological distress** was measured by the Hospital Anxiety and Depression Scale (HADS) (201) ranging from 0-42, with an increasing score indicating increasing burden.

4.3.3 Endpoint registries

In **Paper II**, recurrent cardiovascular events were identified by linking the Nor-COAST participants to the following national registries by using their Norwegian personal identification number:

- The Norwegian Stroke Registry
- The Norwegian Cardiovascular Disease Registry
- The Norwegian Causes of Death Registry

These registries are regulated according to the Act relating to Personal Health Data Registries and are not based on patient consent. **The Norwegian Stroke Registry** is a mandatory medical quality register where since 1 January 2012, all Norwegian Hospitals have entered medical data on all residents > 18 years admitted to hospital and fulfilling the WHO criteria for an acute stroke (202). **The Norwegian Cardiovascular Disease Registry** is an administrative health register based on data from the Norwegian Patient Registry, containing information about all hospital admissions, included in the public reimbursement policy in Norway since 2008. For admissions to hospital, the registry contains information about dates of admission and discharge and main and secondary diagnoses according to the International Classification of Disease (ICD), in addition to other demographic, administrative, and health-related data (202). **The Norwegian Cause of Death Registry** is a mandatory registry covering all deaths in Norway and includes date of death, and underlying- and contributing causes according to ICD (203).

4.4 Outcome assessments

The main outcome in **Paper I** was the degree of medication adherence, achievement of risk factor control, and determinants of risk factor control. The main outcome in **Paper II** was recurrent cardiovascular events, both those observed and the estimated future risk, in addition to the impact of optimization of risk factors. In **Paper III**, the main outcome was the use of LLT in subgroups of stroke patients and the expected benefit of up-titrating LLT used at 3 months.

4.4.1 Medication adherence

Appropriate **secondary preventive medications** encompassed the following drugs with the Anatomical Therapeutic Chemical (**ATC**) Classification System codes defined by the WHO Collaborating Centre for Drug Statistics Methodology (204) in parentheses:

1. **Antihypertensive drugs**: thiazide diuretics (C03A), beta receptor blockers (C07), calcium channel blockers (C08), angiotensin-converting enzyme inhibitors (C09A, B), angiotensin receptor blockers (C09C, D), “other” (C02A, C02C, C02D)

2. **Antithrombotic drugs** (B01A): vitamin K antagonists (B01AA), heparin groups (B01AB), platelet aggregation inhibitors (B01AC), direct thrombin inhibitors (B01AE), direct factor Xa inhibitors (B01AF)

3. **Blood glucose-lowering drugs** (A10): insulins and analogs (A10A), blood glucose-lowering drugs, excl. insulins (A10B), other drugs used in diabetes (A10X)

4. **Lipid-lowering therapy**: HMG-CoA reductase inhibitors/statins (C10AA), bile acid sequestrants (C10AC), other lipid modifying agents (C10AX), combinations of lipid-lowering drugs (C10B)

These four classes of medications were assessed mainly as categorical variables (used, yes/no); and for antihypertensive drugs, we assessed the number of agents. In Papers I and III, we assessed doses for LLT. For easier comparison of doses across timepoints, the Defined Daily Doses (DDDs) (204) for statins, which are 20 mg for atorvastatin, 30 mg for simvastatin, 10 mg for rosuvastatin, 60 mg for fluvastatin and 30 mg for pravastatin, were used to convert the doses to **atorvastatin equivalent doses** by using the following formula: (Dose of statin / DDD for that statin) x DDD for atorvastatin = atorvastatin equivalent dose. **High-intensity statin (HIS)** treatment was defined as drugs known to lower LDL-C by approximately 50%, which corresponds to ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day (65). Lower doses of these statins or use of fluvastatin or pravastatin irrespective of dose were defined as non-HIS treatment.

Medication adherence was assessed at 3- and 18 months by two measures:

1. Self-reporting using the Morisky Medication Adherence Scale 4 (MMAS-4) (205)
2. Persistence of medication use

MMAS-4 [¥] is a general medication-taking behavior scale validated in patients with various diseases and treatments (206). It has shown a sensitivity ranging from 32 to 81% and a specificity ranging from 44 to 73% depending on the validation population; however, it is seen as an adequate screening and monitoring tool in clinical practice (206). Each item in the MMAS-4 has a dichotomous response option (yes=0, no=1) and is based on the following questions: 1) Do you ever forget to take your mediations? 2) Do you ever have problems

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remembering to take your medications? 3) When you feel better, do you sometimes stop taking your medications? 4) Sometimes if you feel worse when you take your medications, do you stop taking them? The sum creates a total score ranging from 0 to 4, where a score of 4 corresponds to high adherence, scores of 2-3 correspond to medium adherence, and 0-1 corresponds to low adherence. We defined **persistence** as medication continuation from hospital discharge to 3 and 18 months poststroke. Individuals were also considered persistent if there had been a switch of medication within the same class.

4.4.2 Risk factor control

Vascular risk factor control was based on recommended treatment targets in the Norwegian guidelines (19, 67) at the time of the study. In Paper I, the three outcome measures – BP, LDL-C and HbA1c – were seen as surrogate markers of medication adherence; therefore, lifestyle factors were not categorized as outcome variables. In Paper II, LDL-C, BP, and smoking cessation were assessed in addition to antithrombotic treatment, as robust effect estimates for the magnitude of the relative risk reduction of macrovascular CVD endpoints exist for these risk factors (207, 208). **BP control** was defined as systolic BP < 140 mmHg and diastolic BP < 90 mmHg (19, 67). **Glycemic control** was defined as HbA1c ≤ 53 mmol/mol (≤7%) (67). **LDL-C control** was defined as LDL-C < 2.0 mmol/L in Paper I, as most physicians were probably treating toward this target at the time of the study (19), and ≤1.8 mmol/L in Papers II and III, as this is the recommended target for high-risk CVD patients (19, 67).

4.4.3 Recurrent cardiovascular events

4.4.3.1 *Observed 2-year risk of recurrent cardiovascular events*

Recurrent cardiovascular events were defined as stroke, MI, or cardiovascular death. All hospitalized events from 3 months poststroke (stable phase) to 31 December 2018 were identified by linkage to endpoint registries. We defined **recurrent stroke** as either registration in the Norwegian Stroke Registry or having a main diagnosis of stroke in the Norwegian Cardiovascular Disease Registry (202) using ICD-10 codes I61 (non-traumatic intracerebral hemorrhage), I63 (cerebral infarction), or I64 (stroke, not specified as hemorrhage or

infarction). We used data from both registries for stroke endpoints because the Norwegian Stroke Registry had a coverage of 87% in 2018, and the Norwegian Cardiovascular Disease Registry is more complete; however, it is less correct when both main and second diagnoses of stroke are included. Therefore, we restricted our analyses to main diagnoses (positive predictive value 93.5%) (202). We defined **subsequent MI** as admission with a main or secondary diagnosis of MI according to the Norwegian Cardiovascular Disease Registry (209), which are described as adequately complete (sensitivity 85.8%) and highly correct (positive predictive value 95.1%) (209). We used ICD-10 codes I21 (acute MI), I22 (subsequent ST-elevation and non-ST elevation MI), and I24 (other acute ischemic heart disease) to define MI endpoints. **Cardiovascular death** was defined as the ICD-codes I00-I99 registered as underlying cause of death (210) in the Norwegian Cause of Death Registry or death within 28 days after a recurrent stroke or MI.

4.4.3.2 *Estimated future risk of recurrent cardiovascular events*

In Paper II (and Paper III), we estimated 10-year and lifetime risk of recurrent cardiovascular events by using the **SMART-REACH model** (140), which is a competing-risk adjusted Fine and Gray model for lifetime predictions of major cardiovascular events and non-cardiovascular mortality in patients with (any type of) clinically manifest cardiovascular disease (140) (i.e., CeVD, CAD, PAD, or abdominal aortic aneurism (AAA)). The model was derived based on data from 14,259 cardiovascular patients above 45 years from Western Europe enrolled in the Reduction of Atherothrombosis for Continued Health (REACH) registry. Individuals in the REACH registry were enrolled from outpatient clinics between 2003 and 2004 and outcomes were reported annually by a local investigator (211).

The model was externally validated in 19,179 cardiovascular patients from the REACH registry North America, and 6,959 patients aged 40 to 79 years from the Netherlands enrolled in the Secondary Manifestations of ARTerial Disease (SMART) cohort, with C-statistics of 0.68 (95% CI 0.67 to 0.70) and 0.67 (95% CI 0.66 to 0.68), respectively, and calibration plots showing high correspondence between predicted versus observed risk (140). Patients in the SMART cohort were enrolled between 1996 and 2014 at a single hospital outpatient clinic and the occurrence of outcomes was evaluated by an endpoint committee (212).

The model was developed using statistical methods previously described in detail (140, 143). A **Fine and Gray model** is an extension of the traditional Cox model (155, 160), where a subdistribution hazard is defined for the event of interest incorporating the disturbing influence of competing events (155). Two competing risk models were fitted for cause-specific estimates of the cumulative incidence: one for recurrent CVD events and one for non-CVD mortality (140). Patients who experience a competing event are not censored as in traditional survival analysis, but remain in the risk set (155, 160) and are no longer at risk of a CVD event (143, 160).

The model uses **age as an underlying timescale** (143, 213) and is adapted to allow for left truncation and right censoring (140, 214). In practice, this was performed by using a weighted Cox model as previously described (214). Compared to a "regular" Fine and Gray model, the main difference is the possibility of allowing left truncation, but still allowing competing risk-adjusted coefficients. Left truncation means that the participant enters the study at his or her age at study entry, not at the study at time zero (143), excluding follow-up time before the observation period (213). Time to event or censoring is defined by the age of study exit, called right censoring. Each study participant then contributes with data to the survival model from the age of entry until the age of censoring or CVD event (143), enabling predictions limited by the age distribution of the study participants instead of the study follow-up time. The age-specific baseline survivals can be found in the supplemental material of the original SMART-REACH publication (140) and the models' formula is as follows:

Cardiovascular model*

1-year survival = (age-specific 1-yr baseline survival¥)^exp(A)

A = 0.0720 (if male) + 0.4309 (if current smoker) + 0.4357 (if diabetes mellitus) – 0.0281* systolic blood pressure (in mmHg) + 0.0001* *squared* systolic blood pressure (in mmHg) – 0.3671*total cholesterol (in mmol/L) + 0.0356**squared* total cholesterol (in mmol/L) + 0.0061*creatinine (in µmol/L) + 0.3176 (if two locations of cardiovascular disease)§ + 0.2896 (if three locations of cardiovascular disease)§ + 0.2143 (if history of atrial fibrillation) + 0.4447 (if history of congestive heart failure) – *regional expected/observed-ratio#*

Non-cardiovascular mortality model*

1-year survival = (age-specific 1-yr baseline survival¥)^exp(B)

B = 0.5986 (if male) + 4.2538 (if current smoker) – 0.0486*age (if current smoker) + 0.4065 (if diabetes mellitus) – 0.0074*systolic blood pressure (in mmHg) - 0.0030*total cholesterol (in mmol/L) - 0.0189*creatinine (in µmol/L) + 0.0001**squared* creatinine (in µmol/L) + 0.1442 (if two locations of cardiovascular disease)§ + 0.5694 (if three locations of cardiovascular disease)§ + 0.3213 (if history of atrial fibrillation) + 0.2061 (if history of congestive heart failure – *regional expected/observed-ratio#*

¥*Age-specific **baseline survivals** are reported in the supplemental material of the SMART-REACH article* (140)*. These were calculated by predicting the risk based on mean risk factor levels for every life year.* §*0.3176 should be added to A and 0.1442 to B if the patient has two locations of CVD. If the patient has three locations, add 0.2896 to A and*

0.5694 to B. The coefficients for the locations of CVD should not be added up. #Regional recalibration factor, see section 4.6.2.

The model estimates **10-year risk** (%) of recurrent CVD events, **lifetime risk (%),** and **life expectancy (years) without a recurrent CVD event** for individual patients. To estimate life expectancy without a recurrent CVD event, lifetables calculating risks for every 1-year interval are made beginning at the starting age of each individual and repeated up to the maximum age of 90 years (140, 143). The CVD-free life-expectancy of an individual was defined as median estimated survival, which is the age at which the predicted survival curve equals 50%. The 10-year risk is estimated using the same competing risk-adjusted model and calculated as the cumulative cause-specific CVD risk truncated at 10 years after the starting age (adjusted for non-CVD mortality). Lifetime risk is defined as the risk of having an event before the 90th life-year.

4.4.3.3 *Predictor variables in the SMART-REACH model*

The SMART-REACH model includes the following predictors: sex, diabetes mellitus, history of AF, history of heart failure, number of locations of cardiovascular disease (CeVD, CAD and PAD), current smoking, serum creatinine concentration, systolic BP and total cholesterol, based on the predictors in the original 20-month REACH model (149) and 10-year SMART risk score (145).

We used clinical measurements at the 3-month visit in Nor-COAST because the model is intended for patients with stable CVD and we aimed to simulate predictions being made in clinical practice (roughly corresponding to the recommended follow-up appointment 1-3 months post-event (19, 67)) where the model can serve as a clinical decision-making support tool. For the baseline characteristics age, sex, diabetes mellitus, CAD, PAD, heart failure, and AF, we assumed that registrations at index stay were also valid at the 3-month visit. BP, smoking status, cholesterol, and creatinine were measured at the 3-month visit as described in section 4.3.2. Baseline characteristics for patients in the derivation and validation cohorts are shown in **Table 4.2.**

Table 4.2. Baseline characteristics in the REACH, SMART and Nor-COAST cohort				
	REACH Western Europe (n=14.259)	**SMART cohort study (n=6.959)**	**REACH North America (n=19.179)**	**Nor-COAST study (n= 465)**
Age, years	68 (10)	60 (10)	70 (10)	69 (8)
<55	1481 (10)	2093 (30)	1658 (9)	30 (6)
55-65 years	3525 (25)	2382 (34)	4325 (23)	105 (23)
65 to 75 years	5509 (39)	2005 (29)	6413 (33)	187 (40)
≥75 years	3744 (26)	470 (7)	6774 (35)	143 (31)
Sex, male	10 270 (72)	5098 (73)	11 861 (62)	287 (62)
Current smoker	2283 (16)	2195 (32)	2546 (13)	55 (12)
Systolic blood pressure	140 (18)	140 (21)	132 (18)	140 (19)
Diastolic blood pressure	80 (10)	81 (11)	75 (11)	83 (12)
Diabetes mellitus	771 (33)	1227 (18)	8118 (42)	92 (20)
Coronary artery disease	9860 (69)	4367 (63)	15 512 (81)	79 (17)
Peripheral artery disease	3343 (23)	1377 (20)	2329 (12)	35 (8)
Cerebrovascular disease	4451 (31)	2124 (31)	5348 (28)	465 (100)
Heart failure	2208 (15)	…	3692 (19)	11 (2)
Atrial fibrillation	1629 (11)	79 (1)	2605 (14)	101 (22)
Creatinine (µmol/L)	93 (28)	88 (77)	100 (35)	83 (23)
Total cholesterol (mmol/L)	5.1 (1.2)	4.8 (1.2)	4.6 (1.1)	4.0 (0.9)
Statin	10 176 (71)	4683 (67)	14 787 (77)	412 (89)
Antithrombotics	9529 (67)	4022 (68)	14 459 (75)	455 (98)
Antihypertensives	12 900 (90)	5183 (74)	17 933 (94)	338 (73)
Follow-up (years), median (IQR)	1.8 (1.5 to 2.2)	6.5 (3.4 to 9.9)	1.8 (1.5 to 1.8)	2.2 (1.8 to 2.6)
CVD events	1555	1077	1743	52
Non-CVD mortality events	490	554	679	15

Numbers are mean (SD) or n (%). Abbreviations: CVD, cardiovascular disease; IQR, interquartile range.

4.4.4 Expected benefit from guideline-based optimization of treatment

It has previously been shown that risk estimations (retrieved by a risk prediction tool) can be combined with relative treatment effects (i.e., relative risk reductions or hazard ratios (HRs)) from meta-analyses and RCTs to calculate absolute individualized treatment effects (143, 144, 183).

4.4.4.1 *Expected benefit of reaching risk factor targets*

In Paper II, the expected benefit if (four) major risk factors were controlled according to the Norwegian guidelines (67) was quantified by the SMART-REACH model. The relative effect of

treating risk factors to recommended targets was retrieved from meta-analyses (68, 74, 78) and combined with the competing risk-adjusted Cox proportional hazard function from the SMART-REACH model according to previously described methods (140, 143, 144). Risk factor targets and effect measures used when calculating treatment benefits are shown in **Table 4.3**.

Table 4.3. Guideline-recommended targets and effect measures from trials used when calculating treatment benefits

Risk factor target	Effect measures
LDL-C ≤ 1.8 mmol/L (67)	**HR 0.78 was assumed per 1.0 mmol/L reduction in LDL-C** (78), regardless of whether this was achieved by lifestyle modification or medication. The individual expected relative risk reduction was calculated by $0.78^{\text{LDL-C reduction in mmol/L}}$. **LDL-C reduction** in mmol/L was defined as the 3-month LDL-C level minus 1.8 mmol/L. We assumed no further risk reduction from lowering LDL-C below 1.8 mmol/L.
Systolic BP ≤ 140 mmHg (67)	**A 10-mmHg reduction in systolic BP was assumed to correspond to a cardiovascular specific HR of 0.80** (74), regardless of whether this was achieved by lifestyle modification or medication. The individual expected relative cardiovascular risk reduction was calculated by $0.80^{(\text{BP reduction in mmHg}/10)}$. **BP reduction** in mmHg was defined as the 3-month systolic BP minus the target systolic BP of 140. We assumed no further risk reduction from lowering BP below 140 mmHg.
Antithrombotic treatment (67)	Estimated risk was based on the assumption that standard care was provided. Such standard care (HR 1.00) included ASA or an equivalent type of antithrombotic therapy, including vitamin K antagonists or DOACs, regardless of the number of antithrombotic drugs in use. We assumed that **no use of antithrombotic therapy was associated with the inverse effect of starting (at least) ASA (i.e., HR 1/0.81 = 1.23)** (68).
Smoking cessation (67)	In the absence of effect estimates from RCTs, we used effect estimates from large observational studies with high methodological quality. The effect of smoking cessation was estimated in current smokers. Smoking cessation is assumed to reduce the HR for CVD events of current smokers versus never smokers (HR 1.98 (92)) to that of ex-smokers versus never smokers (HR 1.18 (92)). **The resulting HR for CVD events for current smokers when converting to ex-smokers was thus assumed to be 1.18/1.98 = 0.60** (92)**.** Smoking cessation is also assumed to reduce the HR for non-CVD mortality of current smokers versus never smokers (HR 1.83 (92)) to that of ex-smokers versus never smokers (HR 1.34 (91)). **The resulting HR for non-CVD mortality for current smokers who are now ex-smokers was thus assumed to be 1.34/1.83 = 0.73** (91)**.**

Abbreviations: LDL, low-density lipoprotein; BP, blood pressure; HR, hazard ratio; DOACs, direct oral anticoagulants; CVD, cardiovascular disease; RCT, randomized controlled trials.

To estimate the benefit of reaching the guideline-recommended risk factor targets, the cardiovascular risk was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month risk factor levels and treatment. Next, we estimated the risk with the assumption that all risk factors met the guideline-recommended targets. The difference between estimated risk with 3-month risk factor levels and estimated risk when risk factors were at target corresponds to an individual's estimated absolute risk reduction (ARR). We then obtained the following estimates from the model: 1) 10-year risk of CVD events, 2) lifetime risk of CVD events, and 3) life expectancy free of CVD events. We calculated the following treatment effects: 1) absolute CVD risk reduction in the next 10 years, 2) absolute lifetime CVD risk reduction, and 3) gain in CVD-free life expectancy.

4.4.4.2 *Expected benefit of intensification of lipid-lowering therapy*

In Paper III, we estimated the expected benefit from up-titrating conventional LLT. Guidelines recommend statins at a maximally tolerated dose as first-line therapy (Step 1) and the use of ezetimibe in patients who are unable to achieve the LDL-C target with statins alone or who are statin-intolerant (Step 2) (65, 67). While statins and ezetimibe are well-established treatments available at low costs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are more potent and expensive and are recommended for consideration for patients who are still not reaching targets (Step 3) (65, 67).

We estimated the effect of up-titrating current LLT, defined as the drug and dose used at the 3-month visit including those discontinuing LLT between 0 and 3 months, with a stepwise approach to achieve LDL-C ≤1.8 mmol/L (67). When information about drug and dose was missing at 3 months (6%), we used the drug and dose prescribed at discharge. We estimated the effect of up-titrating LLT using the mean percent reduction in LDL-C derived from RCTs as shown in **Table 4.4**.

Table 4.4. Mean and standard deviation percentage change in LDL-C reduction with statins and ezetimibe, as presented and validated by Cannon et al. (215)			
Drug	**Dose, mg**	**Mean % reduction**	**Standard deviation**
Atorvastatin	10	35.5%	10.6%
	20	41.4%	13.5%
	40	46.2%	12.5%
	80	50.2%	13.8%
Fluvastatin	20	17.0%	8.0%
	40	23.0%	10.0%
	80	26.0%	9.0%
Lovastatin	10	21.0%	10.1%
	20	24.0%	11.0%
	40	30.0%	11.0%
	60	34.5%	11.7%
Pravastatin	10	20.0%	11.0%
	20	24.0%	11.0%
	40	30.0%	13.0%
	80	33.0%	11.2%
Rosuvastatin	5	38.8%	13.2%
	10	44.1%	12.5%
	20	49.5%	13.3%
	40	54.7%	12.9%
Simvastatin	5	23.0%	11.0%
	10	27.4%	13.7%
	20	33.0%	10.4%
	40	38.9%	14.0%
	80	45.0%	11.7%
Ezetimibe	10	22.7%	16.5%

We estimated potentially achievable LDL-C levels when up-titrating therapy for those not already at the target at 3 months. For patients already using a HIS, achieved LDL-C levels at 3 months were used when calculating the effect of adding ezetimibe. For patients using non-HIS we calculated additional LDL-C reduction (based on LDL-C levels achieved at 3 months) by switching from non-HIS to HIS. For example, for switching from atorvastatin 10 mg (associated with 35.5% LDL-C reduction) to atorvastatin 80 mg (associated with 50.2% LDL-C reduction), the assumed additional relative LDL-C reduction is 23% (1-(1-0.502)/(1-0.355)) (215). After up-titrating all to a HIS, we assumed a mean 22.7% reduction in LDL-C (88, 215) when adding ezetimibe.

The estimated benefit in terms of **gain in months** free from recurrent cardiovascular events and **10-year ARR** were estimated by the SMART-REACH model with the same methods as

those described in paragraph 4.4.4.1 (**Table 4.3**) using the current 3-month LDL-C levels and the LDL-C levels attained with the abovementioned stepwise approach. Patients were assigned to intensification of treatment only if they had not attained the LDL-C target in the previous step. Patients already reaching the target were modeled with no LDL-C reduction.

4.5 Assessment of predictor variables

We selected potential predictors of degree risk factor control (Paper I) and prescribing patterns of LLT (in Paper III) a priori based on clinical reasoning and previously published studies (15, 16, 107, 114, 191, 216-220), as well as available variables in the Nor-COAST dataset. Relationships between clinical and demographic variables to the predictors and outcome variables were investigated using directed acyclic graphs to assess their status as confounders, mediators, or colliders (221).

4.5.1 Potential predictors of risk factor control (Paper I)

In Paper I, the outcome variable (dependent variable) was risk factor target achievement in patients prescribed pharmacotherapy (dichotomized in main analyses). Predictor variables chosen were age, education, frailty, cognitive impairment evaluated at all timepoints, MMAS-4 evaluated at 3 and 18 months, follow-up with the GP between discharge and 3 months and psychological distress measured by HADS at 3 and 18 months. In a separate analysis, we included statin dose intensity as a predictor for LDL-C target achievement. These variables are known as barriers to medication adherence; however, few have assessed these factors' direct relation to risk factor control.

4.5.2 Potential predictors of prescription patterns of LLT (Paper III)

In Paper III, the outcome variables (dependent variables) were LLT prescription (yes/no) and statin dose (mg) at discharge. The two main variables determining a patient's LDL-C reduction are 1) the type of drug and dose intensity that the doctor prescribes and 2) the patient's

adherence to therapy (105, 114). Although there might be overlap between predictors for prescription patterns and medication adherence, they might also be different (**Figure 4.3**).

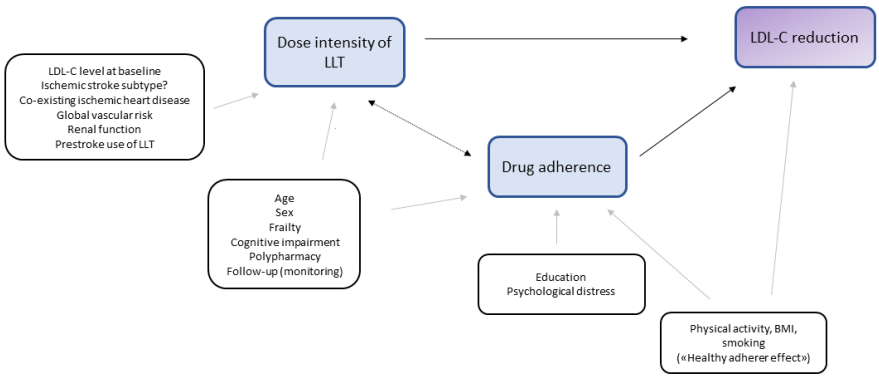

Figure 4.3 Examples of factors potentially influencing dose intensity prescribed, drug adherence, and LDL-reduction.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; BMI, body mass index.

Subgroups previously identified as undertreated with LLT, are older and younger patients (114, 219, 220) and females (114, 217, 219, 220, 222). Other factors that might influence how LLT are prescribed are renal failure and frailty (19, 67). We hypothesized that index stroke etiology was a predictor due to the diversity of representation of ischemic stroke subtypes in large clinical trials of statin benefit (81, 86), as well as CAD, as evidence for statins has historically been more robust in this population. We hypothesized that potential predictors were different for prescription yes/no vs. dose prescribed. The following predictors were included in the regression analyses: age, sex, baseline LDL-C level, prestroke use of LLT, frailty, cognitive impairment, CAD, estimated GFR, and the TOAST classification.

4.6 Statistical analysis

We performed statistical analyses using Stata version 16 and R statistical software V.4.0.2. Descriptive data were expressed as mean (standard deviation (SD)) or median (interquartile

range (IQR)) and proportions as appropriate. The Nor-COAST study aimed to include approximately 900 participants so that at least 100 participants could be recruited for each stroke subtype. Post hoc power calculations for this sub-study were not done (223). We report uncertainty in the results in terms of confidence intervals (CI). We report odds ratios (OR) or coefficients with 95% CI where relevant. Two-sided *P*-values < 0.05 were regarded as statistically significant. However, due to multiple hypotheses, *P*-values between 0.01 and 0.05 should be interpreted with caution. Reporting is according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (224).

4.6.1 Paper I

In Paper I, we used data from baseline, 3 and 18 months with a longitudinal design utilizing repeated data on BP, LDL-C, and HbA1c and predictors. We first calculated proportions reaching treatment targets for available cases at each time-point. Available case analyses are unbiased only if data are missing completely at random (MCAR) (225). To minimize bias due to attrition (11% (n=70) at 3 months and 21% (n=142) at 18 months), we employed a model-based descriptive analysis using a mixed model logistic regression model**.** We used blood pressure, LDL-C, and HbA1c, dichotomized, one at a time as dependent variables, and time point as a categorical covariate, to calculate proportions reaching treatment targets. Proportions reaching targets at each time point were calculated by odds converted to probability (*P*) by *P* = odds/(1 + odds) for all participants and separately for those using relevant pharmacotherapy.

Assessment of associations between potential predictors and target achievement in patients with prescribed pharmacotherapy included the following covariates in the model, one at a time: age and education analyzed as continuous variables, sex, frailty as a continuous variable from 0 (robustness) to 5 (frail), cognitive function as a continuous variable from 1 (normal cognitive function) to 7 (severe dementia), number of medications used as a continuous variable, self-reported medication adherence as a continuous variable from 0 (low adherence) to 4 (high adherence), follow-up appointment by a GP (yes/no), and HADS score as a continuous variable (score 0 to 42). We conducted unadjusted analyses and analyses adjusted for age, sex and education. To assess the robustness of the results, we performed sensitivity analyses excluding patients with only baseline measurements and no prestroke

pharmacotherapy. We also carried out supplementary analyses with systolic BP and LDL-C as continuous dependent variables, as well as separate analyses for patients above and under 75 years. These age cut-offs are arbitrary, but consistent with the majority of the available evidence. A separate analysis was performed to study the effect of statin dose intensity on LDL-C, where statin dose was expressed as atorvastatin equivalent dose.

4.6.2 Paper II

In Paper II, we used data from the 3 month visit and endpoint registries. We imputed missing data for clinical measurements at 3 months to predict the CVD risk by means of single imputations using predictive mean matching. With this method, the imputed value is taken randomly from a set of observed values whose predicted values are closest to the predicted value from a specified regression model (226). We included all variables to be used in the analyses in the imputation model (226). The percentage of missing data for relevant variables is shown in **Table 4.5**.

Table 4.5. Missing values for relevant variables in Paper II

	% missing at index stay	% missing at 3 months
Current smoking	0%	15%
Systolic blood pressure	7%	15%
Total cholesterol	2%	24%
HDL cholesterol	3%	25%
LDL cholesterol	3%	25%
Creatinine	0%	26%
Information about medications	1%	7%

The **external validity** of the SMART-REACH model was assessed for risks at 2 years of follow-up. To evaluate the model's predictive accuracy, we assessed discrimination and calibration (154, 227). We expressed discrimination with Harrell's C-statistic (227). The C-statistic gives the probability that a patient who had a recurrent event also had a higher estimated risk than those who were event-free (227). A C-statistic above 0.50 implies better discrimination than chance alone (228). Because estimated risks can be unreliable even if discrimination is good (156), i.e., the risk estimates may be systematically high or low irrespective of whether they experienced an event (156), reporting calibration is recommended (229). Calibration is the accuracy of risk estimates, meaning the agreement between estimated and observed event

rates (230, 231), and is especially important when the aim is to support clinical decision-making (130, 156). We showed the agreement between predicted and observed 2-year risk (calibration) in a flexible calibration curve based on local polynomial regression fitting (using the *loess* function in R) (156, 232). Flexible calibration curves are less influenced by an arbitrary grouping of patients in comparison to a traditional calibration plot (155, 232). First, the cohort was divided into 100 quantiles of predicted risk. Then, a local regression was used to smoothly explain the observed cumulative incidence per group by the mean predicted risk per group. The smooth calibration plot and confidence intervals were subsequently predicted from this model over the whole range of relevant predicted risks (cohort predicted risk quantile 0.025 up to 0.975). A curve close to the diagonal indicates that predicted risks correspond well with the observed proportion of events (154).

As event rates vary between geographic locations (44, 130) and may be influenced by the selection of study participants, **recalibration** to the population of interest is often necessary (130, 140, 142, 156, 157, 233). Recalibration is important to ensuring the estimated risk reflects the current level of risk in the population. Recalibration of the model was considered based on the calibration plot and performed using "calibration-in-the-large" by subtracting the expected/observed ratio from the linear predictor for both the CVD hazard function and the non-CVD mortality (156, 234) (A and B in model formula section 4.4.3.2). The expected/observed ratio was calculated by dividing the expected incidence (mean of all predicted 2-year risks) by the observed incidence (cumulative incidence in the study population at 2 years, adjusted for competing risks). We conducted sensitivity analyses excluding cardioembolic stroke when validation the model and assessed sex-specific calibration curves and C-statistics.

4.6.3 Paper III

In paper III, we used medication data, LDL-C and predictor variables from baseline, 3- and 18 months. Logistic and linear regression was used with LLT prescription (yes/no) and atorvastatin equivalent dose (mg/d) as dependent variables, respectively, to identify variables predictive of LLT use and intensity. We included the following covariates, first one at a time and, next, adjusted for age and sex: age, sex, LDL-C (measured the first day after admission), prestroke use of LLT, frailty by a modified version of the 5-item Fried criteria (199) as a continuous

variable from 0 (robustness) to 5 (frail), and the Global Deterioration Scale as a continuous variable from 1 (normal cognitive function) to 7 (severe dementia). A history of CAD was included as a categorical variable (yes/no) and was defined as in **Table 4.1**. Stroke subtype was divided into five categories according to the TOAST classification: LAD, cardioembolic stroke, SVD, other etiology, and undetermined strokes. As the subtype "other etiology" comprised a small number, it was grouped with "undetermined".

Missing data were also imputed in Paper III for LDL-C and other clinical measurements at 3 months for the prediction of CVD risk by the same methods as described in section 4.6.2. The amount of missing data is described in **Table 4.5**.

4.7 Ethical considerations

The Regional Committee for Medical and Health Research Ethics North Norway (REC number 2015/171) approved the Nor-COAST study and the current substudy (REC number 2017/1462). Before inclusion, written informed consent was signed by the participants or by the next of kin if the participant was unable to give informed consent. The study was conducted in accordance with the Declaration of Helsinki. The Nor-COAST study was registered at Clinicaltrials.gov (NCT02650531).

5 RESULTS

5.1 Baseline characteristics

Baseline characteristics for participants included in the three papers are shown in **Table 5.1.**

Table 5.1. Baseline characteristics of participants included in the three papers

	Paper I (n=664)	Paper II (n=465)	Paper III (n=462)
Demographics and clinical characteristics			
Age, years	72.9 (11.5)	69.0 (8.1)	69.0 (8.1)
Female sex	287 (43%)	178 (38%)	177 (38%)
Charlson comorbidity index	4.1 (2.0)	3.7 (1.9)	3.6 (1.8)
Cognitive impairment	84 (13%)	13 (3%)	13 (3%)
Frail	98 (15%)	34 (7%)	32 (7%)
Home care	63 (10%)	20 (4%)	20 (4%)
Vascular risk factors			
Atrial fibrillation	154 (23%)	101 (22%)	100 (22%)
Diabetes mellitus	129 (19%)	92 (20%)	90 (20%)
Hypertension	380 (57%)	252 (54%)	250 (54%)
Hypercholesterolemia	222 (33%)	253 (54%)	252 (55%)
Previous stroke/TIA	158 (24%)	108 (23%)	107 (23%)
Coronary artery disease	122 (18%)	79 (17%)	79 (17%)
Heart failure	23 (4%)	11 (2%)	11 (2%)
Peripheral artery disease	54 (8%)	35 (8%)	34 (7%)
Number of vascular beds involved[a]			
One	519 (78%)	369 (79%)	367 (79%)
Two	114 (17%)	78 (17%)	77 (17%)
Three	31 (5%)	18 (4%)	18 (4%)
Estimated GFR	75 (18)	79 (16)	78.6 (16.0)
Current smoking	112 (17%)	109 (24%)	109 (24%)
Body mass index (kg/m^2)	26.1 (4.2)	26.6 (4.2)	26.7 (4.2)
Poststroke clinical characteristics			
NIHSS at discharge (n=628)	1.7 (2.4)	1.7 (2.4)	1.7 (2.4)
Independent at discharge	415 (63%)	326 (70%)	324 (70%)
Stroke subtype (n=645)			
Large artery disease	68 (11%)	49 (11%)	49 (11%)
Cardioembolic	148 (23%)	103 (23%)	103 (23%)
Small vessel disease	145 (23%)	105 (23%)	104 (23%)
Other causes	17 (3%)	12 (3%)	12 (3%)
Undetermined or multiple possible etiologies	267 (41%)	181 (40%)	179 (40%)
N medications at discharge	5.3 (2.6)	5.1 (2.6)	5.1 (2.6)

Numbers are mean (SD) or n (%). Abbreviations: GFR, glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale. [a]*One if only cerebrovascular, two if co-existing CAD or PAD, three if cerebrovascular, CAD, and PAD.*

5.2 Paper I

Title: *Vascular risk factor control and adherence to secondary preventive medication after ischemic stroke*

Of the 664 home-dwelling patients included, 97% were prescribed antithrombotic drugs, 88% LLT, 68% antihypertensives, and 12% antidiabetic drugs at discharge. The persistence was 99%, 88%, 93%, and 95%, respectively, at 18 months. After 3 and 18 months, 80% and 73% reported high adherence.

After 3 and 18 months, 40.7% and 47.0% of the total cohort gained BP control; the corresponding proportions for patients using antihypertensive drugs were 37.8% and 43.6%. In total, 48.4% and 44.6% achieved LDL-C control; the corresponding proportions for patients using LLT were 54.3 % and 49.4%. For patients with diabetes, 69.2% and 69.5% in total achieved HbA1c control; the corresponding proportions for participants using antidiabetic drugs were 36.3% and 48.0%.

In patients prescribed pharmacotherapy, advanced age was associated with increased LDL-C control (OR 1.03 per year, 95% CI 1.01 to 1.06) and reduced BP control (OR 0.98 per year, 95% CI 0.96 to 0.99). Women had poorer LDL-C control (OR 0.60, 95% CI 0.37 to 0.98). An increasing number of medications in use was associated with increased odds for LDL-C control (OR 1.29 per drug, 95% CI 1.18 to 1.41) and reduced HbA1c control (OR 0.76, 95% CI 0.60 to 0.98). We found no significant associations between self-reported medication adherence, follow-up by the GP or psychological distress, and target achievement. However, sensitivity analyses with LDL-C as a continuous outcome showed a significant association between adherence and lower LDL-C (coefficient -0.08 mmol/L, p=0.025).

5.3 Paper II

Title: *Risk stratification in patients with ischemic stroke and residual cardiovascular risk with current secondary prevention*

Of the 465 home-dwelling patients between 45 and 80 years included, 11.2% (n=52) had a new cardiovascular event over a median follow-up time of 2.2 years (IQR 1.79 to 2.62) (when excluding events between 0-3 months), for a total of 991 patient-years. Of these, 61% had a non-fatal ischemic stroke, 31% had a non-fatal MI, and 8% died due to cardiovascular causes.

Mean LDL-C was 2.1 mmol/L (SD 0.8) and 43% reached the target at 3 months. Mean systolic BP was 140 mmHg (SD 19); 51% reached the BP target and 50% (55/109) of smokers quit smoking at 3 months. Antithrombotic drugs were used by 98%; the corresponding proportions for LLT and antihypertensive drugs were 89% and 73%, respectively.

The average observed 2-year risk was higher than the average predicted 2-year risk with the SMART-REACH model (expected/observed ratio 0.54). After recalibration, the calibration curve showed adequate agreement between predicted and observed risk (**Figure 5.1**) and modest discrimination (C-statistics 0.63, 95% CI 0.55 to 0.71). Discrimination was slightly lower when patients with cardioembolic stroke etiology were excluded (C-statistics 0.61, 95% CI 0.53 to 0.70). Sex-specific analyses showed C-statistics 0.65 (95% CI 0.56 to 0.73) for men and 0.57 (95% CI 0.41 to 0.74) for women.

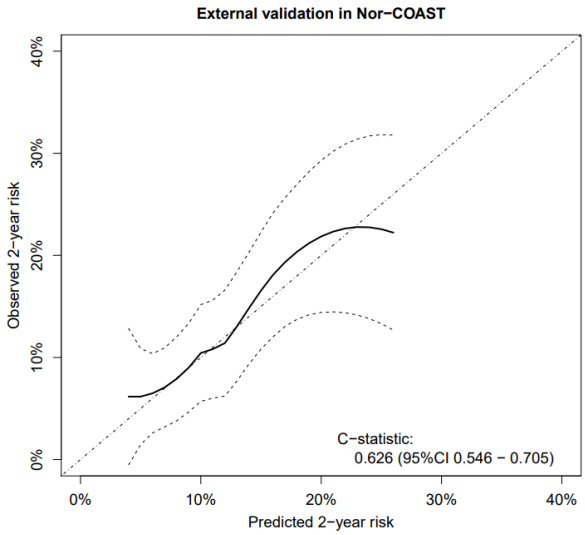

Figure 5.1. Flexible calibration curve showing the agreement between the estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk after recalibration

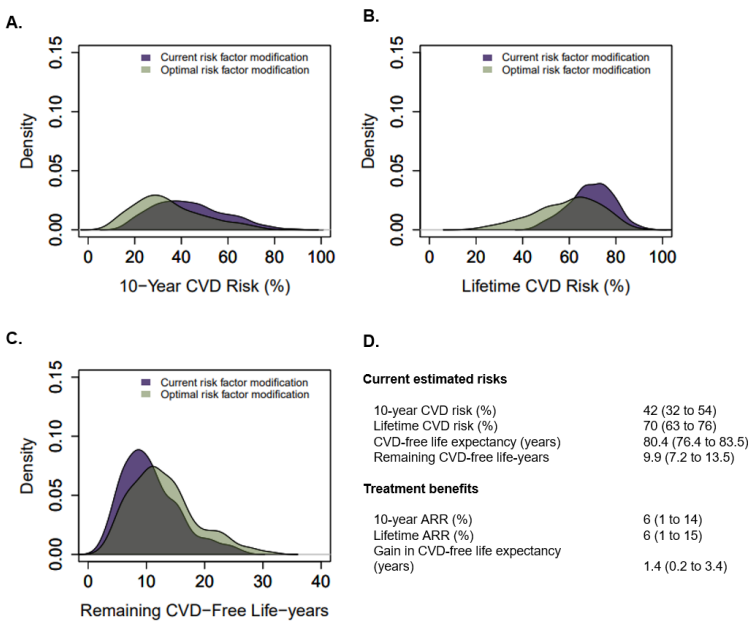

Figure 5.2. Distribution of current cardiovascular disease (CVD) risk and potential benefit from optimization of all risk factors. Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from optimization of risk factors defined as systolic blood pressure ≤140 mmHg, LDL-cholesterol ≤1.8 mmol/L, smoking cessation and use of antithrombotic medication. Abbreviation: ARR, absolute risk reduction.

Overall estimated risks and benefit from optimization of risk factors are shown in **Figure 5.2**. Ten-year cardiovascular risk increased with age, while lifetime risk was highest in younger patients. Through optimal guideline-based therapy, the cohorts' median estimated 10-year risk could be reduced to 32% and the median lifetime risk could be reduced to 61%. For risk factors separately, the estimated benefit if patients with elevated BP reached the target was 8% (IQR 3 to 14) and 1.6 CVD-free life years gained (IQR 0.6 to 1.3). Smoking cessation led to 14% (IQR 12 to 16) 10-year ARR and a median of 3.4 CVD-free life years gained (IQR 2.4 to 4.3). If patients with elevated LDL-C reached the target, the 10-year ARR was 4% (IQR 2 to 7) and the number of CVD-free life years gained was 0.8 (IQR 0.4 to 1.6). Treatment benefits in terms of gain in CVD-free life years were highest in younger patients with elevated risk factor levels.

5.4 Paper III

Title: Prescription patterns for lipid-lowering therapy after ischemic stroke and expected benefit from intensification of treatment

Of the 462 patients included, 92% (n=427) were prescribed LLT at discharge; 97% of these received statin monotherapy and 64% received HIS. Patients with prestroke cognitive impairment and cardioembolic stroke etiology were less likely to receive LLT at discharge**.** Older patients (-0.30 mg per year, 95% CI -0.55 to -0.05) and women (-5.1 mg, 95% CI -9.2 to -0.9) were treated with lower dose intensity. Individuals with higher baseline LDL-C levels, a history of CAD, and LAD as stroke etiology received higher dose intensity. In total, 45% achieved LDL-C ≤1.8 mmol/L at 3 months. Target achievement was observed in 40-50% of patients irrespective of age, sex, LLT intensity, and stroke subtype (except 52% at targets in the subgroup with LAD etiology). However, 58% (n=249) had LDL-C ≤2.0 mmol/L, and mean LDL-C values were not far from the target (mean distance from target 0.7 mmol/L, SD 0.6). Patients with the largest relative LDL-C reduction were younger, had higher LDL-C at index stay, and were prescribed HIS. Among patients with the smallest LDL-C reduction, 78% had prestroke LLT. If treatment with statin and/or ezetimibe were hypothetically up-titrated according to guidelines, 81% of the cohort could achieve LDL-C ≤ 1.8 mmol/L, resulting in a median of 11 months (IQR 7 to 17) of CVD-free life-gain for patients with elevated LDL-C, with a large range

(0 to 59 months). Two illustrative patient examples are provided in **Figure 5.3** to show the clinical benefit from using the SMART-REACH model in daily practice.

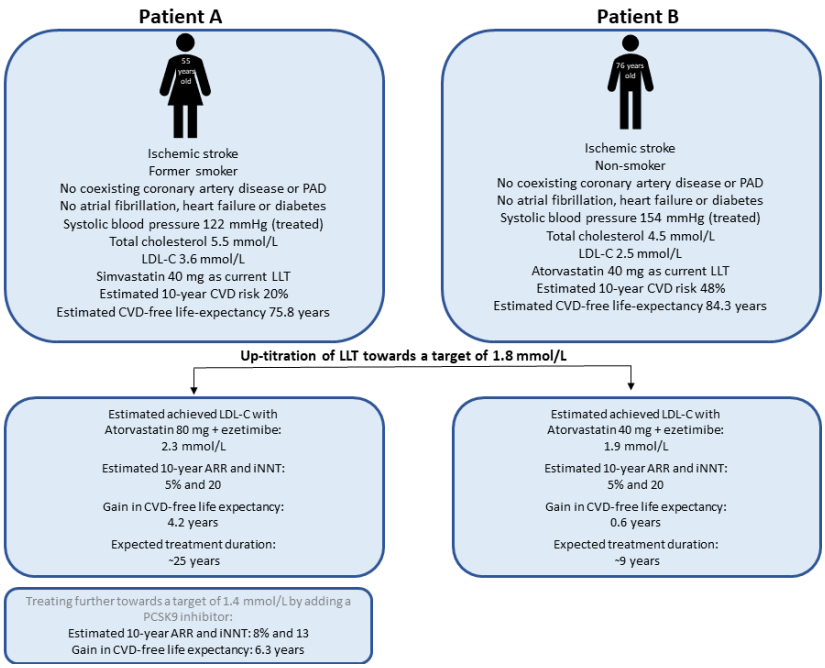

Figure 5.3 Illustrative patient examples. The benefit of intensification of current lipid-lowering therapy estimated by the SMART-REACH model for patients aged 55 and 76 years and expected treatment duration (= life expectancy minus current age). Abbreviations: PAD, peripheral artery disease; LLT, lipid-lowering therapy; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ARR, absolute risk reduction; iNNT, individualized number needed to treat (1 divided by ARR); PCSK9, proprotein convertase subtilisin/kexin type 9.

6 DISCUSSION

6.1 Main findings

The current thesis focuses on residual CVD risk after initial secondary prevention. It demonstrated that control of vascular risk factors was suboptimal, even though self-reported medication adherence was relatively high and persistence to drugs declined only modestly during 18 months of follow-up, especially for LLT. Multiple factors interfered with target attainment for BP, LDL-C, and HbA1c. Older patients had lower odds for BP control, while younger patients and women had lower odds for LDL-C control. Higher total number of medications in use was associated with higher odds for BP and LDL-C control, but lower odds for HbA1c control. Higher self-reported medication adherence was significantly associated with lower LDL-C, while higher statin dose was associated with better LDL-C control. Multiple factors – like index stroke etiology, co-existing CAD, age, and sex – interfered with dose intensity for statins in patients below 80 years. A larger proportion could achieve LDL-C targets if conventional LLT use (including ezetimibe) was theoretically optimized. A notable proportion suffered from a recurrent event the first 2 years poststroke (after excluding events in the subacute phase). The SMART-REACH model generates prognostic vascular risk information reasonably well in ischemic stroke patients aged 45 to 80 years. A substantial interindividual variation in estimated future cardiovascular risk was estimated, with a corresponding variation in absolute treatment benefit from intensification of secondary prevention. A remaining preventive potential exists and residual risk remains high even after optimization according to current guideline recommendations. The results presented in this thesis may have several implications for clinical practice and may provide suggestions for future research on how to improve and individualize secondary prevention and follow-up after stroke. However, methodological considerations must first be taken into account.

6.2 General methodological considerations

Validity concerns whether a study reaches the correct conclusions. It can be separated into: i) the validity of the inferences when it comes to members of the studied population (internal validity) and ii) the validity of the inferences when it comes to people or settings outside the

study population (external validity or generalizability) (235, 236). In epidemiological studies, internal validity is generally challenged by selection bias, information bias and confounding (235, 236).

6.2.1 Study design and selection bias

Cohort studies are often prone to healthy participant bias, arising from inclusion criteria, inclusion methods or participation rates (236). The Nor-COAST main study was a multicenter, prospective, observational cohort study, with poststroke cognitive impairment as the primary outcome (192). To study the true incidence of cognitive impairment after stroke, the study had broad inclusion criteria aiming to include a population representative of the Norwegian stroke population. Consecutive inclusion, enrolling every eligible case for a period of time, is a major strength of the Nor-COAST study and decreases systematic bias associated with convenience sampling. Including patients from multiple hospitals, both large university hospitals and local hospitals, representing three of four health regions in Norway (all except the smallest one, Northern Norway), increases the probability of representativeness for patients admitted with acute ischemic stroke to Norwegian stroke units.

Although the participation rate in Nor-COAST was 42%, the main reason for non-inclusion was a failure to be screened due to breaks in inclusion in weekends and holidays (67%), regarded as missing (completely) at random (225, 226). Previous work has investigated selection bias in Nor-COAST by comparing baseline characteristics for participants with non-participants by retrieving data from the Norwegian Stroke Registry (193). As in other stroke trials, the participants in Nor-COAST had a slightly better prestroke health status and milder strokes than non-participants (193), also probably influenced by expected survival of less than three months being an exclusion criterion (192). However, when the participants in Nor-COAST were compared with the general Norwegian stroke population registered in the Norwegian Stroke Registry (7), the baseline characteristics were comparable, i.e., for age (75 versus 76 years), sex (45% female in both), stroke severity (69% mild strokes versus 65%), and prestroke functional status (87% independent versus 85%) (8).

The longitudinal short- and long-term follow-up is a strength compared to other studies assessing medication adherence and risk factor control after stroke (12-14, 237). However,

longitudinal studies are also prone to attrition bias (235). In Paper I, attrition bias might have led to a greater extent of adherence to medication and target achievement. Patients who were lost to follow-up were older and had more severe strokes, a higher burden of comorbidity, cognitive impairment, and disability. Our model-based analyses showed systematically lower target attainment compared to available case analysis, indicating that participants lost to follow-up probably had an even poorer risk factor control.

We excluded patients living in nursing homes from the validation of the SMART-REACH model, which can introduce selection bias. Those discharged to long-term, or community care are more likely to have greater index stroke severity and potentially poorer risk factor control and a higher risk of recurrent events. However, the highest clinical utility of the SMART-REACH model is for patients with stable vascular disease in whom additional prevention is considered. Furthermore, patients expected to have difficulties returning to follow-up visits and patients not independent in daily activities were also excluded in the derivation and original validation cohorts (140, 211, 212).

6.2.2 Information bias

Information bias may occur during data collection and can be caused by measurement errors or inconsistency in the measurements (235). The most important type is misclassification bias, which is present when an individual is assigned to a different category than the one they should have been assigned to.

6.2.2.1 *Medication adherence*

Ascertainment of **medication adherence** is challenging and susceptible to information bias (235). Self-reporting is associated with overestimation (236) and our adherence rate is higher than in other studies (107, 114, 118, 238). MMAS-4 is a universal tool, not specific to secondary preventive medications unless you use a separate questionnaire per drug. Patients may consider their overall adherence as good even though adherence to a single drug is non-optimal. In addition, MMAS-4 is not validated in stroke patients or in the Norwegian language;

however, most of the questions correspond to the validated Norwegian version of MMAS-8 (239), which showed satisfactory internal consistency in a population with Norwegian pregnant women (239). Our **persistence** rate is also higher compared to other studies (108, 240, 241), and information bias due to obtaining medication lists by interview is possible. Clinical interviews might overestimate medication persistence to an even higher degree than self-report questionnaire registrations (236, 242). We estimated persistence only in patients who had available medication lists and had survived the entire period. Furthermore, our methods for assessing adherence provide no information about other aspects of taking medications, such as dose timing and drug holidays, both of which may be important in determining clinical outcomes (16).

Other objective methods for determining medication adherence, such as pharmacy registry data or serum concentration measurements of the drugs used, could possibly have found different results and modified the lack of association between medication adherence and risk factor targets. However, all these methods have their specific limitations and pitfalls. The Norwegian national prescription database does not include data on daily dose (only the tablet strength and number of tablets prescribed) or reasons why patients discontinued, and we do not know whether the patient actually took the medication. Measuring serum concentrations also has disadvantages, with substantial inter-individual variability due to the extent of absorption, distribution, and elimination of drugs, leading to differences in steady-state concentrations. Studies also show a tendency toward increased adherence during the days preceding and following an appointment with a health care provider (cf. “white coat adherence” (132)). Therefore, a single drug concentration measured does not necessarily represent the average long-term steady-state drug concentration. Because there is no golden standard, a combination of methods might be the most beneficial approach.

6.2.2.2 *Measurement of risk factors*

Although BP was measured based on a standardized protocol using validated semiautomatic devices, this happened in a setting with concomitant physical and cognitive testing and might therefore have been higher than in a habitual situation. Accessing detailed information from GP’s records might have provided other results, as GPs presumably rely on multiple

measurements over time or 24-hour measurements (5). Blood samples at index stay were taken the first day and previous studies have reported that LDL-C may be reduced by 10-20% in the acute phase of an MI (243, 244) and critical limb ischemia (245). Response to different statins varies considerably between individuals and using LDL-C as a surrogate marker of LLT adherence might be unprecise (246). We minimized measurement bias for risk factors by following patients over time with repeated clinical measurements in Paper I.

6.2.2.3 *Registry data as a source of CVD endpoints*

Registration in the Norwegian Stroke Registry and the Norwegian Cardiovascular Disease registry is mandatory, although only strokes and MIs leading to hospitalization are registered. These registries have shown adequate completeness and correctness to serve as sources for research studies (202). While the **Norwegian Stroke Registry** is highly correct (positive predictive value (PPV) 98.6%) (202), the completeness was 87% in 2018 (8, 193). The linkage to the **Norwegian Cardiovascular Disease Registry** gives more complete data (247). However, the registry is less correct for stroke diagnoses, which might lead to an overestimation of stroke endpoints. Still, it is more correct when restricted to the main diagnoses of stroke (202). In Paper II, 85% of the stroke diagnoses registered had the Norwegian Stroke Registry as source, which is largely comparable with the registry's coverage in 2018 (7). For MI, the Norwegian Cardiovascular Disease Registry has a sensitivity of 85.8% and a PPV of 95.1%. However, when restricted to main diagnoses only, the sensitivity decreased to 66.4%, while the PPV was 96.9% (209). Therefore, we also included secondary diagnoses of MI, though only two of the MI endpoints registered were secondary diagnoses. The **Norwegian Cause of Death** registry's degree of coverage is nearly complete (203). However, the use of unspecific codes for the underlying cause of death is high (203), which might have led to information bias for cause of death. It is possible that other methods for determining outcomes, such as medical record review, would have yielded other results. However, a Norwegian single-hospital study assessing recurrent strokes (and TIA) by reviewing medical records found a recurrence rate of 5.4% the first year (excluding patients discharged to palliative care), comparable to our 1-year stroke recurrence rate (34).

6.2.2.4 *Other predictor variables*

A history of heart failure, CAD, and PAD as predictors in the SMART-REACH model were based on review of hospital medical and might be affected by misclassification bias, mainly in the direction of classifying diseased individuals as non-diseased. The prevalence of heart failure in other ischemic stroke cohorts is higher (219, 248). The prevalence of PAD is comparable to that of other cohorts (49), while the prevalence of CAD is slightly lower (13, 49, 249). However, the prevalence might also be influenced by exclusion criteria in the current thesis and highly dependent on the age distribution of the cohorts studied. The Norwegian Stroke Registry contains no information about the prevalence of co-existing heart failure and PAD for comparison.

In Nor-COAST, few patients were categorized as frail – fewer than in other stroke trials (199). A possible explanation might be that participants with missing data on modified Fried criteria were given 0 points for the missing criteria, which indicates a robust score. Weight loss, fatigue, and physical activity level were based on self-reported prestroke status, while gait speed and grip strength were assessed poststroke and may have been influenced by the index stroke. Furthermore, self-report might be a methodological challenge, as older patients more often underestimate their disability than younger patients (199). In Paper I, this might contribute to the lack of association between frailty and target achievement. In Paper III, few patients below 80 years were categorized as frail (7%), making the assessment of prescription patterns in subgroups of frailty less reliable.

We used the GDS (198) as a measure of cognition, due mostly to the existence of more complete data than the Montreal Cognitive Assessment, which also was available, and the extended test battery for cognition in Nor-COAST described in previous work (200). However, the prevalence of cognitive impairment varies by the diagnostic approach and GDS might underestimate the true prevalence of cognitive impairment (200). Prestroke cognitive function was based on interviews with caregivers and might be influenced by recall bias.

6.2.3 Confounding

Not appropriately controlling for confounders may introduce biased effect estimates. Firstly, incomplete adjustment of potential confounders, either due to imprecise or incomplete measurement of confounders, may lead to residual confounding (235). Secondly, inappropriate adjustment for a covariate that is a common consequence of the exposure and outcome, may yield collider bias (250). Overadjustment of statistical models, defined as controlling for an intermediate variable (mediator) (251), may lead to underestimation of the true causal effect (250, 251). Unnecessary adjustment, defined as "controlling for a variable that does not affect bias of the relation between exposure and outcome", may affect precision (251). These concepts were considered when the statistical analyses in Paper I and III were planned. Directed acyclic graphs were used to determine the best strategy. Assessing factors influencing risk factor control (Paper I) and statin prescribing patterns (Paper III) is highly complex, presumably with a high degree of correlation between exposure variables, and identifying independent factors for risk factor control is difficult. We aimed to adjust only for clear confounders to minimize the risk of bias and imprecision, leading to adjustment for solely age, sex and education in Paper I and age and sex in Paper III.

6.2.4 Generalizability

Participants in Nor-COAST seem to be representative of the general Norwegian stroke population, given the multicenter design and comparability with patients in the Norwegian Stroke Registry as described in section 6.2.1. (193). Considering the inclusion criteria in the present thesis, it seems plausible that the home-dwelling subpopulation with ischemic stroke would be even more similar to the corresponding population in the Norwegian Stroke Registry. It is reasonable to assume that the results might be representative of other stroke populations in comparable geographical regions with public health care, drug treatment reimbursed by the government, and adequate systems for follow-up. However, the results in Papers II and III are generalizable only to patients between 45 and 80 years.

6.3 Methodological considerations in Papers I, II and III

6.3.1 Paper I

We reduced the number of independent variables in the regression analyses after the widely used guideline of maximum (number of observations)/10 candidate predictors could be considered for inclusion (221). We avoided including variables that were alternative measures of another predictor (like number of medications and Charlson comorbidity index, frailty, and modified Rankin scale) (221). We lacked information about some prognostic factors that might influence risk factor control, like adverse drug reactions, participation in rehabilitation programs, information from hospital discharge letters and detailed information about GP follow-up (109, 134, 135, 241). In a substudy with Nor-COAST participants admitted to St. Olavs Hospital, there were large variations in the number of GP consultations in the 18-month follow-up period and content of the consultations (252), in line with patterns reported in Norwegian CAD patients (253).

Dichotomizing outcome variables might lead to a loss of statistical power. However, because the risk factor targets are established cut-offs from guidelines, it was natural to dichotomize. Yet, analyses using the original continuous outcome variables revealed additional significant associations between self-reported adherence and lower LDL-C. Mixed model regression analyses were used to minimize bias due to attrition. Such analyses are unbiased under the less restrictive missing at random assumption (MAR) (254) and yields less bias (even if data are missing not at random (MNAR)) than using methods valid under the missing completely at random (MCAR) assumption (i.e. available case analysis) (225, 254). All data are included in the analysis, including data from participants with missing data for one or more variables at one or more time points. To assess the robustness of the results, we performed sensitivity analyses excluding participants with only baseline measurements of risk factor levels who used no relevant pharmacotherapy at admission. We hypothesized that these patients would contribute to lower target achievement. However, the results did not change substantially.

6.3.2 Paper II

Assessments at 3 months were considered as a baseline for the validation and recalibration of the SMART-REACH model and the benefit calculations. In accordance with the model derivation, we did not account for time-varying risk factors and medications used during follow-up. Previous studies have shown that changes in risk factor treatment during follow-up in model development had only a limited impact on model performance (255). There was, in general, a small amount of missingness for predictor variables. However, for clinical measurements like blood pressure and blood tests, 15% and 25% were missing, respectively, due to physical non-attendance of the 3-month visit. Although values were largely available at the index stay, we used imputation based on predictive mean matching instead of the last observation carried forward in Paper II (and Paper III) as patients are in an unstable phase at index and data at 3 months were not missing completely at random (MCAR) (256).

6.3.2.1 *The validation of the SMART-REACH model*

We included all patients regardless of index stroke etiology in the validation. In the original derivation and validation cohorts, inclusion criteria for patients with atherosclerotic CeVD were TIA or cerebral infarction verified by clinician or imaging (140, 211, 212). A mixed population of ischemic CeVD patients was presumably included, though, probably dominated by stroke patients with LAD etiology (140, 211, 212). Therefore, applying the model to cardioembolic stroke patients might be debatable, especially if the burden of atherosclerosis and associated risk factors is low or absent. On the other hand, 41% of patients with cardioembolic stroke had either coexisting CAD, PAD, or previous CeVD, 83% were prescribed LLT, and 28% were prescribed antiplatelet agents, suggesting a high burden of atherosclerosis in this subgroup. This is in line with other studies showing an overlap between stroke etiologies (21, 22) and a high burden of atherosclerosis (54). A sensitivity analysis excluding patients with cardioembolic stroke led to slightly lower discrimination; however, this result may also be influenced by the reduced sample size or by reducing the heterogeneity of the validation sample. Furthermore, one study assessing predictors for recurrent vascular events in stroke patients with AF identified increasing age, previous thromboembolism, CAD, systolic BP > 160 mmHg, and long-lasting AF as independent risk factors (257). These predictors are already in large extent incorporated into the model. Moreover, AF almost never comes alone (29). Based on the predictors in the SMART-REACH model, stroke patients with a

cardioembolic source (or undetermined source) with otherwise low levels of other predictors would presumably also be assigned to lower risk strata and, correspondingly, the benefit of intensifying therapy would be lower.

Whether the calibration curve shows good agreement is often a subjective matter (156). The calibration curve lies close to the diagonal (**Figure 5.1**). However, the confidence intervals are large, especially for the highest risk individuals. A larger validation cohort, for example by merging datasets from Norwegian patients with various manifestations of vascular disease, would probably have given narrower confidence intervals for both the calibration curve and the c-statistic and enabled reliable sex-specific analyses, which could be of relevance given the sex-specific differences in the prevalence of the included predictors in the model (5, 258). The C-statistic was lower for women, presumably due to the small sample size and low number of events. However, "removing" an important predictor such as sex from the model might also lead to poorer discrimination.

Important predictors for stroke patients' prognosis might also be omitted from the model. CVD imaging parameters like left ventricular hypertrophy, neuroradiological findings (176), and carotid intima media thickness, stroke subtyping (22, 36, 259), or biomarkers like high-sensitive CRP, troponin or N-terminal pro-B-type natriuretic peptide (NT-proBNP) might enhance performance but would limit the applicability of the model in clinical care (119, 145, 154, 159, 260). There is a tradeoff between making the model highly precise and the ease of use by generalists in a busy, routine practice (161). Frailty and multimorbidity may also be important CVD risk modifiers, as well as duration of co-existing CVD (time since first diagnosis) and exposure to risk factors (5, 145).

6.3.2.2 *Recalibration of the model*

The predicted 2-year risk with the SMART-REACH model was lower than the observed event rate in Nor-COAST before recalibration. There could be several reasons for differences between estimated and observed risk, a part of why regular recalibrations of most risk models are often necessary. The most important reason might be that Nor-COAST was less prone to healthy participant bias than the outpatient populations in SMART (212) and REACH (58, 211), resulting in inclusion of a population with higher CVD risk. The SMART and REACH cohorts also

included patients with TIA, while Nor-COAST included solely stroke (with a variety of underlying etiologies). The relatively recent stroke event might also contribute, as patients in SMART- and REACH were usually included several months after an event (140, 211, 212). One might argue that 3 months poststroke is "too early after an acute event" to represent the chronic stable CVD patient, as the SMART-REACH model is intended for. The transition from the subacute to chronic stable phases is a continuum and the risk factors associated with recurrent events and mortality in these phases differ (9, 32, 33). In a validation of the original SMART risk score, model performance was weaker among those with newly diagnosed established CVD (261). A validation starting at a later timepoint post-event might have been preferable, though counterbalanced by the selection of healthier survivors. Hence, this probably influences mostly the baseline risk (the average level of risk in the population and the expected/observed ratio) and, to a lesser extent, the linear relation between risk factors and the outcome. The relative effect of common risk factors on the risk of CVD events seems to be stable across populations and with time, at least in primary preventive settings (137, 233). There were also other differences in characteristics compared to the original derivation and validation cohorts like recruitment time period and definitions of outcomes (140), which might influence the average risk level in the population.

We recalibrated the model through a simple adjustment to the model's intercept (156). A full re-fit of the model coefficients might have led to even better performance (157). However, simple recalibration methods (like the current "calibration-in-the-large") are often considered sufficient (153, 157). Performing external validation and recalibration based on 2-year predictions might be a weakness. Yet, left truncation allows the model to perform accurate predictions beyond the observed follow-up time. Temporal validation of lifetime prediction models based on the same principles as the SMART-REACH model has been shown to be reliable for predictions up to at least 17 years (143). However, it is plausible that the degree of recalibration required is not proportional over time and the model may benefit from further long-term validation.

6.3.2.3 *The benefit assumptions*

We assumed the benefits were the same for all subgroups of stroke patients, as relative effect estimates are broadly similar in several subgroups of patients in the meta-analyses used as a basis for calculations (74, 77-79, 84, 262). We aimed to choose the most conservative estimates from clinical trials, which might have resulted in an underestimation of the actual absolute benefit of the intensification of therapy. For example, we assumed that patients with no antithrombotic drugs started ASA. However, the relative risk reductions achieved with ASA plus dipyridamole, or clopidogrel or anticoagulation in AF patients are larger (19). We assumed that standard care was provided for those using antithrombotic drugs (which actually was not known), without distinguishing between different treatment regimens.

It was assumed that treatment effects for LDL-C and BP-lowering were independent of each other. However, synergistic effects between preventive drugs have been reported (263). Not taking lifestyle factors into account is a major limitation, as these are important modifiable predictors of recurrent events (2, 61, 264). However, we found no RCTs with robust effect estimates in secondary preventive settings reporting the magnitude of the relative risk reduction of physical activity, weight reduction, and dietary changes, nor for intensive HbA1c reduction on macrovascular outcomes (207, 208). We assumed that treatment effects were constant for lifetime duration, which requires extrapolation beyond the follow-up times in the clinical trials (265). For LDL-C reduction, the actual long-term effect may be larger because the effect of LDL-C lowering on CVD outcomes is cumulative and increases over time (266, 267). However, efficacy may also be altered over time in individuals developing other comorbidities (265). We assumed no association between LDL-C and blood pressure and non-CVD mortality. However, BP reduction reduces the risk of non-vascular death as well (73, 74).

6.3.3 Paper III

Many of the methodological considerations for Paper III are covered under the previous sections for Papers I and II. To estimate the effect of up-titration, we used mean percent reduction in LDL-C for different drugs and doses of LLT derived from RCTs. There is large interindividual variation in the extent of LDL-C lowering achieved with LLT, due to factors such as age, ethnicity, genetics, sex, pre-treatment LDL-C levels and metabolic factors (246, 268). In another study, the percentage of patients experiencing suboptimal response with statins (<30% reduction in LDL-C) ranged from 5.3 to 53.3% (246). Self-reported medication use is

associated with overreporting. Because we calculated the additional effect of up-titration based on self-reported LLT use, the estimates of proportions reaching the target might be conservative.

6.4 Discussion of the main findings and comparison with other studies

6.4.1 The adequacy of current secondary prevention

The prescribing of and persistence to antithrombotic medications was high in Nor-COAST compared to other studies (11, 14, 108, 237, 238) or comparable (240), and number of current smokers at follow-up were lower than they were in other studies (12-14, 253). The finding of suboptimal control of BP and LDL-C is not unique in the secondary preventive setting; rather, it is highly coherent with other reports from Europe (11-14, 124) and worldwide (269, 270). The EUROASPIRE surveys have shown large variations in secondary prevention provided across Europe, presumably also due to differences in access to healthcare facilities and follow-up routines (11, 14, 112). Although BP was slightly better controlled in Nor-COAST than in the stroke-specific module of EUROASPIRE III (14) and the ASPIRE-S study (13), these studies are not directly comparable due to time of assessment post-event and time of the conducting of the study. These studies may also be hampered by low participation rates (14) and their retrospective (14) or cross-sectional design (13). Other observational studies on adequacy of secondary prevention also often have cross-sectional design (12-14, 124, 237), some with assessment of drug prescription solely at hospital discharge (249, 271), in contrast to Nor-COAST which had a longitudinal and prospective design. The proportion of patients with blood pressure control was slightly lower in Nor-COAST compared to Norwegian coronary patients (218), however, though it remained largely comparable in patients below 80 years.

Proportions reaching the LDL-C target were slightly higher (14, 237, 269) or in line with other studies (12, 13, 124), though prescription rates and mean statin dose were higher in Nor-COAST than in other studies (14, 105, 114, 124, 191, 219, 249, 269, 271) and prescription rates were comparable to Norwegian CAD patients (12, 253). A more recent publication from the Tromsø study including participants with a history of MI or ischemic stroke showed that 80% were using LLT, though only 9% reached an LDL-C target of 1.8 mmol/L (237). A potential

reason for this difference compared to Nor-COAST might be variations in time since the event with decreasing adherence (108, 237). To the best of my knowledge, there is a lack of up-to-date studies describing risk factor control in stroke patients after hospital discharge in other Nordic countries. Furthermore, although differences in persistence between drug classes were observed in Nor-COAST, most patients remained on their medications (a moderate proportion for LLT) and reported relatively good adherence compared to other studies (102, 107-109, 240). Although different methods for adherence measurement might influence these findings (107), and overestimation of adherence in Nor-COAST is possible, this also underlines that patients' non-adherence to medications is not the only barrier to optimal secondary prevention.

6.4.2 Possible explanations for suboptimal risk factor control

Previous studies have shown that age (12, 111, 237), sex (111, 123, 237), patients' adherence (217, 272), drug-related adverse effects (217), intensity of pharmacological treatment (123, 217), presence of atherosclerotic risk factors (12), and comorbidities, among others, may influence risk factor control. We found poorer BP control in the elderly compared to younger individuals. This finding is in alignment with those of several other studies (12, 237, 269, 273). Hypertension is more prevalent in the elderly in general, especially after 75 years of age (273) and in older women (273). Guidelines have been inconsistent regarding treatment thresholds for BP in older individuals and underlined risk of side effects and holistic clinical judgment for frail elderly with short life expectancy. This might also lead to treating BP less intensively in non-frail elderly. However, there is no evidence that relative risk reductions for CVD prevention are less effective in old age (77).

Younger patients prescribed LLT had poorer LDL-C control than the elderly, which is in line with other studies (11, 111, 269). Young age has previously been associated with statin non-adherence and discontinuation, yet studies are inconsistent (220). Women prescribed pharmacotherapy also had more inadequate LDL-C control than men. Additionally, women had higher LDL-C levels at index stay and received lower statin doses compared to men, similar to Norwegian coronary patients (12) and Irish stroke patients (249). Previous studies have demonstrated that women are less likely than men to receive statins (220, 222, 258). There are

no sex-specific guideline recommendations on statin dose, and the benefit of therapy is similar between men and women (5, 262). Still, sex-differences in prescription and adherence to CVD medications are a well-known issue (5, 119, 258, 274). Women are treated less intensively than men at similar CVD risk, have lower awareness of their CVD risk (5), and are more prone to side effects (258, 274) and also, consequently to non-adherence (118, 275).

Undertreatment or lack of treatment intensification when targets are not reached might be an explanation for suboptimal risk factor control (75, 114, 276). Approximately half of the patients who did not reach the BP target received only one antihypertensive agent. The majority of patients who did not reach the LDL-C target remained on the same statin dose during follow-up and few patients received additional LLT like ezetimibe; however, this might reflect a delay of implementation in clinical practice. Furthermore, 11-12 % discontinued statins during follow-up. A large proportion of those not reaching the LDL-C target were already receiving HIS, illustrating that the highest tolerated statin dose monotherapy might, in many cases, not be enough to meet the guideline targets (124, 276) and that combination therapy is needed (276). This was also exemplified in the Treat Stroke to Target trial, in which combination therapy with statin and ezetimibe tripled the proportion reaching the target (86). Why treatment is not intensified remains uncertain, but factors like age, sex, and comorbidities like dementia seem to be central. Furthermore, the findings of the study could have been put into perspective if information regarding perceived side-effects were available.

Furthermore, stroke etiology is an important factor that other studies have lacked information about (124, 219). Because stroke is a heterogeneous syndrome, it might, in some cases, better harmonize with the individual patients expected benefit to treat lipids less intensively. However, the large overlap between ischemic stroke subtypes such as LAD, SVD, and cardioembolic stroke, and the high prevalence of atherosclerosis regardless of stroke etiology, illustrate the need for optimal lipid control in (at least) all these subtypes that constitute the majority of the ischemic stroke population (21). The consistency in relative treatment effect across multiple subgroups of patients in general also supports this argument (65, 78, 277, 278). However, cardioembolic stroke was associated with no LLT and LAD etiology was associated with higher dose intensity. Coexisting CAD was also associated with higher dose intensity. Hence, evidence has historically been more robust for patients with CAD and LAD (81, 86, 124, 191) and previous studies have reported that patients with CAD receive LLT and HIS more often than patients with peripheral and cerebrovascular disease (124, 191, 237, 269).

Several factors with the potential to influence physicians' choice of drug and dose intensity have been reported in the literature (114, 125-127, 216, 219, 268), such as lack of monitoring (125, 129) and lack of awareness of the recommended target (125), as well as appropriate inaction due to good clinical judgment (127, 279). Levels were often not far from targets; the physician might then take a more pragmatic approach. Specific reasons like prior statin intolerance or narrow reimbursement criteria for PCSK9 inhibitors may account for some of the treatment gaps (114). Lack of knowledge of the expected efficiency of different LLT regimens might have an impact. In Nor-COAST, we had no information about qualitative aspects of importance in risk factor management like physicians' and patients' preferences. However, uncertainty about the individual patient's benefit from further intensifying therapy, especially LLT, might lead to misinterpretations about the benefit/harm tradeoffs (123, 124, 190, 191). Clinicians might weigh comorbidity and side effects heavier than benefit, and patients could miss treatment opportunities with potential benefit, and vice versa.

6.4.3 The SMART-REACH model for individualized prevention in stroke patients

The SMART-REACH model aims to serve as a clinical decision-making support tool by giving objective estimates of individual patients' risk and benefit of intensification of secondary prevention. The estimated two-year risk with the SMART-REACH model corresponded adequately with the observed risk in Nor-COAST after recalibration. C-statistics were slightly lower than in the original derivation and validation cohorts (140), which is common and the model may still be useful (6, 154, 280). C-statistics was similar to that in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) participants (188) and in line with prognostic models already in clinical use in secondary preventive settings (140, 145, 149, 261). Stroke patients, as well as the selected RCT population in COMPASS, might, in contrast to a mixed population of outpatients with coronary, peripheral, and cerebrovascular disease, be more homogeneous, making discrimination between high- and low-risk individuals more difficult (130). The same trend was seen when the SMART risk score was validated separately in the subgroup with solely cerebrovascular patients (142, 145). When the discriminative abilities are compared to risk stratification tools in primary preventive settings (137, 233), a C-statistic of 0.63 might seem mediocre. However, this does not necessarily reflect lower quality of the model, but is also highly related to the distribution of risk in the

population (228). The selection of patients with a certain disease (established CVD) results in a relatively homogeneous population compared to healthy people (130). Furthermore, the age distribution in secondary preventive settings is often more homogeneous (145).

How useful the SMART-REACH model is for stroke patients depends on the available alternatives (153). Existing risk stratification tools for stroke patients have shown varying performance in external datasets (161), with **C-statistics** for moderate-term predictions (>90 days to 5 years) ranging from 0.54 to 0.76 (161). However, most scores are point-based with points weighted relatively equally on an ordinal scale without accounting for the weighting of the predictors (regression coefficients) (164, 174, 178). None of the existing risk prediction tools have a statistical methodology to provide long-term estimates or provide a risk estimate (between 0 to 100%) with the ability to be combined with relative risk reductions from clinical trials (at least not yet). Some models have focused on stroke patients with a specific underlying etiology (163, 169, 174, 178), presumably because differences are seen between stroke subtypes in regards to the short-term risk of recurrent stroke and vascular events (35, 36). However, for long-term risk, the distinction between these stroke subtypes seems to diminish, indicating that other factors are at least as important as the index stroke etiology (6, 31, 35, 38, 164). Other authors have highlighted that factors like dyslipidemia, heart failure, and atherosclerotic burden in terms of the number of vascular risk factors and vascular territories affected should be included in future risk estimation (259).

To the best of my knowledge, few external validation studies for stroke risk stratification tools have reported **calibration** (164), which has been generally lacking in studies validating prediction models (156, 228, 229). Furthermore, the relative importance of calibration and discrimination depends on the model intended use (130, 155, 228). If predictions are used in clinical decision-making and communication with patients, estimated risk must reflect the true risk (calibration) (130). Patients are concerned about the likelihood of a new stroke, MI, or death, not necessarily how high risk they have compared to another stroke patient (130, 228, 281). There is at least one ongoing trial aiming to develop a well-validated prognostic tool for CVD risk in ischemic stroke patients regardless of the underlying etiology (clinicaltrials.gov NCT04189497). However, efforts to implement an already available, validated risk score in clinical practice might be more pragmatic and cost-effective than developing a new one if the risk estimates are reliable (157, 280). If doctors are faced with multiple models for the same disease or manifestations of CVD, the result might be an impracticable situation in which

doctors have to choose which model to use; this, in turn, might lead to an overall lack of use (157). The SMART-REACH model has now been validated in various settings and geographic areas (140, 188), and has shown adequate performance, which suggests that the model is reasonably robust for use in clinical care (281), although additional validations in stroke cohorts could make it even more reassuring. It was also recently recommended by the 2021 European Society of Cardiology Guideline on Prevention of Cardiovascular Disease in Clinical Practice (5). Finally, the best measure of performance is whether the risk and benefit estimates are likely to be useful and used in clinical care, which again depends on the clinical situation and preferences of the patient and clinician (130, 261). All risk prediction models include varying degrees of uncertainty and cannot replace good clinical judgment but help structure and guide clinicians in their medical decision-making process (130) – "All models are wrong, but some are useful" (282).

6.4.4 High residual cardiovascular risk

The observed 2-year event rates are roughly comparable to other cohorts of patients with minor stroke (9, 34, 58) or higher (41). A recent meta-analysis with an average follow-up of 3.5 years reported that risk of recurrent stroke was 4.26% per year (higher the first year) and that the risk of MI was 1.67% per year (9). The cumulative 1-year recurrence rate for stroke was 6% for the total Nor-COAST population (all ages including nursing home patients and events the first 3 months) and 2.7% for MI, where the MI rate is comparable to the findings in a recent meta-analysis (48). Event rates are highly dependent on inclusion criteria in the studies, age distribution, and inclusion (or not) of the first "unstable" month's post-event (9, 31). The Oxford Vascular Study (TIA and stroke patients included between 2002 and 2014) have reported 8.6 vascular events per 100 person-years of follow-up (39), rather comparable to Nor-COAST. Comparison with other historical cohorts is difficult due to improvements in secondary prevention in the last years, which may again be counterbalanced by the aging of the population (9). When the post 90-days event are compared to corresponding outpatient age groups with various manifestations of vascular disease, event rates for Nor-COAST were 5.1 per 100 person-years, while the corresponding event rate was similar in the REACH registry (included between 2003 and 2004) and 2.4 per 100 person-years in the SMART study (57, 58).

These discrepancies are probably influenced by the broad inclusion criteria in Nor-COAST and relatively recent event.

The current thesis has demonstrated large interindividual variations in 10-year and lifetime CVD risk for stroke patients on today's secondary prevention. This knowledge constitutes an important contribution to existing evidence. Even after risk factors are theoretically treated to levels recommended by guidelines, the residual risk remains, on average, quite high compared to that of other studies of patients with vascular disease in general (140, 142, 188). However, these studies are not directly comparable due to differences in study design (mostly RCTs), setting (outpatient setting versus after acute hospitalization), inclusion criteria (broad versus narrow), and recruitment (consecutive versus convenience sampling) (140, 142, 188). For a comparison of the estimated future risk of CVD events, there are few up-to-date studies with >10-year follow-up of stroke patients. Nevertheless, other studies underline the importance of a long-term perspective in vascular patients as the risk persists (38, 39, 49, 283), illustrating the need for long-term continuation of preventive treatment and follow-up.

The high residual risk might be explained by non-modifiable risk factors like age, genetic disposition, or cumulative exposure to risk factors over time, resulting in already severely progressed atherosclerosis, highlighting the importance of optimal primary prevention (2, 61, 284). However, modifiable risk factors like inflammation or further reduction of BP and LDL-C are important (5, 65, 74, 75, 78, 284). Mean risk factor levels in Nor-COAST are not far from guideline-targets at the time of the study and more in line with guideline-recommendations compared to other populations (11, 13, 14, 124), yielding less possibilities for benefit based on current cut-offs. However, BP and LDL-C are linearly related to CVD risk (74, 78) and newer guidelines have recommended more stringent treatment targets for both BP and LDL-C (65, 75).

6.4.5 More CVD-free life to gain?

The substantial variation in risk between individuals remains coherent with other populations with established vascular disease (140, 142, 188) and leads to a distribution of benefit, where intensification of treatment produces substantial benefit for a certain proportion of the population. Benefit at the group level is highly dependent on risk distribution in the

population, how well the population is treated from before, and the cut-offs used for risk factor targets in the analyses. Furthermore, estimates at the group level (as in Paper II) do not answer the clinical implications for the individual patient. Hence, stratified analyses by quartiles of risk and benefit were an effort to obtain insight into the kind of patients who were expected to benefit the most.

In Paper III, there were substantial variations in expected benefit from intensification of LLT. Similar examples can be found in other studies (141, 182, 188). Older patients have a high 10-year risk of CVD events. However, a high 10-year risk does not necessarily mean a high benefit of more intensive treatment (140, 143). Patient B in the patient example in **Figure 5.3** has a high 10-year risk, but actual CVD-free life to gain is limited due to advanced age and limited remaining life expectancy. Reduction in CVD risk will also be counterbalanced by competing risks, as well as higher rates of adverse drug effects and interactions due to polypharmacy. In contrast, patient A has a relatively low 10-year risk, but CVD-free life to gain is substantial (counting only a first recurrent event) due to a relatively young age, long remaining life expectancy, and lower risk of competing events. However, this comes at the cost of a longer duration of medication use and longer time exposed to potential side-effects (143).

These patient examples highlight the importance of both 10-year and lifetime measures of risk and benefit, and the usefulness of risk prediction tools. The individualized treatment benefit can be presented in various ways; 10-year ARR/NNT, lifetime ARR/NNT, or CVD-free years/months gained, which might be more intuitive for both the patient and the physician than the average group-level estimates retrieved from RCTs (115, 144). However, no risk or benefit thresholds currently exists in secondary prevention, and what amount of benefit is considered high enough to support intensification of treatment is highly subjective and conditional on patient preferences, adverse-effects and costs (167). Treatment harms were not incorporated into the estimations, as the weight of these features may be highly subjective and difficult to predict, i.e., perceived statin intolerance or the discomfort of taking medications every day (144, 285). However, if the benefits are known, these can be weighed against expected treatment harm and patients' and physicians' preferences.

6.4.5.1 *Reaching guideline-recommended targets – the ultimate marker of success?*

Patients and their treating physicians might have several reasons to deviate from the recommended drugs and the treatment-to-target approach (5, 279, 286). In Nor-COAST, the reasons for drug discontinuation and non-intensification were not known, and it is highly possible that the GPs already made treatment decisions that were more in line with the individual patient's risk, benefits, and preferences. Stroke patients are heterogeneous (18, 53) and explicitly following guideline recommendations could lead to considerable polypharmacy for patients with co-existing diseases; also, follow-up could be rather complex with competing demands and challenges regarding how to best prioritize (5, 265, 279, 286). The additional benefit of a medication, when added to an already complex regimen, might also be uncertain and increase the risk of drug-drug interactions and adverse effects (5, 286). Guidelines are single-disease based; most of the evidence originates from clinical trials with relatively young individuals with less comorbidity, and guidelines give advice on how to treat "the average patient" (who actually does not exist) (5, 144, 189, 265, 286). Average follow-up time in these studies is shorter than the long-term or lifelong prescription being practiced in clinical care, and efficacy and safety may be altered as time passes into old age (265). Overall prognosis, life expectancy, functional status, and quality of life become increasingly important as age and comorbidity increase, highlighting the need for more patient-centered care (119).

A "one size fits all" approach for secondary prevention have traditionally been recommended (130). However, a trend toward more benefit-based treatment decisions (instead of a solely risk factor- or risk-based approach) is now reflected in the newest ESC Guideline on CVD Prevention in Clinical Practice (5) where a "2-step approach" for treatment intensification was introduced – with treatment goals "for all" (Step 1) and "ultimate goals" for those who benefit the most (Step 2). A recent microsimulation study has shown that risk reduction guided by estimates of lifetime benefit leads to more CVD-free life years and avoidance of more CVD events compared to a risk factor-based approach (287). A recent meta-analysis concluded that BP-lowering treatment based on estimated CVD risk is more effective than guided by BP levels alone (288), and a BP-lowering strategy based on the individual's net benefit is warranted rather than the treatment of the BP to a specific target (74).

7 CLINICAL IMPLICATIONS

Although secondary prevention has improved tremendously in the last decade, there are still gaps between guideline recommendations and achievement in clinical care, especially for BP and LDL-C. This also applies to Norway, with public health care and drug treatment reimbursed by the government and (at least) apparently well-functioning systems of follow-up. Secondary prevention is highly effective and safe medications and lifestyle interventions are available at low costs. There is a potential for improvement, and allocating resources for appropriate implementation of preventive strategies in clinical practice will have significant importance for patient outcomes, public health and society.

However, barriers to optimal medication adherence and risk factor control are multifactorial (15, 16) and related to both the patient (i.e., poor medication adherence and persistence and patient characteristics such as age, sex, and comorbidity) and the physician (i.e., prescription of low doses and lack of up-titration), as well as the healthcare system (i.e., organization of follow-up routines and transition routines from specialist to primary health care, although not directly assessed in this thesis). Although many of the factors we address as being associated with poor risk factor control are not modifiable, like age and female sex, we identify groups at risk of undertreatment. Adherence is a dynamic phenomenon, highlighting the need for long-term follow-up with focus both on patients' adherence and optimal prescription of effective medications and doses. Stroke is an acute event, but stroke patients are also chronic patients who continues to be at high risk of CVD events, who require long-term CVD monitoring (beyond the first 3 months) and treatment with a global vascular and presumably more multidimensional approach (289). Risk stratification may have an important role in selecting patients with highest benefit from more intensive and structured follow-up.

Identifying patients with elevated residual risk is also increasingly important in this "new era" with more stringent treatment target recommendations and effective preventive strategies becoming available. Objective estimates of the individual patients' benefit of intensification, may help avoid undertreatment as well as overtreatment. However, prognostic tools are not yet in routine use for patients with established CVD in Norway or internationally. The external validation of the SMART-REACH model may have clinical implications, not only for Norwegian stroke patients, but also for patients with other manifestations of vascular disease like CAD and PAD, and the model has certain advantages. Firstly, it can be used for all patients with

established CVD and might better meet the GP's clinical needs, which provide secondary prevention follow-up for patients with various manifestations of CVD. Secondly, because secondary prevention presumably is to be continued lifelong (or at least until conditions leading to limited remaining life expectancy appear), it might be more intuitive to estimate (at least) 10-year risk and lifetime estimates, both of which are useful in different ways. The model accounts for competing risks, which reflects the way risk in general is interpreted in clinical care. The ability to combine risk estimates with HR from clinical trials is an important advantage. The principles used to calculate the benefits of therapies can also be applied to other interventions as long as a robust effect estimate for CVD outcomes exists. Thirdly, the model includes readily available variables measured as a part of routine care and is already implemented in online tools like u-prevent.com and the ESC CVD risk prediction app, which may ease the implementation in clinical care. Poor correlation between physicians' perceived risk and calculated risk suggests that the use of risk prediction models might better select the right patients for the right treatment (290, 291). It is reasonable to assume that providing estimates of benefit would even improve this further (130). Poor communication between patient and physician, and lack of knowledge of CVD risk and benefit associated with taking medications have previously been identified as barriers to adherence (15). The model can provide objective estimates that may serve as a supplement to clinical intuition and guidelines (130, 153), to make more well-balanced treatment decisions, more precise communication and may consequently improve patients' adherence and prognosis (130, 131, 153, 157).

8 FUTURE PERSPECTIVES

This thesis emphasizes the need for further research on how to improve implementation of secondary prevention, as well as primary prevention, in clinical practice. Efforts at hospital discharge, the long-term follow-up in primary care, the dialog between GPs and hospital, and extended follow-up at hospital level, especially for patients at the highest risk, must be considered.

Building a gold standard program for secondary prevention follow-up is challenging, and there is not necessarily one correct strategy due to the complexity of the population. A program needs to be individualized according to patient preferences and adapted to the local community structures. A multidisciplinary, structured approach will probably have the largest

effect (40, 66, 103, 114, 240, 289, 292, 293) inspired by the core components of cardiac rehabilitation programs (289, 292-294). There is a need for a prospective multicenter RCT determining the most effective program for stroke patients (i.e., time window, frequency and duration, characteristics of the multidisciplinary team), and selection of the best candidates for such an approach. This thesis and other studies underline that focus on optimal prescription of drugs, up-titration and medication adherence are essential components of such programs (289). Both investment in resources for a more multidisciplinary follow-up as well as implementing low-cost long-term telephone or text-message reminders and digital educational and rehabilitation support to increase patients' self-monitoring (alongside) are warranted.

The concept of estimating future risk and benefit to individualize secondary prevention is quite new and has not yet been investigated in large outcome trials. An impact study is needed, assessing whether risk and benefit stratification influences the clinician's treatment decisions, improves risk factor control and patients' adherence and outcome, and is cost-effective compared to not using the tool (130, 152, 153, 157, 290). This also creates an opportunity to assess barriers to implementing such tools in clinical care (130). Efforts for automatic implementation in electronic patient records might be beneficial. More research is also needed on how to communicate risk and benefit most effectively to patients (115).

More research is needed to assess potential strategies for further lowering the high residual cardiovascular risk. So far, we have been unable to engage in risk-stratified interventions in secondary preventive settings. However, tools like the SMART-REACH model enables this, which may help improve focus and efficiency in future trials.

CVD risk prediction models in secondary preventive settings aimed at the age group above 80 years, constituting one third of the Norwegian stroke population, do not exist (8). An 80-year-old Norwegian male or female has an average life expectancy of 8.7 and 10.3 years (295), respectively. Yet, large biological heterogeneity exists, and tools to objectively support decisions to start, intensify, or stop secondary prevention are also highly relevant for this group. More RCTs in this age group on the magnitude of benefits of intensive secondary prevention are warranted (296).

Longitudinal studies exploring barriers in follow-up routines in primary health care and transition routines from hospital to primary care are needed (289). National monitoring of the adequacy of secondary prevention is needed, and The Norwegian Stroke Registry might serve

as an opportunity, at least at the 3-month visit. In the Norwegian Stroke Registry, medications at discharge are implemented as a quality indicator, however, adding quality indicators for risk factor levels and medications at follow-up would give useful information.

9 CONCLUSION

Secondary prevention after stroke is suboptimal with a potential for improvement. This thesis identifies patient groups at risk of undertreatment and illustrates a potential for further optimization of prescription of conventional LLT. An already available risk prediction tool for patients with established vascular disease generates prognostic risk information reasonably well in stroke patients. The predicted future risk is high, with considerable individual variation in the net benefit from intensification of secondary prevention. The SMART-REACH model can be used to objectively estimate future risk and expected benefit, which may assist in making well-balanced treatment decisions regarding whether to intensify preventive treatment and identify stroke patients who need more structured and multidisciplinary follow-up. This might result in more precision-based and personalized medicine also in secondary prevention of CVD.

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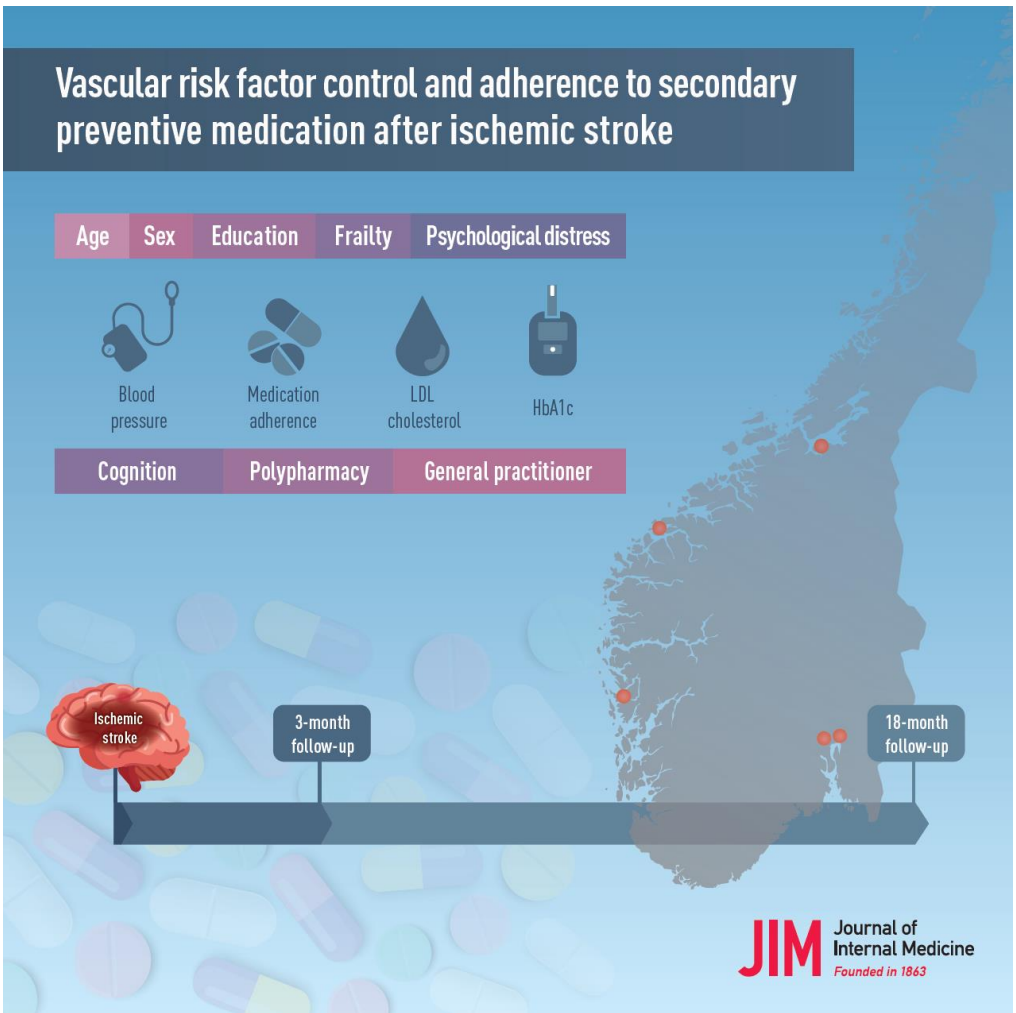
Paper I


Vascular risk factor control and adherence to secondary preventive medication after ischemic stroke
Age
Sex
Education
Frailty
Psychological distress
Blood pressure
Medication adherence
LDL cholesterol
HbA1c
Cognition
Polypharmacy
General practitioner
Ischemic stroke
3-month follow-up
18-month follow-up
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Vascular risk factor control and adherence to secondary preventive medication after ischaemic stroke

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Abstract. Gynnild MN, Aakerøy R, Spigset O, Askim T, Beyer MK, Ihle-Hansen H, Munthe-Kaas R, Knapskog AB, Lydersen S, Næss H, Røsstad TG, Seljeseth YM, Thingstad P, Saltvedt I, Ellekjær H (Norwegian University of Science and Technology, Trondheim, Norway; Trondheim University Hospital, Trondheim, Norway; University of Oslo, Oslo, Norway; Oslo University Hospital, Oslo, Norway; Bærum Hospital, Drammen, Norway; Haukeland University Hospital, Bergen, Norway; Stavanger University Hospital, Stavanger, Norway; University of Bergen, Bergen, Norway; City of Trondheim, Trondheim, Norway; Møre and Romsdal Health Trust, Ålesund, Norway). Vascular risk factor control and adherence to secondary preventive medication after ischaemic stroke (Original Article). *J Intern Med* 2021; **289**: 355–368. https://doi.org/10.1111/joim.13161

Background. Studies regarding adequacy of secondary stroke prevention are limited. We report medication adherence, risk factor control and factors influencing vascular risk profile following ischaemic stroke.

Methods. A total of 664 home-dwelling participants in the Norwegian Cognitive Impairment After Stroke study, a multicenter observational study, were evaluated 3 and 18 months poststroke. We assessed medication adherence by self-reporting (4-item Morisky Medication Adherence Scale) and medication persistence (defined as continuation of medication(s) prescribed at discharge), achievement of guideline-defined targets of blood pressure (BP) (<140/90 mmHg), low-density lipoprotein cholesterol (LDL-C) (<2.0 mmol L^{-1}) and haemoglobin A1c (HbA1c) (≤53 mmol mol^{-1}) and determinants of risk factor control.

Results. At discharge, 97% were prescribed antithrombotics, 88% lipid-lowering drugs, 68% antihypertensives and 12% antidiabetic drugs. Persistence of users declined to 99%, 88%, 93% and 95%, respectively, at 18 months. After 3 and 18 months, 80% and 73% reported high adherence. After 3 and 18 months, 40.7% and 47.0% gained BP control, 48.4% and 44.6% achieved LDL-C control, and 69.2% and 69.5% of diabetic patients achieved HbA1c control. Advanced age was associated with increased LDL-C control (OR 1.03, 95% CI 1.01 to 1.06) and reduced BP control (OR 0.98, 0.96 to 0.99). Women had poorer LDL-C control (OR 0.60, 0.37 to 0.98). Polypharmacy was associated with increased LDL-C control (OR 1.29, 1.18 to 1.41) and reduced HbA1c control (OR 0.76, 0.60 to 0.98).

Conclusion. Risk factor control is suboptimal despite high medication persistence and adherence. Improved understanding of this complex clinical setting is needed for optimization of secondary preventive strategies.

Keywords: blood pressure, cardiovascular disease, medication adherence, secondary prevention, stroke.

ClinicalTrials.gov Identifier: NCT02650531.

Introduction

Patients with acute ischaemic stroke are at increased risk of recurrent stroke and other vascular events. Estimates of cumulative event rate range from approximately 6.2% to 11.1% the first year and 12.9% to 26.4% at 5 years [1-3]. Although the risk is highest the first year after an index event, observational studies have shown that the risk persists after these first years [1,3]. A review of the burden of stroke reported that approximately 90% of strokes were attributable to modifiable risk factors [4] and suggested that attainment of risk factor control could prevent more than three quarters of the stroke burden worldwide. Quantitative modelling estimates that optimal secondary prevention may reduce the risk of recurrence by 80% [5].

International [6, 7] and national Norwegian guidelines [8] give clear recommendations for secondary prevention after stroke, where pharmacotherapy is a cornerstone, in addition to lifestyle modification and interventional procedures. However, studies suggest that implementation of guidelines in clinical practice is inadequate, with low adherence to secondary preventive medication and poor risk factor control in patients with established vascular disease [9, 10], including ischaemic stroke [11-13]. Adherence to recommended medication regimens is a critical mediator between initiation of treatment and patient outcome [14]. Multiple factors might interfere with both medication adherence [15, 16] and risk factor control in stroke survivors, including factors related to the patient, the physicians and the healthcare systems. However, limited research has explored how these factors influence achievement of risk reduction to recommended targets.

Although studies demonstrate a wide variation in the provision of secondary prevention across Europe for patients with established vascular disease, accurate country-specific data for stroke patients are sparse, especially with longitudinal follow-up, and published data are usually at least five years old [17]. Frequently updated clinical guidelines and an ageing population request an urgent need for reports presenting achievement of secondary stroke prevention in clinical practice. Therefore, by using detailed clinical and longitudinal data in an unselected cohort of ischaemic stroke patients, we aim to examine adherence to secondary preventive drugs and achievement of vascular risk factor control 3 and 18 months poststroke and explore clinical factors associated with the attainment of optimal risk factor control.

Materials and methods

Study population

The study is part of the Nor-COAST (Norwegian Cognitive Impairment After Stroke) study, a Norwegian multicenter observational cohort study. A thorough description of the methods is available elsewhere [18]. Briefly, patients admitted with acute stroke at five Norwegian stroke units in the period from May 2015 to March 2017 were included and followed with scheduled appointments after 3 months, 18 months and 3 years at the outpatient clinic with self-report questionnaires, interview, cognitive and physical clinical examinations and blood sampling. Participants unable to attend the outpatient clinic were assessed by telephone interview or by proxy information.

In the present preplanned sub-study, 729 home-dwelling patients hospitalized with ischaemic stroke were included (Fig. 1) and followed from baseline to 18 months. For all analyses, we excluded patients who died within the first three months poststroke ($n = 29$) and patients living in long-term care facilities (e.g. nursing homes) at three months poststroke ($n = 36$), leaving 664 patients eligible for analysis. The Norwegian Regional Committee for Medical and Health Research Ethics North (REC number 2017/1462) approved the study. All participants signed a written informed consent before inclusion, or by proxy if the participant was unable to give informed consent.

Outcome assessments

The main outcome was control of blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), and haemoglobin A1c (HbA1c) according to the recommendations for treatment targets in the Norwegian National guidelines for treatment and rehabilitation of stroke at the time of the survey [8]. Other outcomes were adherence to secondary preventive pharmacotherapy prescribed at discharge and identification of factors influencing risk factor control.

Assessment of vascular treatment targets

Baseline BP values were measured at discharge or on day seven during the hospital stay. At follow-up, BP was measured three times by the same

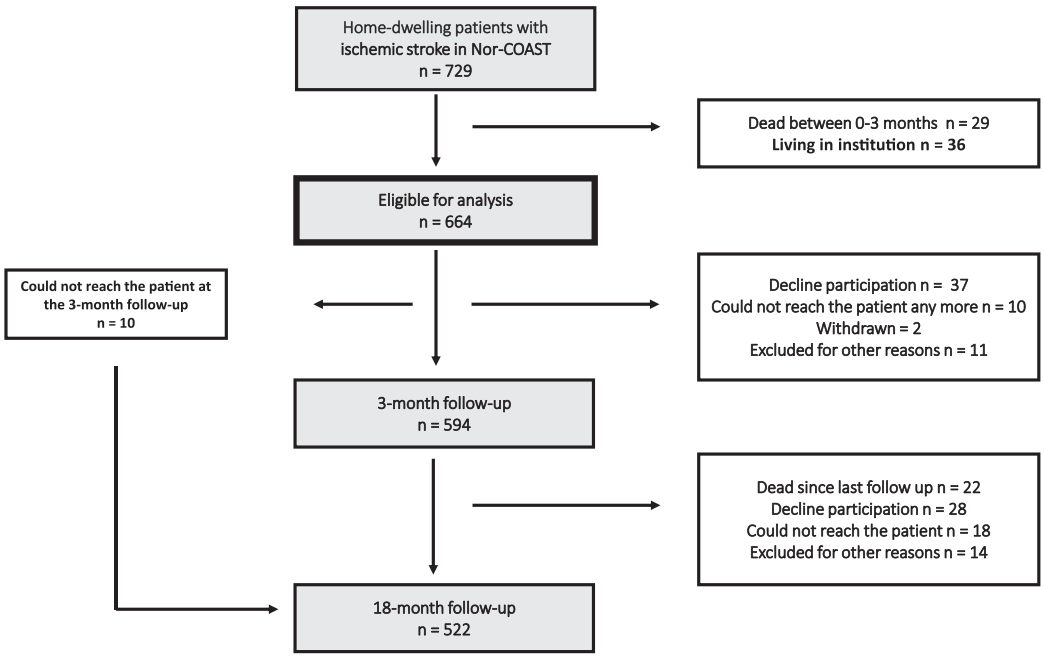

Fig. 1 *Flow chart of inclusion and exclusion of participants in current analysis.*

physician with one-minute intervals and the average of the second and third measurements was used in the analysis. BP control was defined as systolic BP < 140 mmHg and diastolic BP < 90 mmHg [8]. Nonfasting serum concentrations of LDL-C and blood levels of HbA1c from venous blood were measured in fresh samples at each hospital. Blood tests from baseline were taken the first day after admission. LDL-C control was defined as LDL-C < 2.0 $mmolL^{-1}$ [8], and glycemic control was defined as HbA1c ≤ 53 $mmol\ mol^{-1}$ (≤7%) [8].

Assessment of medication adherence

Adherence to pharmacotherapy prescribed at discharge was assessed by two measures: (i) Self-report using the 4-item Morisky Medication Adherence Scale (MMAS-4) [19] and (ii) persistence of medication(s).

MMAS-4 is a general medication-taking behaviour scale which has been validated in patients with various diseases and treatments. The scale is protected by U.S. and International Trademark and Copyright laws and a Morisky Widget license agreement has been made between St. Olavs University Hospital and MMAS Research LLC. Each item in the MMAS-4 has a dichotomous response option where the sum creates a total score ranging from 0 to 4. A score of 4 corresponds to high medication adherence, scores of 2-3 to medium adherence and scores of 0-1 to low adherence.

We defined persistence as medication continuation from hospital discharge to 3 and 18 months post-stroke. Subjects were also considered "persistent" if there had been a switch of medication within the same class. Information regarding medications prescribed at hospital discharge was obtained from the discharge summary. At follow-up, trained health professionals retrieved information of medications in use by interviewing participant/proxy. If information from participant/proxy was missing, we contacted general practitioners and home care services or we used the electronic summary care record for safer healthcare in Norway. Appropriate

preventive medications encompassed the following drugs with The Anatomical Therapeutic Chemical (ATC) Classification System codes in parentheses: antihypertensive drugs (thiazide diuretics (C03A), beta receptor blockers (C07), calcium channel blockers (C08), angiotensin-converting enzyme inhibitors (C09A, B), angiotensin receptor blockers (C09C, D), "other" (C02A, C02C, C02D)), antithrombotic drugs (B01A), lipid-modifying agents (C10) and blood glucose lowering drugs (A10).

Factors influencing vascular risk factor control (independent variables)

Factors influencing achievement of treatment targets were chosen a priori with intention of covering the complexity of medication nonadherence [15, 16], based on measures from previously published studies [20, 21] and biologically plausible assumptions. We analysed age and education as continuous variables, sex with male as reference. Frailty was assessed by the 5-item Fried criteria [22], giving a score from 0 (robustness) to 5 (frail) based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss, all assessed at baseline (supplementary methods). Cognitive function was evaluated by the Global Deterioration Scale [23] at all time-points, a global measure of cognitive function and ability to perform daily life activities. Trained nurses used all available information from a comprehensive cognitive test battery described elsewhere [24], functional tests and interviews with participant/proxy to give a score from 1 (normal cognitive function) to 7 (severe dementia). Medication adherence was assessed by MMAS-4 at 3 and 18 months, analysed as a continuous variable from 0 (low adherence) to 4 (high adherence). Number of medications used at all time-points were analysed as continuous variable. Follow-up appointment at the general practitioner (GP) within three months postdischarge was obtained by the self-report questionnaire and analysed as a categorical variable (yes/no). Psychological distress was measured by the Hospital Anxiety and Depression Scale (HADS) [25] at 3 and 18 months and analysed as a continuous variable (score 0–42). The subscales for depression and anxiety (score 0–21 for each subscale) were analysed separately. A separate analysis was performed to study the effect of statin dose intensity on LDL-C. The statin dose was expressed as atorvastatin equivalent doses using the defined daily doses (DDDs) for the statins as defined by the World Health Organization [26] and the following formula: (Dose of "other statin"/DDD for "other statin") x DDD for atorvastatin.

Statistical analysis

Baseline characteristics were described by means with standard deviations (SD) and proportions as appropriate. We first calculated proportions reaching treatment targets for available cases at each time-point. Since an available case analysis is unbiased only if data are missing completely at random, we also did a model-based descriptive analysis using mixed model logistic regression, which is unbiased under the less restrictive missing at random assumption [27].

In the mixed model logistic regression, we used blood pressure, LDL-C and HbA1c, dichotomized, one at a time as dependent variables, and time-point as a categorical covariate, to calculate proportions reaching treatment targets. Proportions reaching targets at each time-point were calculated by odds converted to probability (P) by $P = \text{odds}/(1 + \text{odds})$ for all participants and separately for those using relevant pharmacotherapy.

Assessment of associations between potential explanatory factors and target achievement in patients with prescribed pharmacotherapy included the following covariates in the model, one at a time: age, sex, education, frailty, cognitive function, number of medications used, self-reported medication adherence, follow-up appointment by general practitioner and HADS score. We did unadjusted analyses and analyses adjusted for age, sex and education. In addition, we carried out supplementary analyses with systolic BP and LDL-C as continuous dependent variables. We report odds ratios (OR) with 95% confidence intervals (CI) where relevant. Two-sided P-values < 0.05 were regarded as statistically significant. However, due to multiple hypotheses, P-values between 0.01 and 0.05 should be interpreted with caution. Data analysis was performed using Stata version 16.

Results

Baseline characteristics

In total, 90% ($n = 594$) was assessed at 3 months and 79% ($n = 522$) at 18 months, reasons for loss of follow-up are shown in Figure 1. The patients lost to follow-up were older with a higher burden of comorbidity, severe strokes, cognitive impairment

and disability (Table S1). The clinical characteristics of the population are shown in Table 1. The mean (SD) age was 72.9 (11.5) years (range 33–96), and 43% were female. A total of 93% (n = 616) had at least one vascular risk factor at baseline (mean 2.8, SD 1.7). The mean number of medications at discharge was 5.3 (SD 2.6, range 0–14), and 99% were prescribed at least one secondary preventive medication.

Achievement of vascular risk factor control

Table 2 shows proportions achieving risk factor targets, estimated by mixed model logistic

Table 1. *Clinical characteristics at the index stroke event (n of the 664 patients eligible for analysis)*

Prestroke demographic and clinical characteristics		Prestroke vascular risk factors		Poststroke clinical characteristics	
Age (years)	72.9 (11.5)	Atrial fibrillation[d]	154/664 (23%)	NIHSS[k] admission	3.9 (4.9)[l]
Sex, female	287/664 (43%)	Diabetes mellitus[e]	129/664 (19%)	NIHSS discharge	1.7 (2.4)[m]
Education (years)	12.1 (3.7)	Hypertension[f]	380/664 (57%)	Independent functional status[a] at discharge	415/662 (63%)
Living alone	235/664 (35%)	Hypercholesterolemia[g]	222/664 (33%)	Number of medications at discharge	5.3 (2.6)
Independent functional status[a]	601/660 (91%)	Previous stroke/TIA[h]	158/664 (24%)		
Charlson Comorbidity Index	4.1 (2.0)	Ischemic heart disease[h]	122/664 (18%)		
Cognitive impairment[b]	84/657 (13%)	Chronic kidney disease[i]	112/659 (17%)		
Frail[c]	98/664 (15%)	Current tobacco smoking	128/664 (19%)		
Home care	63/664 (10%)	BMI	26.1 (4.2) (619)		
		Physically active[j]	145/664 (22%)		

Values are n/N (%) or mean (standard deviation (SD)) (n observations).
[a] Independent functional status defined as Modified Rankin Scale ≤ 2.
[b] Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale.
[c] Frailty measured by Fried frailty index.
[d] Atrial fibrillation was defined by self-report or documented on electrocardiogram or telemetry during admission.
[e] Prestroke diabetes mellitus was defined as self-reported diabetes or HbA1c ≥ 48 mmol mol^{-1} or prescribed antidiabetic drugs at admission.
[f] Hypertension was defined as self-reported hypertension or use of antihypertensive drugs.
[g] Hypercholesterolemia was defined by use of lipid lowering drugs at admission.
[h] Prevalence of previous cerebrovascular disease and coronary heart disease was retrieved from hospital medical records.
[i] Chronic kidney disease was defined as GFR < 60 $mLmin^{-1}/1.73\ m^2$ (CKD-EPI equation based on gender, age and the serum creatinine concentration at admission).
[j] Self-reported adherence to physical activity guidelines defined as minimum 75 min per week of high-intensity exercise or minimum 150 min per week of moderate intensity exercise.
[k] Stroke severity according to National Institutes of Health Stroke Scale (NIHSS).
[l] n = 643
[m] n = 627
Abbreviations: TIA, Transient ischemic attack; BMI, Body Mass Index.

regression. Corresponding proportions for available case analysis are shown in Table S2.

Blood pressure control

Ninety-four per cent ($n = 622$) had blood pressure measurements at discharge, 90% ($n = 535$) at 3 months and 84% ($n = 440$) at 18 months with corresponding mean BP of 142/79 mmHg (SD 20/13), 141/82 mmHg (SD 20/12) and 140/82 mmHg (SD 19/12), respectively. At 3 months and 18 months, 40.7% and 47.0% achieved blood pressure control, with corresponding results for patients using antihypertensive drugs of 37.8% and 43.6%. For patients using antihypertensives not reaching target, the mean number of antihypertensive agents (i.e. the number of active ingredients) was 1.6 (SD 0.7) and 1.7 (SD 0.8) at 3 and 18 months, respectively, and 54% and 53% were using only one agent.

LDL cholesterol control and glycemic control

Reasons for missing values of LDL-C and HbA1c for patients still in follow-up were mainly unsuccessful phlebotomy, too low blood volume obtained and patient refusal. LDL-C was measured in 97% ($n = 645$), 80% ($n = 476$) and 70% ($n = 365$) at baseline, 3 and 18 months, respectively. The mean LDL-C level at 3 months was 2.13 (SD 0.77) and at 18 months 2.18 (SD 0.83). At 3 and 18 months, 48.4% and 44.6% had LDL-C control, and corresponding values for participants using lipid-lowering drugs were 54.3% and 49.4%.

For patients using statins not reaching target at 3 and 18 months, 67% and 55% used high-intensity statins, defined as ≥40 mg per day atorvastatin or equivalent dose of other statin. The corresponding proportions amongst those reaching the LDL target were 59% and 54% ($P = 0.134$ and 0.787, respectively). Notably, 70% of the patients not reaching the LDL target at 18 months remained on the same dose intensity, whilst 8% increased and 22% reduced the dose during follow-up. Analysis of the relation between intensity of the lipid-lowering treatment as continuous variable and LDL-C control showed no significant association, although increasing statin dose was associated with lower LDL-C level (Table S3).

HbA1c was measured in 97% (125/129) of the diabetic patients at baseline, in 78% (88/113) at 3 months and in 58% (56/96) at 18 months. Mean HbA1c level was 51.6 mmol mol^{-1} (SD 11.9) and 51.5 mmol mol^{-1} (SD 21.0) at 3 and 18 months. At 3 and 18 months, 69.2% and 69.5% achieved glycemic control, and corresponding values for participants using antidiabetic drugs were 36.3% and 48.0%.

Optimal control of all targets

A total of 77% ($n = 460$) and 67% ($n = 352$) completed the three measurements for BP, LDL-C and HbA1c at 3 and 18 months, with a corresponding optimal control of all three risk factor targets in 20.9% and 21.6% of the patients. Ten per cent were still smoking at 3 months (55/558), and 10% were smoking at 18 months (48/492).

Adherence to secondary preventive medication

At 3 and 18 months, 80% (415/521) and 73% (358/488) reported high medication adherence according to MMAS-4. In all, 75% ($n = 482$) had follow-up data on medication use at both 3 and 18 months. Sixty-nine per cent ($n = 331$) were discharged with antihypertensive medications, 88% ($n = 426$) with lipid-lowering drugs, and 98% ($n = 474$) with antithrombotic drugs, and 66% ($n = 57$) of diabetic patients were on antidiabetic medication. The proportions persistent to medication during the first 3 months were above or equal to 95% for all drug classes (Table 3). At 18 months, the rates decreased to 93% for antihypertensive drugs and 88% for lipid-lowering drugs. The proportion receiving help from either home care services or next of kin for medication administration remained unchanged during follow-up, 19% (89/482) at 3 months and 20% (98/482) at 18 months.

Factors related to vascular risk factor control

Results from the mixed model logistic regression model reporting odds ratios for explanatory factors associated with vascular risk factor control in patients on pharmacotherapy are shown in Table 4, and results adjusted for age, sex and education are shown in Table S4. Advanced age was associated with reduced odds for blood pressure target achievement (OR 0.976 per year, 95% CI 0.959 to 0.993, $P = 0.007$) and increased odds for LDL-C control (OR 1.032 per year, 95% CI 1.009 to 1.056, $P = 0.007$). An increasing number of medications in use were associated with increased odds for LDL-C control (OR 1.29, 95% CI 1.18 to 1.41, $P < 0.001$) and reduced odds for glycemic control

Table 2. *Proportions achieving vascular risk factor control at hospital stay, at 3 months and at 18 months*

	All patients			Patients prescribed pharmacotherapy[e]		
	n[f]	Probability (%)	95% CI (%)	n[g]	Probability (%)	95% CI (%)
Hospital stay						
Blood pressure control[a]	622	42.9	37.6 to 48.4	435[h]	32.9	27.7 to 38.6
LDL cholesterol control[b]	645	8.2	5.6 to 11.7	556[i]	7.2	4.7 to 10.7
Glycemic control[c,d]	125	56.2	36.3 to 74.4	83[j]	24.9	11.1 to 46.8
3 months						
Blood pressure control	535	40.7	35.2 to 46.7	387	37.8	31.9 to 44.1
LDL cholesterol control	476	48.4	41.2 to 55.8	414	54.3	46.4 to 62.0
Glycemic control	88	69.2	47.5 to 85.3	56	36.3	16.7 to 61.8
18 months						
Blood pressure control	440	47.0	40.7 to 53.5	326	43.6	36.7 to 50.5
LDL cholesterol control	365	44.6	36.7 to 52.9	305	49.4	40.8 to 58.1
Glycemic control	56	69.5	42.8 to 87.4	35	48.0	21.5 to 75.6

Based on mixed model logistic regression with time point as categorical covariate and patient as random effect.
[a] Blood pressure (BP) <140/90 mmHg.
[b] LDL cholesterol <2.0 mmolL^{-1}.
[c]HbA1c ≤ 53 mmol mol^{-1}.
[d]For patients with diabetes mellitus (DM), defined as using blood glucose lowering drugs at admission or discharge or HbA1c ≥ 48 $mmolmol^{-1}$ at admission or self-report of diet-regulated DM.
[e]Prescribed pharmacotherapy at discharge and/or anytime during the 18 months of follow-up, for blood pressure control; on antihypertensives, for LDL control; on lipid lowering drugs, for glycemic control; on antidiabetic medication.
[f]Total N contributing to estimates are 650 for blood pressure control, 658 for LDL cholesterol control and 129 for glycemic control.
[g]Total N contributing to estimates for participants on pharmacotherapy are 511 for blood pressure control (new user during follow-up n = 62), 590 for LDL control (new user during follow-up n = 23) and 89 for glycemic control (new user during follow-up n = 5), most new users were prescribed pharmacotherapy shortly after discharge.
[h]78% of these were on therapy prestroke.
[i]39% of these where on therapy prestroke.
[j]86% of these where on therapy prestroke.
Abbreviations: LDL; low-density lipoprotein.

(OR 0.76, 95% CI 0.60 to 0.98, P = 0.031). When adjusting for age, gender and education, the association between number of medications and BP was statistically significant (OR 1.07, 95% CI 1.00 to 1.15, P = 0.036). Women had reduced odds for LDL-C control (OR 0.60, 95% CI 0.37 to 0.98, P = 0.041) compared with men, also after adjusting for age (OR 0.53, 95% 0.32 to 0.87, P = 0.012). Frailty was associated with increased LDL-C control, and cognitive impairment was associated with reduced HbA1c control in unadjusted analysis, but not when adjusting for age, sex and education. For other associations, the effect estimates were substantially the same in the unadjusted and adjusted analysis. We found no significant association between self-reported medication adherence and target achievement, neither for early follow-up appointment by GP, which 85% of the patients had completed. We found no association between psychological distress and goal achievement. Applying the HADS subscales for depression and anxiety separately did not cause any principal changes in these results (data not shown). The proportion with symptoms of anxiety or depression, defined as score ≥ 8 on subscales, was 15% and 14% at both time points, and mostly included mild symptoms.

Sensitivity and subgroup analyses

Since the model-based analyses showed systematically lower estimated proportions for target achievement for both BP and LDL-C compared with the available case analysis, we did sensitivity analyses excluding participants with only baseline measurements who used no relevant

Table 3. *Persistence to secondary preventive medication at 3 months and 18 months for 482 participants with available follow-up data on medications in use*

	Persistent at 3 months[a] *n/N* (%)	Persistent at 18 months[a] *n/N* (%)
Antihypertensive drugs	319/331 (96)	309/331 (93)
Lipid lowering drugs	412/426 (97)	376/426 (88)
Antidiabetic drugs	54/57 (95)	54/57 (95)
Antithrombotic drugs	469/474 (99)	464/474 (98)
Anticoagulation	144/151 (95)	140/151 (93)
Antiplatelet agent	339/362 (94)	324/362 (90)

[a]Persistence to medication prescribed at discharge.

pharmacotherapy at admission. However, the results did not change substantially (Table S5).

Sensitivity analyses with LDL-C and systolic BP as continuous outcome variables (Tables S6 and S7) showed results in line with the findings using dichotomous outcome variables (Table 4 and S4). However, there was a significant association between high self-reported medication adherence and lower LDL-C (coefficient -0.08 mmol L^{-1}, $P = 0.025$).

Subgroup analyses for factors associated with target achievement for BP and LDL-C in age group < 75 year and ≥75 year (Table S8) showed a negative association with BP control for women, frailty, cognitive function and follow-up by the GP in the oldest age group, and the opposite trend in the youngest age group. Still, none of the associations were statistically significant. For the association between LDL-C target achievement and age group, the effect estimates were in line with findings in Table 4.

Discussion

Principal findings

Our results show that control of traditional vascular risk factors after ischaemic stroke is suboptimal, with a large proportion not reaching guideline-defined treatment targets for blood pressure, LDL-C and HbA1c. We found high self-reported medication adherence during 18 months of follow-up and the persistence to secondary preventive medications declined only modestly in the same period. Age, sex and number of medications in use were associated with vascular risk factor control, although in different directions. However, follow-up by the GP, psychological distress and self-reported medication adherence were not related to achievement of recommended treatment targets, but high self-reported medication adherence was significantly associated with lower LDL-C.

Comparison with other studies

In general, our findings are consistent with previous observational studies describing suboptimal target achievement in patients with established vascular disease [9-12, 20]. Our model-based analyses showed systematically lower estimates of target achievement (Table 2) (except for HbA1c) compared with the available case analysis (Table S2), indicating that the participants lost to follow-up probably had an even poorer risk factor control.

BP is the most crucial risk factor in preventing recurrent stroke of all subtypes [6, 28]. The proportion reaching the BP target in Nor-COAST within 18 months was slightly higher than reported in the stroke-specific module of EUROASPIRE III (European Action on Secondary Prevention through Intervention to Reduce Events) [11]. The ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke) study from Ireland [12] also found a lower proportion at target after 6 months, though not directly comparable due to time of assessment. In line with our findings, these two studies showed lower target achievement in patients on antihypertensive drugs. Half of the patients in Nor-COAST did not reach LDL-C target of 2.0 mmolL^{-1} at 18 months and persistence to lipid-lowering drugs declined by 12% in the same period, a lower nonpersistence rate compared with other studies [21, 29, 30]. The prevalence of nonfavourable LDL-C control will obviously differ considerably based on the choice of cut-off. Proportions at LDL-C target were in line with findings in the ASPIRE-S [12] study when using LDL-C < 2.5 mmolL^{-1} as cutoff (Table S9) and higher compared with EUROASPIRE [11]. For diabetic patients in Nor-COAST, approximately 30% had suboptimal control of HbA1c in total, in line with findings in ASPIRE-S.

Trend studies from the EUROASPIRE core surveys including patients with ischaemic heart disease [31] have shown adverse lifestyle trends but slightly improved control of BP and LDL-C management over time. Our study revealed only minimal improvement in BP management and a

Table 4. *Mixed model logistic regression with vascular risk factor control as dependent variable, for participants prescribed pharmacotherapy*[a]

	Blood pressure control[b]			LDL cholesterol control[c]			Glycemic control[d]		
	n	OR (95% CI)	*P*-value	*n*	OR (95% CI)	*P*-value	*n*	OR (95% CI)	*P*-value
Age, years	511	0.976 (0.959 to 0.993)	0.007	590	1.032 (1.009 to 1.056)	0.007	89	1.042 (0.956 to 1.135)	0.349
Sex, female	511	0.90 (0.63 to 1.29)	0.567	590	0.60 (0.37 to 0.98)	0.041	89	0.96 (0.18 to 5.08)	0.961
Education, years	511	1.010 (0.962 to 1.059)	0.699	590	0.987 (0.925 to 1.052)	0.680	89	1.169 (0.941 to 1.451)	0.158
Frailty[e]	511	0.98 (0.83 to 1.16)	0.817	590	1.25 (1.003 to 1.60)	0.047	89	1.42 (0.69 to 2.94)	0.341
Cognitive function[f]	509	0.94 (0.81 to 1.09)	0.420	588	1.08 (0.88 to 1.32)	0.458	89	0.54 (0.29 to 0.99)	0.048
Number of medications used	511	1.05 (0.99 to 1.12)	0.108	590	1.29 (1.18 to 1.41)	<0.001	89	0.76 (0.60 to 0.98)	0.031
Medication adherence[g]	425	0.90 (0.65 to 1.25)	0.548	448	1.31 (0.88 to 1.94)	0.183	61	1.05 (0.33 to 3.31)	0.935
Follow-up[h] at GP after discharge	395	1.04 (0.60 to 1.82)	0.888	488	0.89 (0.41 to 1.90)	0.756	64	1.28 (0.15 to 11.2)	0.826
HADS score[i]	413	1.01 (0.98 to 1.05)	0.483	440	0.99 (0.94 to 1.04	0.684	59	0.93 (0.81 to 1.08)	0.351

Abbreviations: OR, Odds ratio; CI, Confidence interval; GP, General practitioner; HADS, Hospital Anxiety and Depression Scale.
For all models (BP, LDL cholesterol and HbA1c) results are adjusted for time point as categorical covariate and patient as random effect.
[a]Pharmacological treatment with antihypertensives for BP control, lipid lowering drugs for LDL control and antidiabetic drugs for glycemic control.
[b]Blood pressure < 140/90 mmHg.
[c]LDL cholesterol < 2.0 mmol L^{-1}.
[d]HbA1c ≤ 53 mmol mol^{-1}.
[e]Fried criteria 0-5, with 0 as reference corresponding to robust, and 5 to frail.
[f]Measured by Global Deterioration Scale 1–7, with 1 as reference corresponding to normal cognitive function.
[g]Self-reported medication adherence measured by Morisky Medication Adherence Scale 4, range 0–4, with 0 as reference, corresponding to low adherence.
[h]Follow-up appointment between 0 and 3 months.
[i]HADS 0–42, with 0 as reference with increasing scores indicating increasing burden.

decline in LDL-C control in patients on pharmacotherapy from 3 to 18 months. Though we found better control of BP and LDL-C cholesterol compared with EUROASPIRE III [11] conducted between 2006 and 2008, the results are not directly comparable because clinical practice probably has improved over the last decade. The EUROASPIRE core surveys [9, 31] also reported considerable variations between European countries in both risk factor prevalence and the use of secondary preventive medication. Therefore, results are not necessarily comparable due to differences in access to healthcare facilities and follow-up routines. Scandinavian studies reporting adequacy of secondary prevention in stroke patients are lacking. A small Norwegian study exploring GPs' medical records indicates that stroke gains limited attention in the first year of follow-up [32]. A Norwegian study reporting risk factor control in patients with ischaemic heart disease found the same trends as in our study; high proportions on medication, but still unsatisfactory risk factor control [10].

Possible explanations for nonoptimal risk factor control

There are few studies exploring factors influencing risk factor control in stroke patients and existing studies focus mainly on patient-related factors influencing medication adherence [21] with diversity in study design and tools measuring adherence. Nevertheless, we consider studies exploring factors influencing risk factor control in patients with established vascular disease in general, as applicable to stroke patients. However, stroke is a heterogeneous condition affecting mainly the elderly [4], and patients and their treating physician might have several reasons to deviate from the recommended secondary preventive drugs and targets [33, 34].

We demonstrated poorer blood pressure control in the elderly compared with younger patients. However, hypertension is more prevalent in the elderly [35] and several studies document that this patient population frequently have insufficient BP control [10, 13, 35]. International guidelines are inconsistent regarding treatment thresholds for BP in older adults [6, 7, 35], but acknowledge the importance of BP lowering in older age. However, all guidelines recommend thorough monitoring of side effects and clinical judgement to determine BP targets for frail elderly with short life expectancy, when a treatment to target approach might not be beneficial. Due to controversies regarding safety (especially in patients $\geq$ 80 years) and inconsistency in guidelines, clinicians might not pursue target achievement in the oldest patients although indicated.

Our results showed poorer LDL-C control in younger patients treated with lipid-lowering drugs compared to older patients. This finding is in line with other studies [9, 13, 31] and some studies show that younger age is one of the baseline predictors for statin nonadherence and discontinuation [36], yet studies are inconsistent. Although LDL-C declines in the last decades of life, other explanations are also reasonable like lack of treatment modification when therapeutic response is inadequate [37]. A majority of the Nor-COAST patients not reaching LDL target remained on the same statin dose during follow-up. Approximately half of the patients on antihypertensives not reaching target received only one antihypertensive agent. Clinical inertia [38], meaning failure to intensify medication regimen or up-titrating doses, appears to have an impact. Possible explanations might be unawareness of indicated dose or target [38], lack of monitoring [16, 38] or an appropriate inaction as a result of good clinical judgement [33]. The GP's insight into their multimorbid and frail patients over time allows a holistic approach prioritizing other aspects like quality of life rather than striving for treatment targets resulting in a high pill burden [34].

Our study revealed sex differences in target achievement, where women gained significantly lower target achievement for LDL-C compared with men, also reported in Norwegian patients with ischaemic heart disease [10]. This finding is in agreement with other studies demonstrating sex differences in prescription and adherence [9, 31, 39], for example women are treated less aggressively than men at similar cardiovascular risk and are more prone to side effects [13, 40].

An increasing number of medications in use were associated with improved management of LDL-C and BP in our adjusted analysis. The opposite was found for HbA1c, a finding of limited generalizability due to low power in the diabetic subgroup. However, glycemic targets could have been relaxed as age and comorbidity increases [6, 41]. Multiple medications might worsen adherence [16, 30], but factors accompanying polypharmacy could also affect target achievement positively by several

mechanisms. First, patients with a high pill burden might have incorporated better medication-taking routines, for example the use of pill organizers [15, 30]. Polypharmacy related to assistance with medication administration either from home care services or next of kin or a tighter follow-up by GP [20] is another possible explanation. We thereby assume that factors related to comorbidity, assistance and follow-up from primary healthcare services are of importance. However, no significant association with an early GP follow-up appointment was demonstrated.

Strengths and limitations of the study

The main strength of this study is the multicenter design with the inclusion of a relatively large, unselected stroke population and the prospective patient inclusion with longitudinal short- and long-term follow-up covering a more up-to-date period. Most previous studies assessed risk factors at a single time-point [10-12] and/or were retrospective in design [11]. We minimized measurement bias by following patients over time with repeated clinical measurements, which also give valuable information on time trends. By reporting model-based estimates of target achievement, we reduce risk of attrition biased estimates because missing values are clearly not missing at random and we assume that these estimates lie closer to the truth. The NorCOAST population has baseline characteristics comparable to patients included in the Norwegian Stroke Registry [42], which is representative for the Norwegian stroke population. It is therefore plausible that our results are generalizable at least to Norwegian stroke patients and most likely also other stroke populations in comparable geographical regions with public health care, drug treatment reimbursed by the government and adequate systems for follow-up.

Apart from its strengths, our study also has several limitations. Information about drug-related adverse effects was not available. We found no association between medication adherence and target achievement as hypothesized, but self-reporting of medication adherence is associated with overestimation and our adherence rate is higher than in other studies [21]. It is possible that other methods for determining medication adherence, such as pharmacy registry data [16] and concentration measurement of the drugs used [43] could have found other results. However, all these methods have their specific limitations and pitfalls, and no golden standard exists. MMAS-4 is also a universal tool, not specific to secondary preventive medications, and patients can consider their overall adherence as good even though adherence to a single drug is nonoptimal. In addition, MMAS-4 is not validated in stroke patients or in the Norwegian language; however, the majority of the questions correspond to the validated Norwegian version of MMAS-8 [44]. It is also possible that patients with high adherence differ from patients with lower adherence in ways that are difficult to measure [14]. Our persistence rate is also higher compared with other studies [29, 30] and information bias due to obtainment of medication lists by interview is possible. We did not have full access to GPs' health records. GPs' might rely on repeated measurements of treatment targets, and it is possible that the GPs' already make treatment decisions that are more in line with an individual patient's risks and benefits. Our study did not allow insight into qualitative aspects like beliefs regarding medications. Detailed information about postdischarge rehabilitation is also lacking. Our findings are limited by small sample size in the diabetic subgroup which provides limited generalizability and results should be interpreted with caution. At last, identifying independent factors for target achievement is difficult, with a high degree of collinearity and complexity like the interplay between different aetiological factors, lifestyle habits and medication adherence. Analysing a heterogeneous condition like ischaemic stroke makes a straightforward understanding of the importance of various factors even more complicated.

Clinical implications and conclusions

First, secondary prevention after stroke is suboptimal in clinical practice, also in this descriptive overview from Norway and there is a potential for improvement. Secondly, we need to regularly evaluate achievement of treatment targets and medication adherence in clinical practice and prescribe adequate medications and doses or alternative drugs if side effects appear [17]. Thirdly, although many of the factors we address as associated with risk factor control are not modifiable, like age and sex, they identify groups at risk of not achieving risk management targets.

Causes of nonoptimal risk factor control in stroke patients are multifactorial and include factors related to patients, providers and the healthcare system [16]. To recognize challenges in providing

optimal secondary prevention and enhance future treatment of stroke patients, we need longitudinal studies exploring barriers in follow-up routines in primary health care and transition routines from hospital to primary care. We believe that precise transition routines describing treatment targets and recommended frequency of follow-up are essential.

Stroke patients are heterogeneous and the guideline-defined target might not be the ultimate marker of successful treatment for all. However, identification of those with net benefit from a treat to target approach is of importance. Given the complex nature of risk factor control and nonadherence, it might be useful to implement a more structured and multidisciplinary approach for these patients. Multidisciplinary approach monitoring risk factor control in patients with ischaemic heart disease has been established [45] and could also be applicable to stroke patients [45, 46].

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Conflicts of interest

The authors declare they have no competing interests. ABK and IS have been investigators in the drug trial Boehringer-Ingelheim 1346.0023, and ABK has also been an investigator for Roche BN29553.

Author Contribution

Mari Nordbø Gynnild: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Investigation (equal); Visualization (lead); Writing-original draft (lead). **Rachel Aakerøy:** Writing-original draft (supporting); Writing-review & editing (equal). **Olav Spigset:** Writing-original draft (supporting); Writing-review & editing (equal). **Torunn Askim:** Writing-review & editing (equal). **Mona Kristiansen Beyer:** Writing-review & editing (equal). **Ragnhild Munthe-Kaas:** Resources (equal); Writing-review & editing (equal). **Hege Ihle-Hansen:** Resources (equal); Writing-review & editing (equal). **Anne-Brita Knapskog:** Writing-review & editing (equal). **Stian Lydersen:** Formal analysis (supporting); Methodology (equal); Writing-review & editing (equal). **Halvor Næss:** Resources (equal); Writing-review & editing (equal). **Tove Røsstad:** Writing-review & editing (equal). **Yngve Seljeseth:** Resources (equal); Writing-review & editing (equal). **Pernille Thingstad:** Data curation (equal); Writing-review & editing (equal). **Ingvild Saltvedt:** Conceptualization (equal); Funding acquisition (lead); Investigation (lead); Project administration (lead); Writing-review & editing (equal). **Hanne Ellekjær:** Conceptualization (lead); Funding acquisition (lead); Resources (equal); Writing-original draft (supporting); Writing-review & editing (lead).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Attrition analysis for the study population included at baseline (n = 664)

Table S2. Proportion achieving vascular risk factor control at hospital stay, 3 months and 18 months for all patients and patients over and under 75 years with available follow-up data, n/N (%).

Table S3. Association between LDL control / LDL cholesterol (LDL-C) level as dependent variables and statin intensity as continuous independent variable for patients prescribed statins at discharge with available follow-up data.

Table S4. Mixed model logistic regression with vascular risk factor control as dependent variable, for participants prescribed pharmacotherapy. Adjusted for age, sex and education.

Table S5. Sensitivity analysis excluding participants with only baseline assessments in model based descriptive analysis.

Table S6. Mixed model linear regression with systolic blood pressure and LDL cholesterol as continuous dependent variables, for participants prescribed pharmacotherapya.

Table S7. Mixed model linear regression with systolic blood pressure and LDL cholesterol as continuous dependent variables, for participants prescribed pharmacotherapya. Adjusted for age, sex and education.

Table S8. Subgroup analysis. Mixed model logistic regression for vascular risk factor control for participants over and under 75 years on pharmacotherapy.

Table S9. Proportion achieving BP < 150/90 mmHg and LDL < 2.5 mmol/L 3 months and 18 months for all patients and patients over and under 75 years with available follow-up data, n/N (%).

Supplementary Paper I

SUPPLEMENTARY DATA:

"Vascular risk factor control and adherence to secondary preventive medication after ischemic stroke"

Supplementary methods:

Frailty assessment

Frailty was assessed using a modified version of the Fried Criteria where 0 criteria present corresponds to robust / non-frail, 1-2 criteria present corresponds to prefrail and 3-5 criteria present corresponds to frail. We used three premorbid components; weight loss, low physical activity level and exhaustion, and two post-stroke components; slow gait speed and low grip strength.

Supplementary methods 1. Frailty assessment.

Component	Assessment method	Criteria for 1 point
Weight loss	Self-report questionnaire	Unintentional weight loss the last 6 months
Low physical activity	Self-report questionnaire	Physical activities less than once a week
Exhaustion	Self-report questionnaire	Constantly fatigued for more than one week before the index stroke
Slow gait speed	Gait test, 4 meters	Duration ≥ 6 seconds or not able
Weak grip strength	Jamar dynamometer	Best measure on strongest hand. Definition: Limits by Fried et al.[a] or not able.

BMI: Body mass index. [a]Women: BMI ≤ 23.0 or missing BMI, ≤ 17 kg; BMI 23.1 – 26.0, ≤ 17.3 kg; BMI 26.1 – 29.0, ≤ 18.0 kg; BMI > 29.0, ≤ 21.0 kg. Men: BMI ≤ 24.0 or missing BMI, ≤ 29.0 kg; BMI 24.1 – 28.0, ≤ 30.0 kg; BMI > 28, ≤ 32.0 kg.

Supplementary tables:

Table S1. Attrition analysis for the study population included at baseline (n = 664)

	Total (n = 664)	3 months			18 months		
		Still in follow-up (n = 594)	Lost to follow-up (n = 70)	p-value	Still in follow-up (n = 522)	Lost to follow-up (n = 142)	p-value
Age, years	72.9 (11.5)	72.4 (11.4)	77.1 (11.0)	0.001	71.8 (11.3)	77 (11.4)	<0.001
Sex, female	287 (43%)	248 (42%)	39 (55%)	0.026	220 (42%)	67 (47%)	0.283
Education, years	12.1 (3.7)	12.2 (3.7)	10.5 (3.0)	<0.001	12.4 (3.8)	11 (3.3)	<0.001
Living alone	235 (35%)	193 (33%)	42 (60%)	<0.001	162 (31%)	73 (51%)	<0.001
Current or previous smoker	376 (57%)	456 (43%)	32 (46%)	0.676	236 (45%)	52 (37%)	0.067
BMI	26.1 (4.2)	26.1 (4.2)	26.7 (4.3)	0.236	26.3 (4.0)	25.7 (4.7)	0.169
Physically active[a]	145 (22%)	139 (23%)	6 (9%)	0.005	126 (24%)	19 (13%)	0.006
Charlson Comorbidity Index	4.1 (2.0)	4.0 (2.0)	4.7 (2.2)	0.003	3.9 (2.0)	4.7 (2.2)	<0.001
Normal cognitive function, prestroke[b]	573 (87%)	522 (89%)	51 (76%)	0.010	466 (90%)	107 (77%)	<0.001
NIHSS, admission	3.9 (4.9)	3.6 (4.6)	6.1 (6.9)	0.002	3.7 (4.6)	4.8 (5.8)	0.019
Modified Rankin Scale, discharge	2.1 (1.27)	2.00 (1.3)	2.5 (1.3)	0.002	2.0 (1.3)	2.5 (1.3)	<0.001
Baseline systolic blood pressure (mmHg)	142 (20)	141 (20)	146 (20)	0.032	141 (20)	142 (20)	0.880
Baseline LDL cholesterol (mmol/L)	3.03 (1.10)	3.02 (1.09)	3.12 (1.03)	0.491	3.06 (1.12)	2.92 (0.96)	0.192
Baseline HbA1c (mmol/mol)[c]	56.6 (18.0)	56.6 (17.2)	56.4 (24.2)	0.962	57.4 (18)	54.2 (18.2)	0.386

Numbers are mean (SD) or n (%). Two-sample t-test for continuous variables and chi-square test for categorical variables. [a]Self-reported adherence to physical activity guidelines defined as minimum 75 minutes per week of high-intensity exercise or minimum 150 minutes per week of moderate intensity exercise [b]*Cognitive function measured by Global Deterioration Scale (GDS), normal defined as GDS 1 or 2.* [c]*In patients with diabetes mellitus (n=125). Abbreviations: BMI; Body Mass Index, NIHSS; National Institutes of Health Stroke Scale, LDL; Low density lipoprotein, HbA1c; Hemoglobin A1c.*

Table S2. Proportion achieving vascular risk factor control at hospital stay, 3 months and 18 months for all patients and patients over and under 75 years with available follow-up data, n/N (%)

	All	Patients prescribed pharmacotherapy[e]	No pharmacotherapy
Hospital stay			
Blood pressure control[a]	**277 / 622 (44%)**	**158 / 435[f] (36%)**	**119 / 187 (64%)**
< 75 y	153 / 310 (49%)	76/ 204 (37%)	77 / 106 (73%)
≥ 75 y	124 / 312 (40%)	82 / 231 (36%)	42 / 81 (52%)
LDL cholesterol control[b]	**119 / 645 (18%)**	**100 / 556[g] (18%)**	**19 / 89 (21%)**
< 75 y	53 / 327 (16%)	43 / 292 (15%)	10 / 35 (29%)
≥ 75 y	66 / 318 (21%)	57 / 264 (22%)	9 / 54 (17%)
Glycemic control[c+d]	**66 / 125 (53%)**	**29 / 83[h] (35%)**	**37 / 42 (88%)**
< 75 y	35 / 65 (54%)	14 / 43 (33%)	21 / 22 (95%)
≥ 75 y	31 / 60 (52%)	15 / 40 (38%)	16 / 20 (80%)
3 months			
Blood pressure control	**234 / 535 (44%)**	**163 / 387 (42%)**	**71 / 148 (48%)**
< 75 y	146 / 291 (50%)	96 / 203 (47%)	50 / 88 (57%)
≥ 75 y	88 / 244 (36%)	67 / 184 (36%)	21 / 60 (35%)
LDL cholesterol control	**231 / 476 (49%)**	**222 / 414 (54%)**	**9 / 62 (15%)**
< 75 y	127 / 267 (48%)	121 / 243 (50%)	6 / 24 (25%)
≥ 75 y	104 / 209 (50%)	101 / 171 (59%)	3 / 38 (8%)
Glycemic control	**53 / 88 (60%)**	**24 / 56 (43%)**	**29 / 32 (91%)**
< 75 y	32 / 55 (58%)	12 / 33 (36%)	20 / 22 (91%)
≥ 75 y	21 / 33 (64%)	12 / 23 (52%)	9 / 10 (90%)
18 months			
Blood pressure control	**211 / 440 (48%)**	**147 / 326 (45%)**	**64 / 114 (56%)**
< 75 y	142 / 263 (54%)	95 / 191 (50%)	47 / 72 (65%)
≥ 75 y	69 / 177 (39%)	52 / 135 (38%)	17 / 42 (41%)
LDL cholesterol control	**170 / 365 (47%)**	**158 / 305 (52%)**	**12 / 60 (20%)**
< 75 y	100 / 215 (47%)	93 / 188 (50%)	7 / 27 (26%)
≥ 75 y	70 / 150 (47%)	65 / 117 (56%)	5 / 33 (15%)
Glycemic control	**33 / 56 (59%)**	**16 / 35 (46%)**	**17 / 20 (85%)**
< 75 y	24 / 36 (67%)	12 / 23 (52%)	12 / 13 (92%)
≥ 75 y	9 / 20 (45%)	4 / 12 (33%)	5 / 7 (71%)

[a]Blood pressure < 140/90 mmHg, [b]LDL cholesterol < 2.0 mmol/L, [c]HbA1c ≤ 53 mmol/mol. [d]For patients with diabetes mellitus (DM), defined as using blood glucose lowering drugs at admission or discharge, HbA1c ≥ 48 mmol / mol at admission, or self-report of diet-regulated DM. [e]At time of assessment; For blood pressure control; on antihypertensives, for LDL cholesterol control; on lipid lowering drugs, for glycemic control; on antidiabetic medication. [f]78% where on therapy prestroke. [g]39% where on therapy prestroke, [h]86% where on therapy prestroke. Abbreviations: y; years, LDL; Low density lipoprotein, HbA1c; Hemoglobin A1c.

Table S3. Association between LDL control / LDL cholesterol (LDL-C) level as dependent variables and statin intensity as continuous independent variable for patients prescribed statins at discharge with available follow-up data

	LDL control (< 2.0 mmol/L)					
		3 months			**18 months**	
	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value
Statin intensity[a] (per mg)	425	1.002 (0.992 to 1.011)	0.736	331	1.006 (0.996 to 1.016)	0.224
	LDL-C level (mmol/L)					
		3 months			**18 months**	
	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
Statin intensity[a] (per mg)	425	-0.003 (-0.006 to -0.0002)	0.033	331	-0.006 (-0.010 to -0.002)	0.003

[a]Statin intensity per mg atorvastatin equivalent dose with 0 mg as reference. We used the DDD ("Defined Daily Doses") defined by the World Health Organization (WHO) to convert all statin doses to atorvastatin equivalent doses by the formula: (Dose of "other statin" / DDD for "other statin") x DDD for atorvastatin. Abbreviations: LDL; Low density lipoprotein. OR; Odds ratio. CI; Confidence interval.

Supplementary table S4. Mixed model logistic regression with vascular risk factor control as dependent variable, for participants prescribed pharmacotherapy[*]. Adjusted for age, sex and education.

	Blood pressure control[a]			LDL cholesterol control[b]			Glycemic control[c]		
	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value	N	OR (95% CI)	p-value
Frailty[d]	511	1.08 (0.90 to 1.31)	0.405	590	1.27 (0.98 to 1.64)	0.072	89	1.60 (0.70 to 3.61)	0.263
Cognitive function[e]	509	1.00 (0.85 to 1.17)	0.984	588	1.00 (0.81 to 1.23)	0.997	89	0.54 (0.28 to 1.04)	0.063
Number of medications used	511	1.07 (1.00 to 1.15)	0.037	590	1.30 (1.18 to 1.42)	<0.001	89	0.75 (0.59 to 0.97)	0.027
Medication adherence[f]	425	0.92 (0.66 to 1.27)	0.613	448	1.28 (0.86 to 1.90)	0.222	61	1.08 (0.35 to 3.33)	0.890
Follow-up[g] at GP after discharge	395	1.01 (0.58 to 1.75)	0.979	446	1.03 (0.48 to 2.21)	0.937	70	1.10 (0.13 to 9.32)	0.930
HADS score[h]	413	1.01 (0.98 to 1.05)	0.500	440	1.00 (0.95 to 1.05)	0.902	59	0.94 (0.81 to 1.09)	0.397

For all models (BP, LDL cholesterol and HbA1c) results are adjusted for age, sex, education, time point as categorical covariate and patient as random effect. [*]Pharmacological treatment with antihypertensives for BP control, lipid lowering drugs for LDL control and antidiabetic drugs for glycemic control. [a]Blood pressure < 140/90 mmHg, [b]LDL cholesterol < 2.0 mmol/L, [c]HbA1c ≤ 53 mmol/mol. [d]Fried criteria 0-5, with 0 as reference corresponding to robust, and 5 to frail. [e]Measured by Global Deterioration Scale 1 – 7, with 1 as reference corresponding to normal cognitive function. [f]Self-reported medication adherence measured by Morisky Medication Adherence Scale 4, with range 0-4, and as reference, corresponding to low adherence.. [g]Follow-up appointment between 0-3 months. [h]Hospital Anxiety and Depression Scale 0 – 42, with 0 as reference with increasing scores indicating increasing burden. Abbreviations: OR; Odds ratio, CI; Confidence interval, GP; General practitioner. HADS; Hospital Anxiety and Depression Scale.

Supplementary table S5. Sensitivity analysis excluding participants with only baseline assessments* in model based descriptive analysis

	All patients			Patients with prescribed pharmacotherapy		
Hospital stay	**n**	**Probability, %**	**95% CI**	**n**	**Probability, %**	**95% CI**
Blood pressure control[a]	593	43.2 %	37.7 to 48.8	423	33.6 %	28.2 to 39.4
LDL cholesterol control[b]	545	9.1 %	6.3 to 13.0	481	8.1 %	5.3 to 12.1
Glycemic control[c+d]	111	55.0 %	34.0 to 74.4	77	27.4 %	12.3 to 50.5
3 months						
Blood pressure control	506	40.8 %	35.2 to 46.8	375	38.0 %	32.1 to 44.3
LDL cholesterol control	376	49.3 %	42.0 to 56.5	339	55.2 %	47.2 to 62.9
Glycemic control	75	68.7 %	45.6 to 85.2	50	37.9 %	17.6 to 63.5
18 months						
Blood pressure control	411	47.1 %	40.8 to 53.6	314	43.7 %	37.0 to 50.7
LDL cholesterol control	265	44.5 %	37.5 to 53.7	230	50.3 %	41.6 to 59.0
Glycemic control	42	68.9 %	41.9 to 87.2	29	49.7 %	22.5 to 77.0

*Based on mixed model logistic regression with time point as categorical covariate and patient as random effect. *Only baseline assessment and no pharmacological treatment at admission for blood pressure (n = 29), for LDL cholesterol (n = 100) and HbA1c (n = 14), corresponding numbers for analyses of patients on pharmacotherapy; Blood pressure (n=12), LDL cholesterol (n= 75) and HbA1c (n=6). [a]Blood pressure < 140/90 mmHg, [b]LDL cholesterol < 2.0 mmol/L, [c]HbA1c ≤ 53 mmol/mol. [d]For patients with diabetes mellitus (DM), defined as using blood glucose lowering drugs at admission or discharge or HbA1c ≥48 mmol/mol at admission or self-report of diet-regulated DM.*

Supplementary table S6. Mixed model linear regression with systolic blood pressure and LDL cholesterol as continuous dependent variables, for participants prescribed pharmacotherapy[a].

	Systolic blood pressure (mmHg)				LDL cholesterol (mmol/L)			
	n	**Coefficient**	**95% CI**	**p-value**	**n**	**Coefficient**	**95% CI**	**p-value**
Age, years	511	0.31	0.18 to 0.44	<0.001	590	-0.01	-0.02 to -0.01	<0.001
Sex, female	511	2.91	0.22 to 5.59	0.034	590	0.20	0.08 to 0.33	0.001
Education, years	511	-0.07	-0.43 to 0.29	0.697	590	0.01	-0.01 to 0.03	0.220
Frailty[b]	511	0.44	-0.83 to 1.71	0.497	590	-0.05	-0.11 to 0.01	0.114
Cognitive function[c]	509	1.25	0.20 to 2.30	0.020	588	-0.03	-0.08 to 0.03	0.326
Number of medications used	511	-0.39	-0.85 to 0.06	0.092	590	-0.08	-0.10 to -0.06	<0.001
Medication adherence[d]	425	1.00	-0.95 to 2.94	0.317	448	-0.08	-0.15 to -0.10	0.025
Follow-up[e] at GP after discharge	395	1.76	-2.34 to 5.86	0.400	446	0.05	-0.15 to 0.25	0.600
HADS score[f]	413	-0.02	-0.25 to 0.22	0.888	440	0.003	-0.01 to 0.01	0.551

Results are adjusted for time point as categorical covariate and patient as random effect. [a]Pharmacological treatment with antihypertensives for BP control, lipid lowering drugs for LDL-C control. [b]Fried criteria 0-5, with 0 as reference corresponding to robust, and 5 to frail. [c]Measured by Global Deterioration Scale 1 – 7, with 1 as reference corresponding to normal cognitive function. [d]Self-reported medication adherence measured by Morisky Medication Adherence Scale 4 (0-4), with 0 corresponding to low adherence as reference. [e]Follow-up appointment between 0-3 months.[f]Hospital Anxiety and Depression Scale 0 – 42, with 0 as reference with increasing scores indicating increasing burden. Abbreviations: OR; Odds ratio, CI; Confidence interval, GP; General practitioner.

Supplementary table S7. Mixed model linear regression with systolic blood pressure and LDL cholesterol as continuous dependent variables, for participants prescribed pharmacotherapy[a]. Adjusted for age, sex and education.

	Systolic blood pressure (mmHg)				LDL cholesterol (mmol/L)			
	n	**Coefficient**	**95% CI**	**p-value**	**n**	**Coefficient**	**95% CI**	**p-value**
Frailty[b]	511	-0.91	-2.28 to 0.45	0.190	590	-0.04	-0.10 to 0.03	0.251
Cognitive function[c]	509	0.70	-0.42 to 1.81	0.222	588	0.003	-0.05 to 0.06	0.907
Number of medications used	511	-0.62	-1.08 to -0.17	0.009	588	-0.08	-0.10 to -0.06	<0.001
Medication adherence[d]	425	0.85	-1.07 to 2.77	0.383	448	-0.08	-0.15 to -0.004	0.040
Follow-up[e] at GP after discharge	395	1.88	-2.11 to 5.87	0.355	446	-0.02	-0.02 to 0.18	0.883
HADS score[f]	413	-0.04	-0.27 to 0.19	0.747	440	0.002	-0.01 to 0.01	0.744

Results are adjusted for age, sex, education, time point as categorical covariate and patient as random effect. [a]Pharmacological treatment with antihypertensives for BP control, lipid lowering drugs for LDL-C control. [b]Fried criteria 0-5, with 0 as reference corresponding to robust, and 5 to frail. [c]Measured by Global Deterioration Scale 1 – 7, with 1 as reference corresponding to normal cognitive function. [d]Self-reported medication adherence measured by Morisky Medication Adherence Scale 4, with 0 corresponding to low adherence as reference. [e]Follow-up appointment between 0-3 months.[f]Hospital Anxiety and Depression Scale 0 – 42, with 0 as reference with increasing scores indicating increasing burden. Abbreviations: OR; Odds ratio, CI; Confidence interval, GP; General practitioner.

Table S8. Subgroup analysis. Mixed model logistic regression for vascular risk factor control for participants over and under 75 years on pharmacotherapy*

	Blood pressure control[a]						LDL cholesterol control[b]					
	< 75 years (n = 253)			≥ 75 years (n = 268)			< 75 years (n = 315)			≥ 75 years (n = 277)		
	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value
Sex, female	249	1.58 (0.90 to 2.76)	0.109	262	0.63 (0.39 to 1.01)	0.053	314	0.58 (0.30 to 1.13)	0.108	276	0.49 (0.23 to 1.03)	0.061
Education, years	249	0.98 (0.91 to 1.05)	0.516	262	1.03 (0.96 to 1.10)	0.437	314	0.98 (0.90 to 1.06)	0.571	276	1.04 (0.94 to 1.16)	0.460
Frailty	249	1.19 (0.88 to 1.60)	0.259	262	0.95 (0.76 to 1.16)	0.613	314	1.21 (0.85 to 1.72)	0.293	276	1.16 (0.83 to 1.64)	0.381
Cognitive function[c]	248	1.11 (0.86 to 1.43)	0.413	261	0.92 (0.76 to 1.12)	0.408	312	0.93 (0.68 to 1.27)	0.641	276	1.08 (0.81 to 1.43)	0.611
Number of medications used	249	1.07 (0.97 to 1.18)	0.160	262	1.06 (0.97 to 1.15)	0.218	314	1.19 (1.06 to 1.33)	0.004	276	1.41 (1.21 to 1.64)	<0.001
Medication adherence[d]	223	0.95 (0.62 to 1.46)	0.816	202	0.87 (0.52 to 1.43)	0.570	255	1.38 (0.84 to 2.27)	0.198	193	1.21 (0.63 to 2.32)	0.577
Follow-up[e] at GP after discharge	200	1.59 (0.72 to 3.52)	0.251	195	0.68 (0.32 to 1.48)	0.336	242	0.92 (0.34 to 2.46)	0.867	204	0.85 (0.26 to 2.79)	0.794
HADS score[f]	218	1.00 (0.96 to 1.05)	0.898	195	1.04 (0.97 to 1.10)	0.274	254	0.95 (0.90 to 1.02)	0.154	186	1.06 (0.96 to 1.17)	0.246

*For both models results are adjusted time point as categorical covariate, patient as random effect. Results are reported as odds ratio (95% confidence interval). *Pharmacological treatment with antihypertensives for blood pressure control, statins for LDL control and antidiabetic drugs for glycemic control. [a]Blood pressure < 140/90 mmHg, [b]LDL cholesterol < 2.0 mmol/L. [c]Measured by Global Deterioration Scale. [d]Self-reported medication adherence measured by Morisky Medication Adherence Scale 4, with range 0-4, and 0as reference, corresponding to low adherence. [e]Follow-up appointment between 0-3 months. [f]Hospital Anxiety and Depression Scale 0 – 42, with 0 as reference with increasing scores indicating increasing burden. Abbreviations: OR; Odds ratio, CI; Confidence interval, GP; General practitioner, LDL; Low density lipoprotein.*

Supplementary table S9. Proportion achieving BP < 150/90 mmHg and LDL < 2.5 mmol/L 3 months and 18 months for all patients and patients over and under 75 years with available follow-up data, n/N (%)

	All	Patients prescribed pharmacotherapy*	No pharmacotherapy
3 months			
Blood pressure control	**313 / 535 (59%)**	**198 / 337 (59%)**	**73 / 127 (58%)**
< 75 y	180 / 291 (62%)	114 / 183 (62%)	49 / 80 (61%)
≥ 75 y	133 / 244 (55%)	84 / 154 (55%)	24 / 47 (51%)
LDL cholesterol control	**355 / 476 (75%)**	**300 / 366 (82%)**	**14 / 51 (28%)**
< 75 y	203 / 267 (76%)	179 / 223 (80%)	5 / 21 (24%)
≥ 75 y	152 / 209 (73%)	121 / 143 (85%)	9 / 30 (30%)
18 months			
Blood pressure control	**270 / 440 (61%)**	**195 / 326 (60%)**	**75 / 114 (66%)**
< 75 y	175 / 263 (67%)	120 / 191 (63%)	55 / 72 (76%)
≥ 75 y	95 / 177 (54%)	75 / 135 (56%)	20 / 42 (48%)
LDL cholesterol control	**266 / 365 (73%)**	**243 / 305 (80%)**	**23 / 60 (38%)**
< 75 y	156 / 215 (73%)	144 / 188 (77%)	12 / 27 (44%)
≥ 75 y	110 / 150 (73%)	99 / 117 (85%)	11 / 33 (33%)

*[a]Blood pressure < 150/90 mmHg, [b]LDL cholesterol < 2.5 mmol/L *For blood pressure control; on antihypertensives, for LDL cholesterol control; on lipid lowering drugs Abbreviations: y; years.*

Paper II

Clinical Epidemiology

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ORIGINAL RESEARCH

Risk Stratification in Patients with Ischemic Stroke and Residual Cardiovascular Risk with Current Secondary Prevention

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Purpose: Suboptimal secondary prevention in patients with stroke causes a remaining cardiovascular risk desirable to reduce. We have validated a prognostic model for secondary preventive settings and estimated future cardiovascular risk and theoretical benefit of reaching guideline recommended risk factor targets.

Patients and Methods: The SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model for 10-year and lifetime risk of cardiovascular events was applied to 465 patients in the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study, a multicenter observational study with two-year follow-up by linkage to national registries for cardiovascular disease and mortality. The residual risk when reaching recommended targets for blood pressure, low-density lipoprotein cholesterol, smoking cessation and antithrombotics was estimated.

Results: In total, 11.2% had a new event. Calibration plots showed adequate agreement between estimated and observed 2-year prognosis (C-statistics 0.63, 95% confidence interval 0.55–0.71). Median estimated 10-year risk of recurrent cardiovascular events was 42% (Interquartile range (IQR) 32–54%) and could be reduced to 32% by optimal guideline-based therapy. The corresponding numbers for lifetime risk were 70% (IQR 63–76%) and 61%. We estimated an overall median gain of 1.4 (IQR 0.2–3.4) event-free life years if guideline targets were met.

Conclusion: Secondary prevention was suboptimal and residual risk remains elevated even after optimization according to current guidelines. Considerable interindividual variation in risk exists, with a corresponding variation in benefit from intensification of treatment. The SMART-REACH model can be used to identify patients with the largest benefit from more intensive treatment and follow-up.

Keywords: secondary prevention, ischemic stroke, risk factors, risk assessment, risks and benefits, cardiovascular diseases

Introduction

Patients with ischemic stroke have an increased risk of recurrent cardiovascular events.[1] Secondary prevention aims to reduce the risk of recurrence, but implementation of guideline recommendations in clinical practice is suboptimal with poor risk factor control and low adherence to medications.[2–5] Consequently, the residual cardiovascular risk remains elevated. However, there is a substantial interindividual variation in the risk of recurrent events among patients with established cardiovascular disease (CVD).[6–8] This variation results from a composite of several prognostic features like age, genetics, cardiovascular risk factors, effectiveness of preventive

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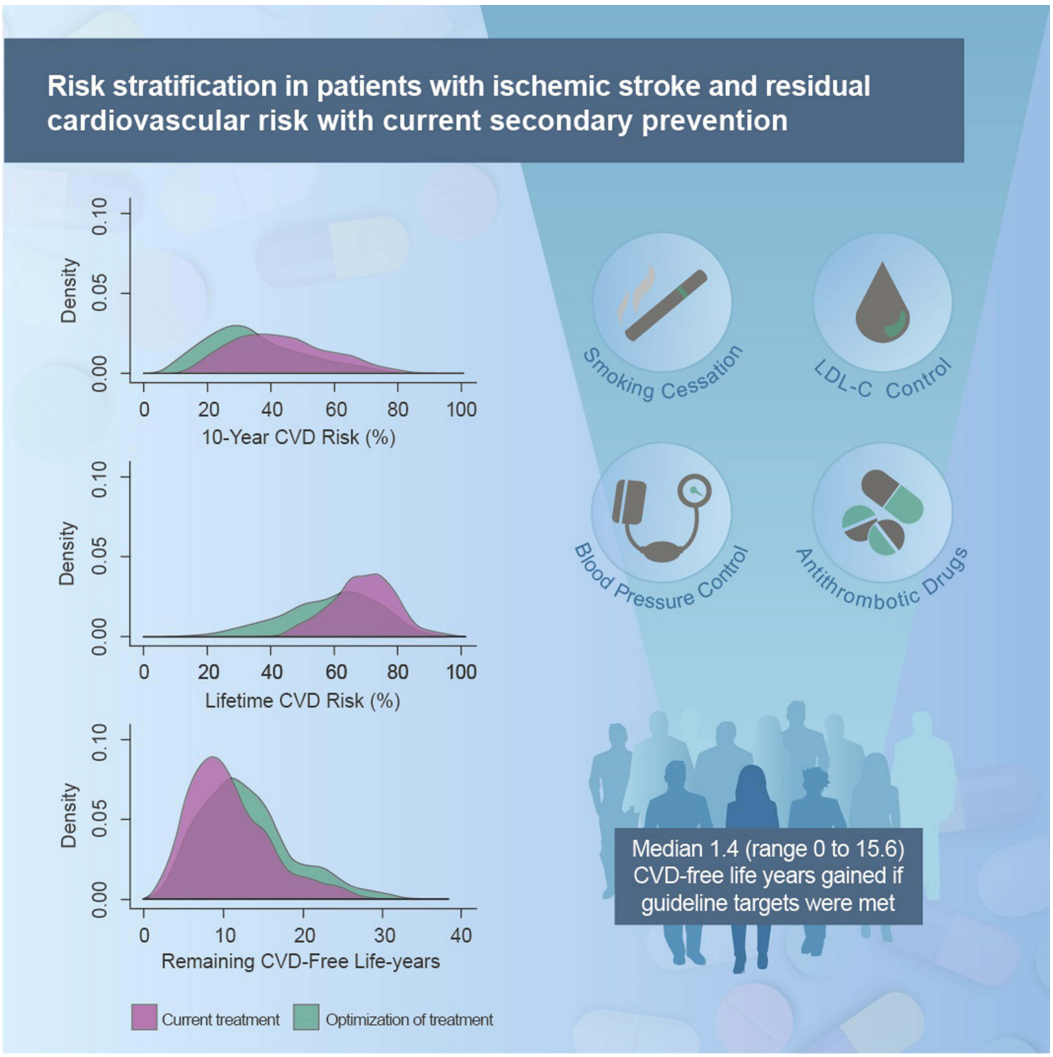
Graphical Abstract



therapy, competing risks and remaining life-expectancy.[6,9,10] Appropriate identification of patients at high risk is important because they most likely gain greatest clinical benefit from intensive treatment of cardiovascular risk factors, novel therapies on top of standard treatment[9,11,12] and a more intensive and multidisciplinary follow-up.

Patients with stroke are heterogeneous and systemic atherosclerotic disease and overlapping stroke etiologies are common.[13–15] Existing risk stratification tools for stroke patients often focus on short-time risk of recurrent stroke,[16–18] while recent long-term follow-up studies have shown that risk of a fatal recurrent stroke and a fatal cardiac

event is similar.[1] The SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model[19] is a previously derived, externally validated model estimating individual residual 10-year risk and lifetime risk for recurrent stroke, myocardial infarction and vascular death. The model is intended for use in all patients with clinically manifest atherosclerotic vascular disease and may be useful in routine clinical stroke care. However, it is unknown if this model gives reliable prognostic risk information in a stroke population. Our aim is to estimate future cardiovascular risk using the SMART-REACH model for secondary preventive settings after first validating the model in a stroke cohort. Furthermore, we aim to estimate the theoretical benefit of reaching guideline-recommended risk factor targets.

Materials and Methods

Study Population

We included 729 home-dwelling patients admitted with acute ischemic stroke in the Nor-COAST (Norwegian Cognitive Impairment After Stroke) Study, a multicenter, prospective cohort study consecutively including patients at five Norwegian stroke units from May 2015 to March 2017. Details have been reported previously.[2,20]

Follow-up for the current substudy started at 3 months poststroke and patients who died before the scheduled 3-month visit (n = 28) were excluded. Since patients expected to have difficulties returning for follow-up visits and patients not independent in daily activities were excluded in the original SMART-REACH derivation and validation cohorts[19] and the model is intended for patients with stable vascular disease in which additional preventive therapy is considered, we excluded patients living in nursing homes (n = 36). As the SMART-REACH model was derived in patients aged 45 to 80 years, patients outside this age range were excluded, leaving 465 patients eligible for analysis (Figure 1). Patients were assessed with self-report questionnaires, clinical assessments and blood sampling 3 months poststroke at the outpatient clinic. Patients unable to attend were assessed by telephone or by proxy information. The Regional Committee for Medical and Health Research Ethics in North Norway (REC numbers 2015/171 and 2017/1462) approved the study. All participants gave their written informed consent before inclusion or by proxy if unable. This study was conducted in accordance with the Declaration of Helsinki.

Outcomes

We defined recurrent cardiovascular events as stroke, myocardial infarction (MI) or cardiovascular death, whichever

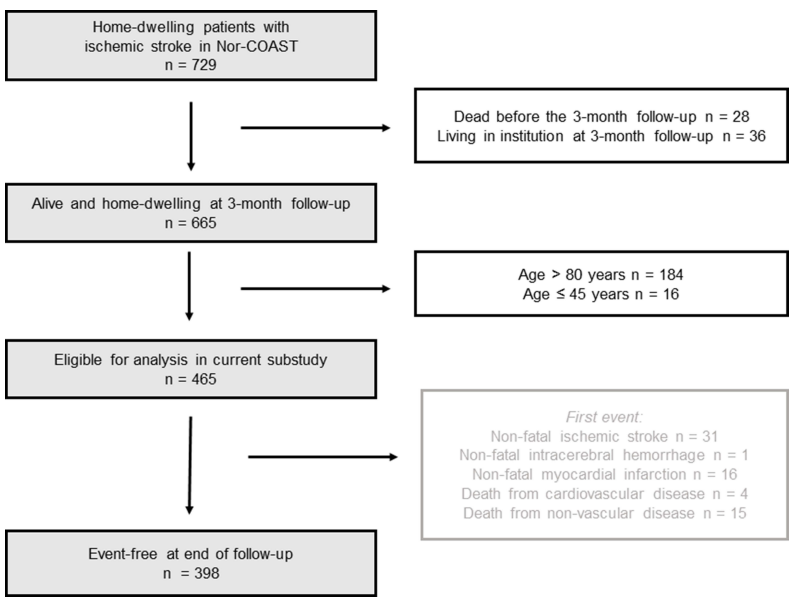


Figure 1 Flowchart of inclusion and exclusion of patients.

occurred first. All hospitalized events from 3 months post-stroke (stable phase) to 31 December 2018 were identified by linkage to the Norwegian Stroke Registry and the Norwegian Cardiovascular Disease Registry. The Norwegian Causes of Death Registry provided follow-up information on the primary cause of death.

We defined recurrent stroke as either registration in the Norwegian Stroke Registry or the Norwegian Cardiovascular Disease Registry (main diagnosis)[21] according to the International Classification of Diseases, 10th revision (ICD-10); I61, I63 and I64. Admission with main or secondary diagnosis of MI (ICD-10; I21, I22 and I24) according to the Norwegian Cardiovascular Disease Registry was defined as subsequent MI.[22] Cardiovascular death was defined as ICD-code I00-I99 registered as the primary cause of death or death within 28 days after a recurrent stroke or MI. The quality of the information in the registries has been described previously[21,22] (Supplementary Methods).

Residual Cardiovascular Risk

The SMART-REACH model[19] was used to predict residual cardiovascular risk after initial treatment. The model is a Fine and Gray competing risk model for 10-year and lifetime predictions of cardiovascular events (non-fatal stroke, non-fatal MI and CVD mortality) and non-cardiovascular mortality, where age is used as the underlying time function.[9,19] The model uses the following predictors: age, sex, current smoking, diabetes mellitus, history of heart failure, history of atrial fibrillation, systolic blood pressure (BP), serum creatinine concentration, number of locations of CVD (cerebrovascular, coronary and peripheral artery disease) and total and low-density lipoprotein cholesterol (LDL-C). Risks were estimated based on clinical measurements at the 3-month visit since the model is intended for patients with stable CVD in which additional therapy is considered. This timepoint also roughly corresponds to the guideline recommendations to examine risk factors and initiate or modify treatment at 1–3 months after an acute event.[23] Table S1 shows detailed definitions of all variables included in the SMART-REACH model and more information about the SMART-REACH model can be found in Supplementary Methods.

External Validation

The external validity of the SMART-REACH model was assessed for risks at 2 years of follow-up. We expressed discrimination (the extent to which patients who develop an event also had higher estimated risk than those who were event-free) with Harrell's C-statistic.[24] We showed the agreement between predicted and observed 2-year risk (calibration) in a flexible calibration curve based on local polynomial regression fitting (loess function in R).[25] First, the cohort was divided into 100 quantiles of predicted risk. Then, a local regression was used to smoothly explain the observed cumulative incidence per group by the mean predicted risk per group. The smooth calibration plot and confidence bounds were subsequently predicted from this model over the whole range of relevant predicted risks (cohort predicted risk quantile 0.025 up to 0.975). As event rates vary between geographic locations[8,26] and may be influenced by the selection of study participants, recalibration to the population of interest is often necessary.[6,19,25] The intercept of the SMART-REACH model for both CVD events and non-CVD mortality was recalibrated ("calibration-in-the-large") to Nor-COAST by subtracting the expected–observed ratio from the linear predictor (Supplementary Methods).[25,27]

Impact of Optimization of Risk Factors

Reaching the recommended targets according to Norwegian guidelines[23] for systolic BP (≤140 mmHg), LDL-C (≤1.8 mmol/L), smoking cessation and use of antithrombotic agents were defined as optimization of risk factor control and possible benefits if each risk factor was controlled was quantified by the SMART-REACH model.

The relative effect of treating risk factors to recommended targets was retrieved from meta-analyses[28–30] (details described in Table S2) and combined with the competing risk-adjusted Cox proportional hazard function from the SMART-REACH model according to previously described methods.[9,10,19] A hazard ratio (HR) of 0.80 was assumed per 10 mmHg reduction in systolic BP[29] and an HR of 0.78 was assumed per 1.0 mmol/L reduction in LDL-C[28] regardless of whether this was achieved by lifestyle changes or medication. Smoking cessation was assumed to reduce the risk of both CVD events (HR 0.60)[31] and non-CVD mortality (HR 0.73).[32] We assumed that no use of antithrombotic therapy was associated with the inverse effect of starting (at least) aspirin (HR 1/0.81 = 1.23).[30] Patients who had already achieved an individual target at 3 months were modeled with an HR of 1.00 for that target.

To estimate the benefit of reaching the guideline-recommended risk factor targets, the cardiovascular risk

was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month risk factor levels and treatment, and next we estimated the risk with the assumption that all risk factors met the guideline-recommended targets. The difference between estimated risk with 3-month risk factor levels and estimated risk when risk factors are at target corresponds to an individual's estimated absolute risk reduction (ARR). We obtained the following estimates from the model: 1) 10-year risk of CVD events, 2) lifetime risk of CVD events, defined as the risk of having an event before the 90th life-year, and 3) the life-expectancy free of CVD events. We calculated the following treatment effects: 1) absolute CVD risk reduction in the next 10 years, 2) absolute lifetime CVD risk reduction and 3) gain in CVD-free life expectancy. The therapy benefits from achieving treatment targets for BP, LDL-C and smoking were first estimated separately. Next, the overall benefit of achieving optimal control of all targets (including use of antithrombotic therapy) was modelled and the relevant ARRs calculated.

Statistics

Baseline characteristics at the index stroke event were described by means with standard deviations (SD) and proportions as appropriate. Estimated risks and ARRs are reported as median with interquartile range (IQR). We visually compared the distribution of estimated risk on current treatment and estimated risk with risk factor(s) at targets in density plots. We imputed missing data for clinical measurements at 3 months for prediction of CVD risk by means of single imputation using predictive mean matching, including all variables used in the analyses. Details and amount of missing data are shown in Table S3. All analyses were conducted using Stata version 16.1 or R statistical software V.4.0.2 (www.r-project.org, packages Hmisc, Survival, Cmprsk, Rms, Pec).

Results

Table 1 shows characteristics at index stay and Table 2 presents achieved risk factor levels 3 months poststroke. Mean LDL-C was 2.1 mmol/L (SD 0.8), mean % relative LDL-C reduction from index stay to 3 months was 24% (SD 33) and 43% reached the target at 3 months. Mean systolic BP was 140 mmHg (SD 19), 51% reached the BP target and 50% (55/109) of smokers quitted smoking at 3 months. Antithrombotic drugs were used by 98%, corresponding numbers for lipid-lowering and antihypertensive drugs were 89% and 73%. Detailed information on cardiovascular medications in use is shown in Table S4. In total, 80% (302/376) reported high adherence at 3 months defined as a score of 4 on Morisky Medication Adherence Scale 4 (MMAS4).[2,33]

Table 1 Characteristics at the Index Stay (N = 465)

	n (% of N) or Mean (SD)
Age	69.0 (8.1)
Sex, male	287 (62%)
Atrial fibrillation	101 (22%)
Diabetes mellitus	92 (20%)
History of hypertension	252 (54%)
History of hypercholesterolemia	253 (54%)
Previous cerebrovascular disease	108 (23%)
Coronary artery disease	79 (17%)
Peripheral artery disease	35 (8%)
Number of vascular areas affected[a] 1, 2 or 3	369 (79%), 78 (17%), 18 (4%)
Heart failure	11 (2%)
Current smoker	109 (24%)
Previous smoker	174 (38%)
Estimated GFR[b] (mL/min/1.73 m^2)	79 (16)
Body Mass Index (kg/m^2)	26.6 (4.2)
High-sensitive CRP concentration (mg/L)	9.6 (18.0)
Stroke subtype[c] (n = 450)	
Large artery disease	49 (11%)
Cardioembolic	103 (23%)
Small vessel disease	105 (23%)
Other causes	12 (3%)
Unknown or multiple causes	181 (40%)
NIHSS[d] at discharge (n = 437)	1.7 (2.4)
Charlson Comorbidity Index	3.7 (1.9)
Frail[e]	34 (7%)
Cognitive impairment[f]	13 (3%)

Notes: [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]GFR calculated by CKD-EPI equation. [c]According to TOAST: Trial of ORG 10172 in Acute Stroke Treatment. [d]Stroke severity according to National Institutes of Health Stroke Scale (NIHSS). [e]Measured by the 5-item Fried criteria. [f]Defined as score ≥ 3 on Global Deterioration Scale. Detailed definitions in Supplementary Methods.

Abbreviations: CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate.

Table 2 Risk Factor Levels at the Index Stay and the 3-Month Visit (n = 465)

	Index Stay[a]	3-Month Visit
Systolic blood pressure (mmHg)	140 (20)	140 (19)
Diastolic blood pressure (mmHg)	80 (13)	83 (12)
LDL-C (mmol/L)	3.1 (1.1)	2.1 (0.8)
HDL-C (mmol/L)	1.4 (0.5)	1.5 (0.5)
Total cholesterol (mmol/L)	4.9 (1.3)	4.0 (0.9)
Current smoking	109 (23%)	55 (12%)
Use of secondary preventive medications		
Lipid-lowering drugs[b]	415 (89%)	412 (89%)
Antihypertensive drugs[c]	320 (69%)	338 (73%)
Antithrombotic drugs[d]	456 (98%)	455 (98%)

Notes: Values are mean (standard deviation) or n (%). Missing values are imputed by single imputation using predictive mean matching. [a]Concentrations of cholesterol were measured the first day after admission and blood pressure levels at day 7 or at the day of discharge, use of medications was assessed at discharge. [b]Use of lipid-lowering drugs was defined as use of drugs belonging to ATC group C10. [c]Use of antihypertensive drugs was defined as use of drugs belonging to ATC groups C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D. [d]Use of antithrombotic drugs was defined as use of drugs belonging to ATC group B01A. Detailed information about types of medications in use are shown in Supplementary Table S4.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ATC, Anatomical Therapeutic Chemical classification system.

In total, 52 cardiovascular events and 15 non-cardiovascular deaths were observed from 3 months post-stroke during a follow-up of median 2.20 years (IQR 1.79 to 2.62), totally 991 patient-years (Figure 1). In total, 61% (n = 32) of the patients with a recurrent cardiovascular event had a non-fatal stroke, 31% (n = 16) experienced a non-fatal MI and 8% (n = 4) died due to cardiovascular causes.

Estimated Risk of Recurrent Events

The average observed 2-year risk in Nor-COAST was higher than the average predicted 2-year risk with the SMART-REACH model (Figure S1) (expected–observed ratio 0.54). After recalibration, the calibration curve showed adequate agreement between predicted and observed risk and modest discrimination (C-statistics 0.63, 95% CI 0.55 to 0.71) (Figure 2). Discrimination was slightly lower when excluding patients with cardioembolic stroke etiology (C-statistics 0.61, 95% CI 0.53 to 0.70, Figure S2). Sex-specific analyses showed C-statistics 0.65 (95% CI 0.56 to 0.73) for men and 0.57 (95% CI 0.41 to 0.74) for women (Figure S3).

Median estimated 10-year risk of recurrent events was 42% (IQR 32 to 54) (Table 3, Figures 3 and S4–S6). Median lifetime risk was 70% (IQR 63 to 76). Ten-year cardiovascular risk increased with age, while lifetime risk was highest in younger patients (Figure S7, Table S5 and S6). In total, 56% of the patients in the highest 10-year risk quartile had polyvascular disease (Table S5), and 22% were smoking; the corresponding proportions for patients in the lowest risk quartile were 2% and 5%, respectively.

Estimated Benefit from Optimization of Risk Factors

Figures S4–S6 shows the benefits of achieving targets for LDL-C, systolic BP and smoking cessation separately. Median 10-year ARR if patients with elevated LDL-C reached the target was 4% (IQR 2 to 7) and gain in CVD-free life-years was 0.8 years (IQR 0.4 to 1.6) (Figure S4B). Median 10-year ARR if patients with elevated BP reached the target was 8% (IQR 3 to 14) and 1.6 CVD-free life-years gained (IQR 0.6 to 3.1) (Figure S5B). Smoking cessation led to 14% (IQR 12 to 16) 10-year ARR and median 3.4 CVD-free life-years gained (IQR 2.4 to 4.3) (Figure S6).

If all targets were achieved, the overall median 10-year ARR was 6% (IQR 1 to 14), and lifetime ARR was 6% (IQR 1 to 15) (Table 3 and Figure 3). The population could gain median 1.4 (IQR 0.2 to 3.4) CVD-free life years. After optimization, the residual median 10-year risk had decreased to 32% (IQR 24 to 44), and lifetime CVD risk had decreased to 61% (IQR 49 to 70) with a CVD-free life expectancy of 82.2 (IQR 78.9 to 85.4) years. If all targets were reached, the 10-year risk would be <20% for 16% of the patients and <30% for 43%. Patient characteristics by quartiles of 10-year ARR are shown in Table S7. Treatment benefits in terms of gain in CVD-free life years were highest in younger patients with elevated risk factor levels (Table S8).

Discussion

In this observational study of patients with ischemic stroke, we found that a notable proportion suffered from a recurrent event the first 2 years poststroke and showed substantial variation in estimated future cardiovascular risk and treatment benefit from intensification of secondary prevention. We revealed a remaining preventive potential by reaching the guideline-recommended treatment targets and demonstrated that the SMART-REACH model generates prognostic risk information reasonably well in stroke patients.

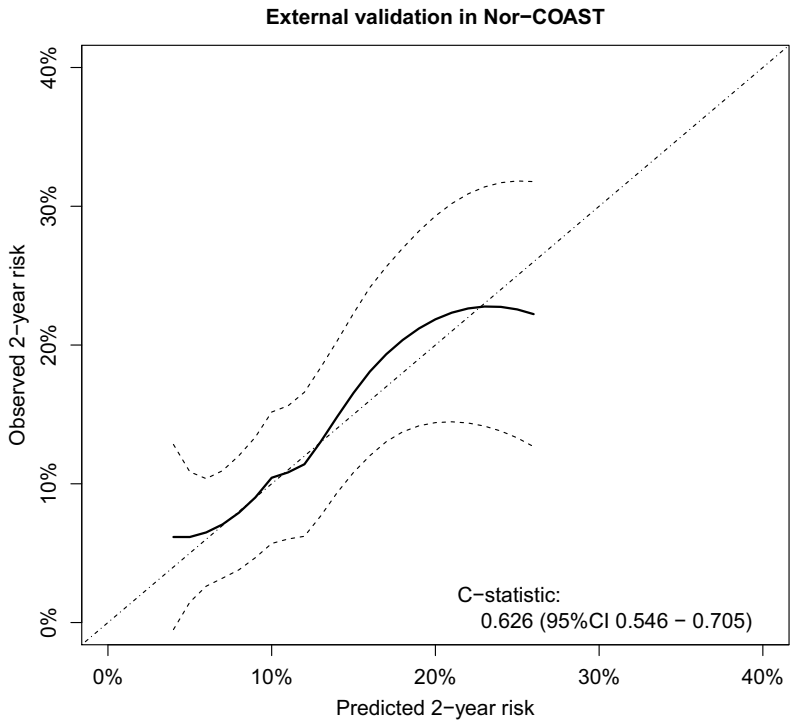


Figure 2 Flexible calibration curve showing the agreement between quantiles of estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk after recalibration.

Studies quantifying future cardiovascular risk in stroke populations are scarce. However, comparable findings of risk and potential benefit variations have been shown in patients with established CVD in general.[6,19,34] The residual risk in Nor-COAST is quite high compared to other studies.[6,19,34] However, Nor-COAST included solely patients with stroke, while other cohorts also included transient ischemic attacks.[7,19] Moreover, the consecutive inclusion of stroke patients minimizes healthy participant bias[35] and higher-risk patients are more likely to be included. Although high residual risk might be explained by non-modifiable factors such as age, already severely progressed atherosclerosis or genetic disposition, modifiable risk factors like inflammation or further reduction of BP and LDL-C are of importance.[23,28,29] Mean risk factor levels in Nor-COAST are not far from targets and more in line with guideline recommendations compared to other populations,[2–4] yielding less possibilities for benefit based on current cut-offs. However, BP and LDL-C are continuously related to CVD risk,[28,29] and an individual patient could still benefit from further reduction.

The predicted 2-year risk corresponded adequately with the observed risk in Nor-COAST after recalibration. Discrimination was acceptable and in line with other prognostic tools already in clinical use,[7,16,18] and previous validations of the SMART-REACH model have shown comparable results.[19,34] Moreover, sex-specific analyses showed lower c-statistics for women; however, these results should be interpreted with caution due to lack of statistical power. Stroke is a heterogeneous condition with multiple possible etiologies where stroke classification is crucial. Performance of the model may be different in patients with cardioembolic stroke etiology, especially if the burden of atherosclerosis and associated risk factors is low or absent. Due to the limited sample size, the performance in this subgroup could not be evaluated. Still, the large overlap between underlying etiologies and other cardiovascular entities[13–15] illustrates the need for optimal

Table 3 Estimated Prognosis and Benefits of Optimal Guideline-Therapy

	Total (n = 465)	Systolic Blood Pressure > 140 mmHg (n = 226)	LDL-C > 1.8 mmol/L (n = 265)	Smokers (n = 55)	No Antithrombotics (n = 10)
Current estimated risk					
10-year CVD risk (%)	42 (32 to 54)	44 (34 to 54)	41 (32 to 52)	52 (39 to 66)	53 (46 to 65)
Lifetime CVD risk[a] (%)	70 (63 to 76)	67 (61 to 75)	69 (63 to 75)	76 (74 to 81)	77 (68 to 84)
CVD-free life expectancy[b] (years)	80.4 (76.4 to 83.5)	81.8 (78.9 to 84.3)	80.7 (76.8 to 83.6)	75.3 (72.2 to 80.1)	79.2 (75.8 to 82.3)
Remaining CVD-free life-years[c]	9.9 (7.2 to 13.5)	9.5 (7.2 to 12.3)	10.0 (7.4 to 13.3)	7.6 (4.8 to 9.9)	8.1 (6.3 to 9.7)
Treatment benefits from optimal guideline therapy[d]					
10-year ARR (%)	6 (1 to 14)	12 (6 to 20)	9 (3 to 16)	17 (15 to 25)	17 (8 to 34)
Lifetime ARR (%)	6 (1 to 15)	14 (7 to 23)	11 (3 to 19)	15 (10 to 30)	22 (4 to 47)
Gain in CVD-free life expectancy (years)	1.4 (0.2 to 3.4)	2.6 (1.2 to 4.6)	2.0 (0.7 to 4.1)	4.4 (2.9 to 8.0)	5.1 (1.2 to 8.8)

Notes: Values are median (interquartile range). [a]Defined as risk of having an event before the 90th life-year. [b]Median life expectancy without a CVD event or death. [c]Number of years without a CVD-event due to current treatment. [d]Defined as systolic blood pressure 140 mmHg, LDL-C 1.8 mmol/L, smoking cessation and use of antithrombotic medications.

Abbreviations: LDL-C, Low density lipoprotein cholesterol; CVD, Cardiovascular disease; ARR, Absolute risk reduction.

atherosclerotic risk factor control in general. Although some short-term risk prediction models developed separately for stroke patients already exist,[16–18] the SMART-REACH[19] model can be used in individuals with any type of atherosclerotic disease, also multiple manifestations, which often is the case in clinical practice. The SMART-REACH model is readily available via online calculators such as u-prevent.com. However, ideally the geographic correction factor should be applied when using the model in clinical practice for similar populations.

Strengths and Limitations

The strengths of this study include the multicenter design, valid registry data, an up-to-date time period and prospective consecutive inclusion of patients reflecting current clinical practice.[35] Another strength is using a prediction tool that estimates both 10-year risk and lifetime risk adjusting for competing risks and remaining life-expectancy. As secondary prevention presumably is continued lifelong, it may be more intuitive to use a lifetime risk prediction model. Furthermore, adjusting for death of other causes avoids overestimating CVD risk and treatment benefit in older individuals.[19] The observed 2-year event rate in Nor-COAST (Figure S8) corresponds reasonably well with event rates in a recent meta-analysis[1] and the Nor-COAST population has characteristics in line with patients in the Norwegian stroke registry.[2,35] Generalization at least to Norwegian stroke patients and comparable stroke populations is therefore plausible.

Not including the oldest patients is a significant limitation and performing external validation and recalibration based on 2-year predictions might be a weakness. However, previous studies have shown that lifetime estimates based on similar methods appear to be reliable for predictions up to at least 17 years.[9] C-statistics for discrimination are moderate. However, demonstrating adequate calibration might be a more relevant measure since knowing that the predicted risk reflects the actual risk is important for clinical treatment decisions.[8,36] We did not account for changes in risk factor levels over time. However, changes in risk factor levels after 3 months are not likely to affect predictive performance.[37] We have previously published detailed data on how adherence to medications and risk factor control changes from discharge to 18 months poststroke in Nor-COAST,[2] which showed that risk factor levels remain relatively unchanged. Risk factor levels also often deteriorate over time due to decrease in drug adherence and healthy lifestyle habits.[2,5] Missing data for clinical measurements at the 3-month follow-up might, however, be a weakness. The relative effects of BP

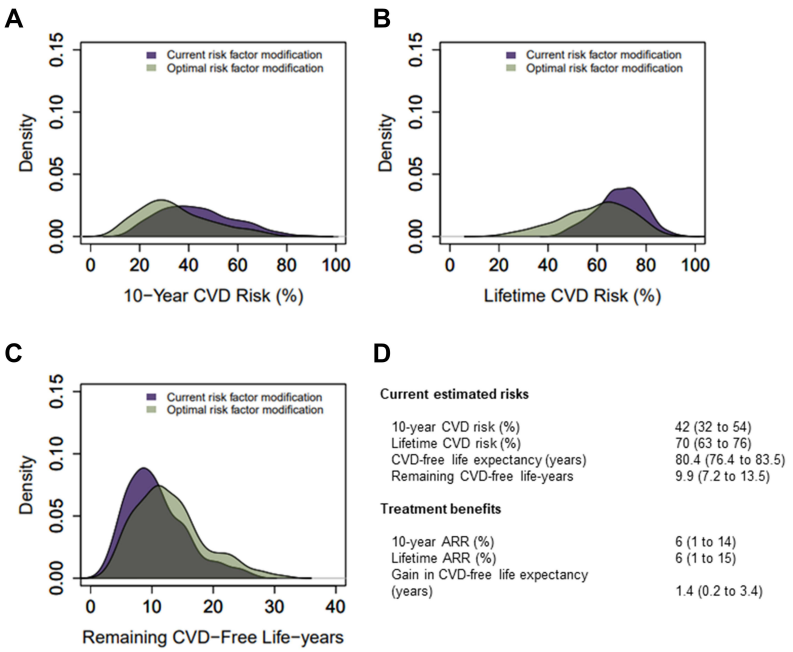


Figure 3 Distribution of current cardiovascular disease (CVD) risk and potential benefit from optimization of all risk factors.
Notes: Distributions of (**A**) ten-year cardiovascular disease risk, (**B**) lifetime CVD risk, (**C**) remaining CVD-free life-years, (**D**) current estimated risks and treatment benefits (median (interquartile range)) from optimization of risk factors defined as systolic blood pressure ≤140 mmHg, LDL-cholesterol ≤1.8 mmol/L, smoking cessation and use of antithrombotic medication.
Abbreviation: ARR, absolute risk reduction.

and LDL-C lowering are based on large meta-analyses synthesizing evidence from primary and secondary preventive settings and benefits might be smaller or larger depending on specific stroke characteristics. However, relative effect estimates are broadly similar across several subgroups of patients.[28,29] Therefore, we consider these relative effects valid for our population. We did not account for disadvantages and harm of pharmacotherapy, like adverse reactions and costs. At last, risk prediction models include varying degrees of uncertainty and cannot replace good clinical judgment but help structure and guide clinicians in their medical decision-making process.[8]

Conclusions

Current risk factor control after ischemic stroke is suboptimal. The predicted future risk is high but with considerable individual variation and a corresponding variation in the benefit from intensification of secondary prevention. An available risk prediction tool such as the SMART-REACH model can be used to identify patients with the largest benefit from intensification of treatment and more intensive short-term or multidisciplinary follow-up. We believe the model can be a useful tool for more personalized surveillance of patients in both stroke units and other clinical settings like general practice. More research is needed to assess potential strategies for further lowering of the high residual cardiovascular risk in these patients, and selection of patients by risk stratification may help improve focus and efficiency in future trials.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

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Disclosure

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Supplementary Paper II

Supplementary Methods.

Definitions of variables in Table 1

Hypertension was defined as self-reported hypertension or use of antihypertensive drugs at admission (Anatomical Therapeutic Chemical Classification System codes (ATC): C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D). Hypercholesterolemia was defined by use of lipid lowering drugs at admission (ATC -code: C10). Previous stroke (before the index event) or transient ischemic attack (TIA) was defined as previous ischemic stroke, TIA, hemorrhagic stroke or stroke of undetermined subtype as reported by doctor (based on review of medical records) / patient. GFR (Glomerular filtration rate) was based on the CKD-EPI equation (based on gender, age and the serum creatinine concentration measured at first day during admission) [1]. Blood tests were taken the first day after admission. Stroke subtype was defined according to the TOAST Trial of ORG 10172 in Acute Stroke Treatment classification [2]. Stroke severity was assessed by National Institutes of Health Stroke Scale (NIHSS). Prestroke cognitive impairment was defined as score ≥ 3 on Global Deterioration Scale assessed by study nurses' interviews of caregivers during hospital stay [1]. Frailty was measured using a modified version of the five-item Fried criteria [1], based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss, where 3-5 criteria present corresponds to frail. Definitions of variables also included in the SMART-REACH model are described in Table S1.

Registry data

The Norwegian Stroke Registry is a medical quality register where all Norwegian hospitals have been obligated to enter medical data on all residents > 18 years of age admitted to hospital with acute stroke (ICD-10 codes I61, I61 and I64). The Norwegian Stroke Registry had a coverage (completeness) of 87 % in 2018 [3, 4], we therefore also linked Nor-COAST data to the Norwegian Cardiovascular Disease Registry which is more complete [5]. The Norwegian Cardiovascular Disease Registry is an administrative health register based on data from the Norwegian Patient Register, containing information on all admissions to hospital (main and second diagnosis), both private and public, included in the public reimbursement policy in Norway since 2008. For stroke endpoints we restricted analyses to main diagnoses of stroke which give more correct registrations [5]. For myocardial infarction endpoints we used both main and second diagnoses for higher completeness [6]. The Norwegian Causes of Death Registry provided follow-up information on cardiovascular disease as the primary cause of death. All registries are regulated according to the Act relating to Personal Health Data Registries. The quality of information in the registries have previously been described [5, 6].

The use of the SMART-REACH Fine and Gray competing risk model in Nor-COAST

The SMART-REACH risk model is a competing-risk adjusted Fine and Gray model, which can be used for estimation of both 10-year and lifetime risk of major cardiovascular events and non-cardiovascular mortality in patients with clinically manifest vascular disease. The underlying model formulas and methodology were published in the original SMART-REACH publication [7]. With age as underlying timescale, lifetables calculating risks for every 1-year interval are made beginning at the starting age of each individual [7, 8] and repeated up to the maximum age of 90 years. The model was derived using adapted Fine and Gray models to allow for left truncation and right censoring [9].

For better judgement of the calibration, less influenced by arbitrary grouping in comparison to a traditional calibration plot, we showed a flexible calibration curve based on local polynomial regression fitting (*loess*, function R) [10-12]. First, the cohort was divided in 100 quantiles of predicted risk. Then, a local regression was used to smoothly explain the observed cumulative incidence per group by the mean predicted risk per group. The smooth calibration plot and confidence bounds were subsequently predicted from this model over the whole range of relevant predicted risks (cohort predicted risk quantile 0.025 up to 0.975). A curve close to the diagonal indicates that predicted risks correspond well with the observed proportion of events [10].

Recalibration of the model was considered based on the calibration plot and performed using "calibration-in-the-large" by subtracting the expected-observed ratio from the linear predictor for both the CVD hazard function as for the non-CVD mortality function [10, 13]. The expected-observed ratio was calculated by dividing the expected incidence (mean of all predicted 2-year risks) by the observed incidence (cumulative incidence in the study population at 2 years, corrected for competing risks).

Table S1. Definitions of variables included in the SMART-REACH model [7] and sources	
Variable	**Source when used in present study**
Age (years)	As recorded in medical journals
Sex (male/female)	As recorded in medical journals
Current smoking (yes/no)	Patient response to smoking status at 3 months
Diabetes mellitus (yes/no)	Self-reported diabetes or HbA1c ≥ 48 mmol/mol at admission or prescribed antidiabetic drugs at admission or discharge
Congestive heart failure (yes/no)	History of heart failure as reported by doctor (based on review of medical records) / patient
Atrial fibrillation (yes/no)	Self-reported or documented on electrocardiogram or telemetry during admission
Systolic blood pressure (mmHg)	Measured thrice by the same physician at 3 months with one-minute intervals and the average of the second and third measurements was used in the analysis
Creatinine (µmol/L)	Serum concentration at 3 months
Total cholesterol (mmol/L)	Non-fasting serum concentrations from venous blood measured in fresh samples at 3 months
LDL cholesterol (mmol/L)	Non-fasting serum concentrations from venous blood measured in fresh samples at 3 months
History of cerebrovascular disease (yes/no)	All patients were registered with cerebrovascular disease, since stroke was an inclusion criterion in the Nor-COAST study.
History of coronary heart disease (yes/no)	Previous angina pectoris, myocardial infarction or coronary revascularization (coronary bypass surgery or percutaneous coronary intervention) as reported by doctor (based on review of medical records) / patient
History of peripheral artery disease (yes/no)	Symptomatic or documented obstruction of distal arteries of the leg or surgery of the leg or documented surgery of aorta as reported by doctor (based on review of medical records) / patient
Use of antithrombotic drugs (yes/no)	Use of aspirin or equivalent drug belonging to the Anatomical Therapeutic Chemical (ATC) Classification System group B01A at 3 months. As reported by the patient or doctor, if information regarding medications in use were missing, we contacted general practitioners, home care services or used the electronic summary care record for safer healthcare in Norway.

Abbreviations: HbA1c; Hemoglobin A1c. Nor-COAST; Norwegian Cognitive Impairment after Stroke.

Table S2. Guideline recommended targets and effect measures from meta-analyses used when calculating treatment benefits from optimization of risk factors			
Risk factor target	**Guideline defined treatment and target**	**Effect measures and literature references**	**Comments**
Lipid targets	LDL-C ≤ 1.8 mmol/L [14]	A hazard ratio (HR) of 0.78 was assumed per 1.0 mmol/L reduction in LDL-C [15]. Patients who had already achieved the target were modelled with a HR of 1.00, regardless whether this was achieved by lifestyle or medication. LDL-C reduction in mmol/L was defined as the 3-month LDL-C level minus 1.8 mmol/L. We assumed no further risk reduction from lowering LDL-C below 1.8 mmol/L.	We used the effect measure from a meta-analysis with patients from both primary and secondary preventive settings, where subgroup analyses have shown that the relative risk reduction is more or less the same across several groups of patients suggesting broadly generalizable benefits. We therefore assume these effects also are valid in subgroups of stroke patients.
Blood pressure targets	Systolic blood pressure ≤ 140 mmHg [14]	A 10 mmHg reduction in systolic BP was assumed to correspond to a cardiovascular specific HR of 0.80 [16]. Patients who had already achieved this target were modelled with a HR of 1.00, regardless whether this was achieved by lifestyle or medication. BP reduction in mmHg was defined as the 3-month systolic BP minus the target systolic BP of 140. We assumed no further risk reduction from lowering BP below 140 mmHg.	We used the effect measure from a meta-analysis with patients from both primary and secondary preventive settings (including stroke patients), where subgroup analyses have shown that the relative risk reduction is more or less the same across several groups of patients. A HR of 0.80 for the combined endpoint of major cardiovascular events was used. However, the relative effect for stroke separately seems to be larger (HR 0.73) [16].
Antithrombotic treatment	Aspirin or other equivalent antiplatelet drugs. Anticoagulation if non-valvular atrial fibrillation [14]	Estimated risk is based on the assumption that standard care is provided. Such standard care (HR 1.00) included aspirin or equivalent type of antithrombotic therapy, including vitamin K antagonists or DOACs, regardless of number of antithrombotic drugs in use. We assumed that no use of antithrombotic therapy was associated with the inverse effect of starting (at least) aspirin (i.e., HR 1/0.81 = 1.23) [17].	The HR for long-term aspirin (0.81) monotherapy in secondary preventive setting from the meta-analysis [17] was used. The estimate is based on 16 secondary preventive trials from whom 10 was in stroke or patients with transient ischemic attack. The benefit of different antithrombotic regimens was not assessed since the proportion not using antithrombotic drugs was low.
Smoking target	Smoking cessation [14]	The effect of smoking cessation was estimated in current smokers and was assumed to reduce the risk of both CVD events and non-CVD mortality. The HR for CVD events for current smokers when converting to ex-smoker was assumed to be 0.60 [18]. The HR for non-CVD mortality for current smokers who are now ex-smokers was assumed to be 0.73 [19].	In absence of evidence from RCTs, the effect of smoking cessation was estimated from observational studies, using the hazard ratio between current and former smoking.

Abbreviations: LDL, Low-density lipoprotein; BP, blood pressure; DOACs, Direct Oral Anticoagulants; RCTs, Randomized Controlled Trials; TIA, Transient ischemic attack

Table S3. Overview of missing values at index stay and 3-month visit (n=465)		
	n (%) missing at index stay	n (%) missing at 3-month visit
Age	0	0
Sex	0	0
Current smoking	1 (0.2%)	68 (15%)
Diabetes mellitus	0	0
Systolic blood pressure	34 (7%)	72 (15%)
Total cholesterol	8 (2%)	113 (24%)
HDL cholesterol	12 (3%)	117 (25%)
LDL cholesterol	15 (3%)	115 (25%)
Creatinine	2 (0.4%)	119 (26%)
Coronary artery disease	0	0
Peripheral artery disease (incl. AAA)	0	0
Heart failure	0	0
Atrial fibrillation	0	0
Information about medications	5 (1%)	32 (7%)

Missing values for current smoking, systolic blood pressure, cholesterol, creatinine and information about medications were imputed using single imputation by predictive mean matching for the purpose of CVD risk prediction and assessment of changes in risk factor levels from index stay to 3-months follow-up. With this method, the imputed value is taken randomly from a set of observed values whose predicted values are closest to the predicted value from a specified regression model. For the baseline characteristics age, sex, history of diabetes, coronary artery disease, peripheral artery disease, heart failure and atrial fibrillation, we assumed that registrations at index stay also were valid at the 3-month visit. Abbreviations: eGFR; Estimated glomerular filtration rate. AAA; Abdominal aortic aneurism, HDL; High-density lipoprotein, LDL; Low-density lipoprotein.

Table S4. Cardiovascular medications at discharge from index stay and at 3 months of follow-up for patients with available detailed data on medications in use

	Discharge (n = 460)	3-month visit (n = 433)
Antithrombotic drugs		
No[a]	9 (2%)	8 (2%)
Single antiplatelet therapy	111 (24%)	130 (30%)
Dual antiplatelet therapy	189 (41%)	150 (35%)
Anticoagulation monotherapy	107 (23%)	114 (25%)
Anticoagulation in combination with antiplatelet agent(s)	44 (10%)	31 (7%)
Number of antihypertensive drugs		
0[a]	144 (31%)	118 (27%)
1	167 (36%)	160 (37%)
2	105 (23%)	101 (23%)
3	33 (7%)	43 (10%)
>3	11 (2%)	11 (3%)
Lipid-lowering drugs		
No[a]	45 (10%)	42 (10%)
Any statin monotherapy	407 (88%)	381 (88%)
Low-moderate intensity statin[b]	142 (30%)	133 (31%)
High intensity statin[b]	265 (58%)	248 (57%)
Ezetimibe monotherapy	3 (1%)	6 (1%)
Statin + ezetimibe	5 (1%)	4 (1%)

[a]Of patients with available follow-up information about medications in use at both discharge and 3 months (n=429), 5 out of 8 patients not using (any) antithrombotic drugs (ATC code: B01A) at discharge started antithrombotic treatment between 0 and 3 months, while 4 out of 421 prescribed antithrombotic drugs at discharge discontinued between 0 and 3 months. For antihypertensive drugs (ATC codes: C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D), corresponding numbers were 28 / 133 and 12 / 296. For lipid-lowering drugs (ATC code: C10), corresponding numbers were 12 / 40 and 11 / 389. [b]High-intensity statin was defined as atorvastatin ≥40 mg/d or other equivalent drug as described previously [1]. Low-moderate intensity statin was defined as <40 mg atorvastatin or other equivalent drug. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system.

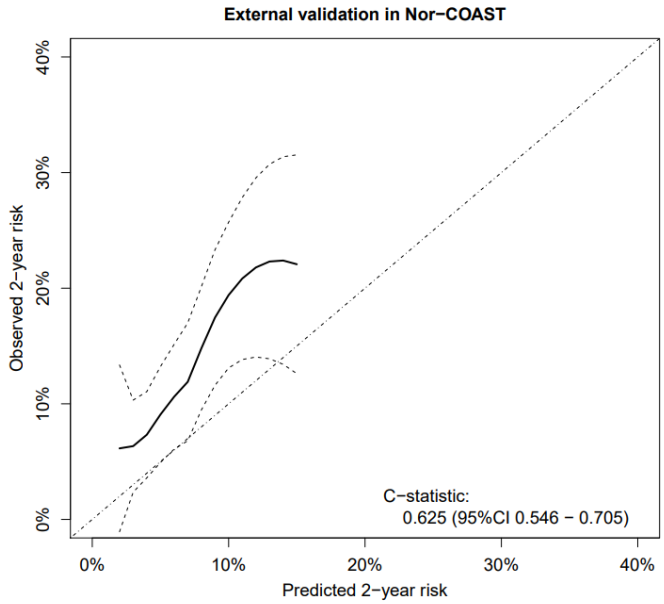


Figure S1. Flexible calibration curve showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model and observed 2-year risk before recalibration

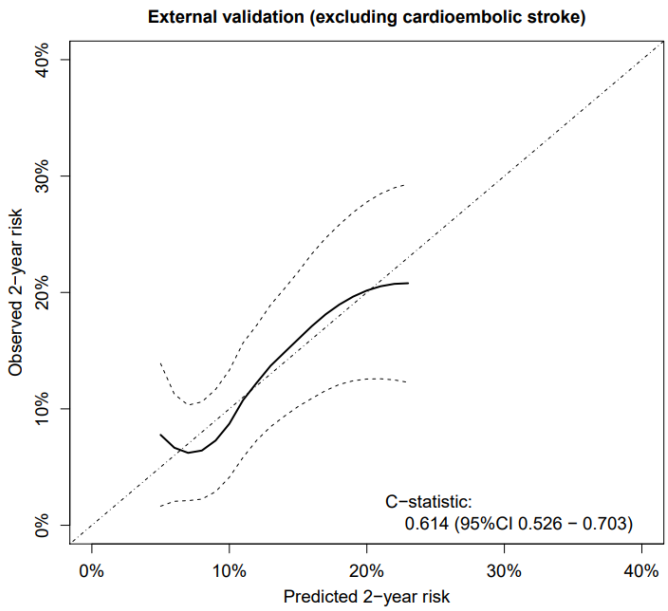


Figure S2. Flexible calibration curve showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk when excluding patients with cardioembolic stroke etiology according to the TOAST-classification

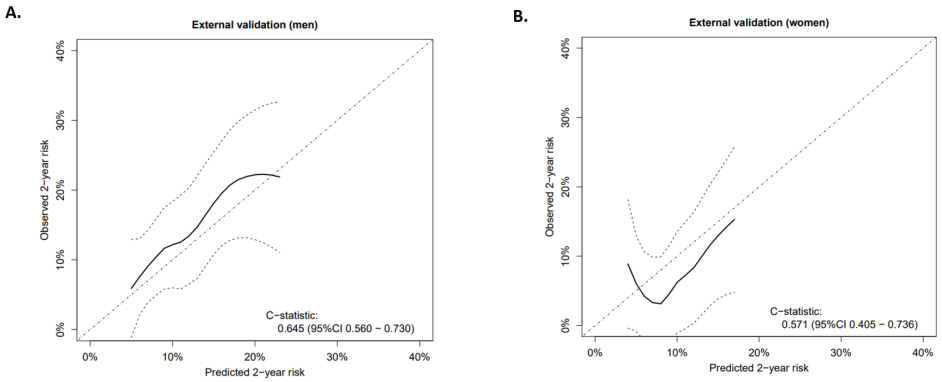


Figure S3. Sex-specific flexible calibration curves showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk for a) men (n=278) and b) women (n=178).

Notes: Number of CVD events for men and women were n=34 and n=18, respectively. Number of non-CVD related deaths were n=10 and n=5 for men and women respectively.

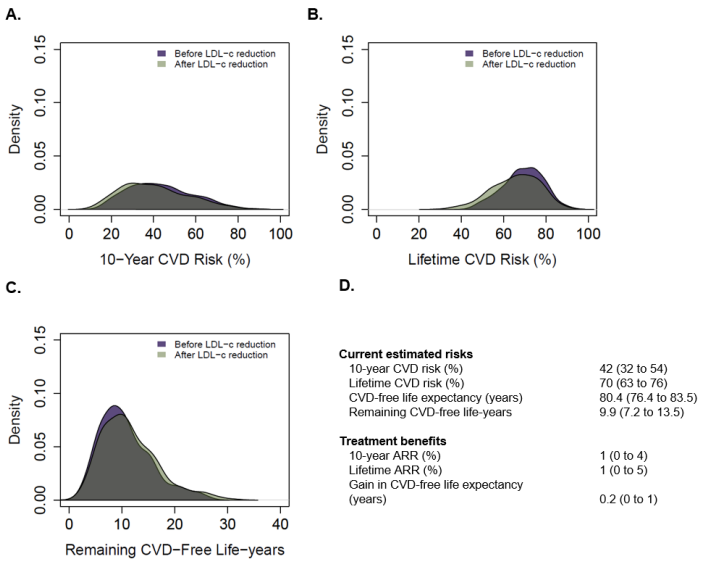


Figure S4a. Current cardiovascular risk and potential benefit from optimization of LDL-C levels (n = 465)

Distributions of **A.** Ten-year cardiovascular disease risk, **B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D**. Current estimated risks and treatment benefits (median (interquartile range)) from optimization of LDL-C level to ≤1.8 mmol/L in all patients. Abbreviations: LDL-C; Low density lipoprotein cholesterol, CVD; Cardiovascular disease, ARR: Absolute risk reduction

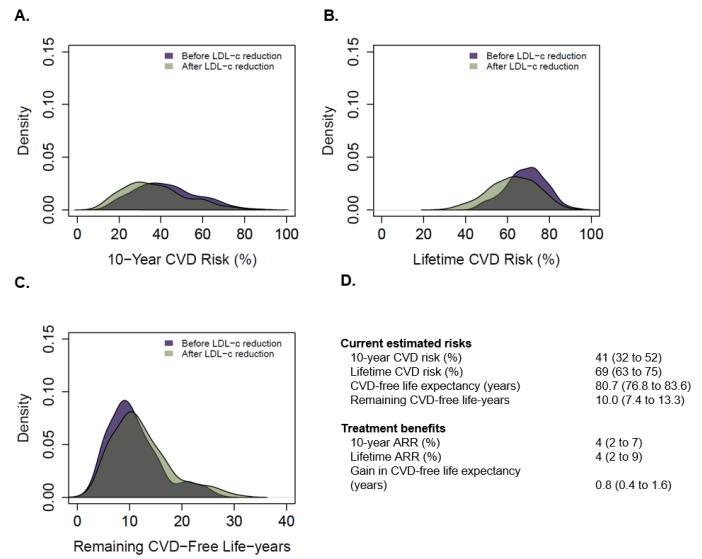
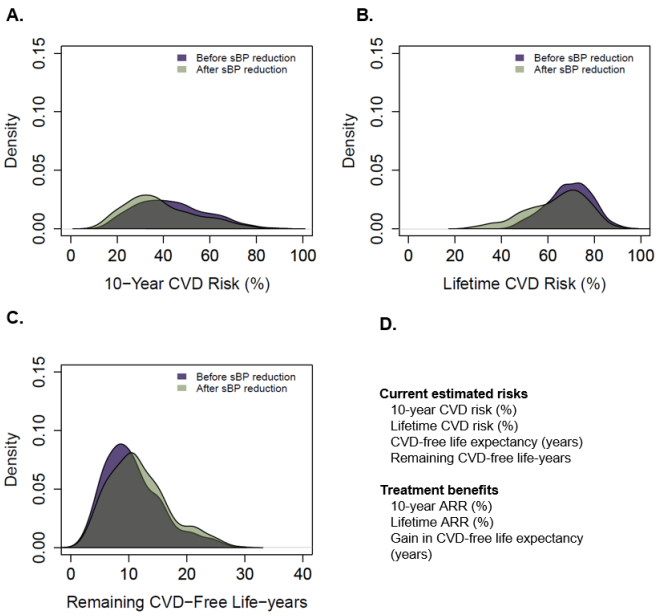


Figure S4b. Current cardiovascular risk and potential benefit from optimization of LDL-C levels in patients with LDL-C > 1.8 mmol/L (n = 265)

Distributions of **A**. Ten-year cardiovascular disease risk, **B**. Lifetime CVD risk, **C.** Remaining CVD-free life-years, **D**. Current estimated risks and treatment benefits (median (interquartile range)) from optimization of LDL-C level to 1.8 mmol/L in

patients with LDL-C > 1.8 mmol/L. Abbreviations: LDL-C; Low density lipoprotein cholesterol, CVD; Cardiovascular disease, ARR: Absolute risk reduction

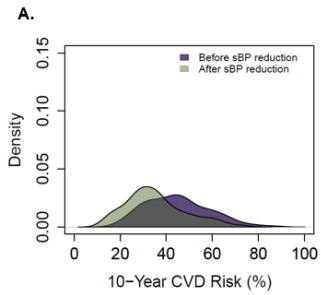


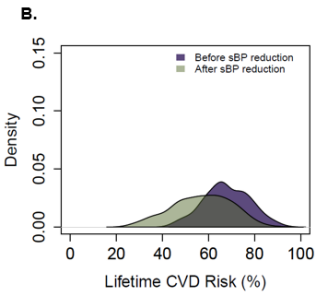
D.

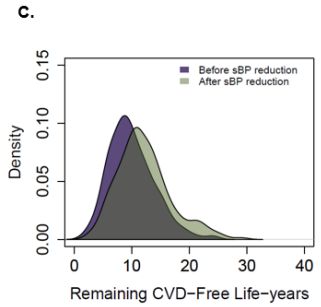
Current estimated risks	
10-year CVD risk (%)	42 (32 to 54)
Lifetime CVD risk (%)	70 (63 to 76)
CVD-free life expectancy (years)	80.4 (76.4 to 83.5)
Remaining CVD-free life-years	9.9 (7.2 to 13.5)
Treatment benefits	
10-year ARR (%)	0 (0 to 7)
Lifetime ARR (%)	0 (0 to 9)
Gain in CVD-free life expectancy (years)	0 (0 to 1.5)

Figure S5a. Current cardiovascular risk and potential benefit from optimization of systolic blood pressure levels (n = 465)

Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from optimization of sBP level to ≤140 mmHg in all patients. Abbreviations: sBP; Systolic blood pressure, CVD; Cardiovascular disease, ARR: Absolute risk reduction







D.

Current estimated risks	
10-year CVD risk (%)	44 (34 to 54)
Lifetime CVD risk (%)	67 (61 to 75)
CVD-free life expectancy (years)	81.8 (78.9 to 84.3)
Remaining CVD-free life-years	9.5 (7.2 to 12.3)
Treatment benefits	
10-year ARR (%)	8 (3 to 14)
Lifetime ARR (%)	9 (3 to 16)
Gain in CVD-free life expectancy (years)	1.6 (0.6 to 3.1)

Figure S5b. Current cardiovascular risk and potential benefit from optimization of systolic blood pressure levels (n = 226) in patients with levels above 140 mmHg.

Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from optimization of sBP level to 140 mmHg in patients with sBP > 140 mmHg (n = 226). Abbreviations: sBP; Systolic blood pressure, CVD; Cardiovascular disease, ARR: Absolute risk reduction

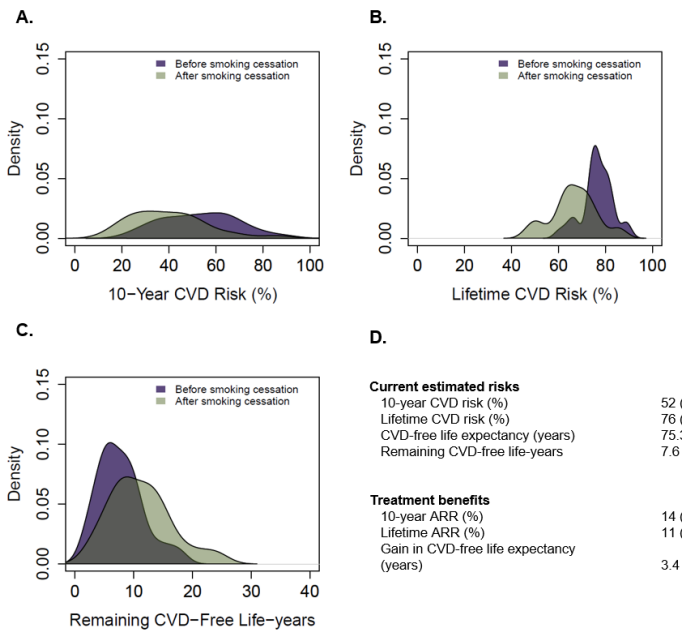


Figure S6: Current cardiovascular risk and potential benefit from smoking cessation in smokers (n = 55)

Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from smoking cessation in patients smoking at 3 months. Abbreviations: ARR: Absolute risk reduction, CVD; Cardiovascular disease

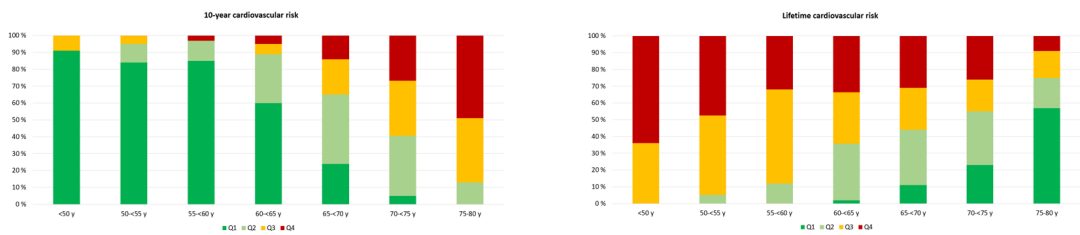


Figure S7. Age-specific subgroups of estimated 10-year and lifetime risk of a recurrent vascular event by the SMART REACH model in patients with ischemic stroke in the Nor-COAST study.

Data are shown as quartiles of risk where Q1 corresponds to lowest risk quartile and Q4 the highest risk quartile.

Table S5. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated 10-year risk of recurrent vascular events and mortality

	10-year CVD risk			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated 10-year risk, %	26 (21 to 29)	37 (34 to 39)	48 (44 to 50)	66 (58 to 68)
Age, y	59.5 (6.2)	68.8 (5.6)	73.0 (5.6)	74.9 (4.5)
Female sex	46 (39%)	49 (42%)	45 (39%)	38 (33%)
Atrial fibrillation	7 (6%)	14 (12%)	30 (26%)	50 (43%)
Diabetes mellitus	2 (2%)	13 (11%)	19 (16%)	58 (50%)
≥ 2 vascular areas[a] affected	2 (2%)	9 (8%)	20 (17%)	65 (56%)
Current smoker[b]	5 (5%)	11 (10%)	13 (11%)	26 (22%)
Systolic blood pressure (mmHg) [b]	137 (16)	139 (15)	144 (18)	140 (25)
Total cholesterol[b], mmol/L	4.0 (0.8)	4.1 (1.0)	4.1 (1.0)	3.9 (0.8)
LDL cholesterol[b], mmol/L	2.1 (0.8)	2.2 (0.8)	2.1 (0.8)	2.0 (0.7)
eGFR (ml/min/1.73 m²)[b, c]	87 (12)	81 (13)	75 (15)	65 (18)
Frail[d]	3 (3%)	6 (5%)	9 (8%)	16 (14%)
Prestroke dementia[e]	0 (0%)	1 (1%)	3 (3%)	9 (8%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S6. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated lifetime risk of recurrent vascular events and mortality

	Lifetime CVD risk			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated life-time risk, %	58 (54 to 61)	67 (65 to 68)	73 (71 to 74)	80 (78 to 83)
Age, y	75.6 (3.7)	69.9 (5.9)	65.7 (8.6)	64.8 (8.8)
Female sex	67 (57%)	49 (42%)	32 (28%)	30 (26%)
Atrial fibrillation	18 (15%)	28 (24%)	23 (20%)	32 (28%)
Diabetes mellitus	0 (0%)	9 (8%)	29 (25%)	55 (47%)
≥ 2 vascular areas[a] affected	6 (6%)	17 (14%)	26 (23%)	47 (41%)
Current smoker[b]	2 (2%)	6 (5%)	18 (16%)	29 (25%)
Systolic blood pressure (mmHg) [b]	144 (16)	142 (19)	136 (18)	138 (23)
Total cholesterol[b], mmol/L	4.2 (0.8)	4.2 (1.0)	4.0 (0.9)	3.8 (0.9)
LDL cholesterol[b], mmol/L	2.2 (0.8)	2.2 (0.8)	2.1 (0.8)	2.0 (0.7)
eGFR (ml/min/1.73 m²)[b, c]	77 (12)	79 (15)	81 (15)	71 (22)
Frail[d]	11 (9%)	10 (9%)	4 (3%)	9 (8%)
Prestroke dementia[e]	5 (4%)	4 (4%)	0 (0%)	4 (4%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive

impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S7. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated 10-year ARR of recurrent vascular events and mortality

	10-year ARR			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated 10-year ARR, %	0% (0 to 0)	3% (2 to 4)	10% (8 to 12)	21% (16 to 27)
Age, y	67.4 (8.5)	67.5 (8.8)	69.4 (7.5)	71.7 (6.8)
Female sex	42 (36%)	42 (36%)	41 (35%)	53 (46%)
Atrial fibrillation	31 (27%)	22 (19%)	22 (19%)	26 (22%)
Diabetes mellitus	17 (15%)	21 (18%)	23 (20%)	31 (27%)
≥ 2 vascular areas[a] affected	18 (16%)	27 (23%)	20 (17%)	31 (27%)
Current smoker[b]	0 (0%)	1 (1%)	8 (7%)	46 (40%)
Systolic blood pressure (mmHg) [b]	128 (10)	132 (12)	146 (13)	155 (23)
Total cholesterol[b], mmol/L	3.4 (0.6)	3.9 (0.5)	4.3 (0.8)	4.5 (1.2)
LDL cholesterol[b], mmol/L	1.6 (0.3)	2.1 (0.4)	2.3 (0.8)	2.6 (1.0)
eGFR (ml/min/1.73 m²)[b, c]	80 (14)	77 (18)	77 (16)	75 (17)
Frail[d]	6 (5%)	7 (6%)	7 (6%)	14 (12%)
Prestroke dementia[e]	2 (2%)	5 (4%)	2 (2%)	4 (4%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: IQR, Interquartile range; ARR, Absolute risk reduction; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S8. Patient characteristics stratified by quartiles (Q1 – Q4) of lifetime benefit from optimization of risk factors				
	Gain in CVD-free life years			
	Q1 (n = 122)	**Q2 (n = 117)**	**Q3 (n = 113)**	**Q4 (n = 113)**
Median (IQR) lifetime benefit (in terms of CVD-free life years)	0 (0 to 0)	0.6 (0.4 to 1.0)	2.3 (1.8 to 2.8)	5.3 (4.3 to 7.1)
Age, y	68.6 (8.2)	69.2 (7.9)	71.2 (7.1)	66.0 (8.7)
Female sex	41 (34%)	43 (37%)	43 (38%)	51 (45%)
Atrial fibrillation	34 (28%)	23 (20%)	25 (22%)	19 (17%)
Diabetes mellitus	22 (18%)	24 (21%)	25 (22%)	21 (19%)
≥ 2 vascular areas[a] affected	25 (20%)	29 (25%)	22 (19%)	20 (18%)
Current smoker[b]	0 (0%)	2 (2%)	16 (14%)	37 (33%)
Systolic blood pressure (mmHg) [b]	128 (10)	133 (14)	143 (17)	157 (19)
Total cholesterol[b], mmol/L	3.4 (0.6)	3.9 (0.6)	4.2 (0.8)	4.6 (1.1)
LDL cholesterol[b], mmol/L	1.6 (0.3)	2.0 (0.4)	2.3 (0.7)	2.7 (1.0)
eGFR (ml/min/1.73 m^2)[b, c]	78 (15)	73 (19)	78 (13)	79 (19)
Frail[d]	8 (7%)	8 (7%)	8 (7%)	10 (9%)
Prestroke dementia[e]	2 (2%)	6 (5%)	4 (4%)	1 (1%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

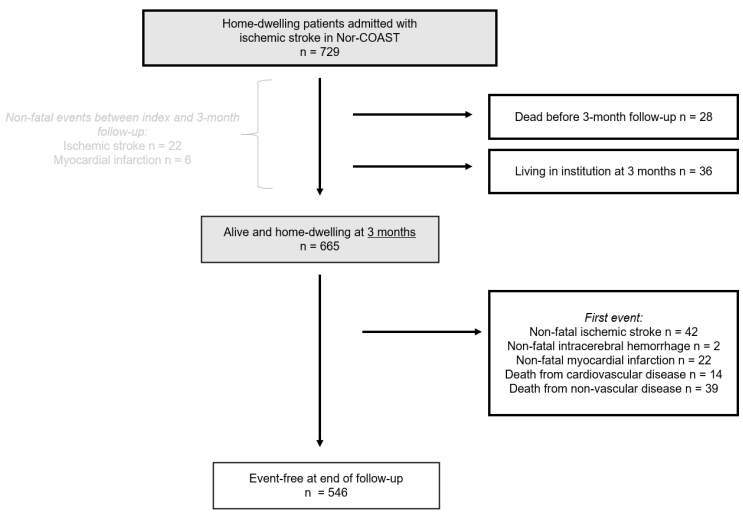


Figure S8. Recurrent stroke, myocardial infarction and death in home-dwelling patients with ischemic stroke in Nor-COAST regardless of age.

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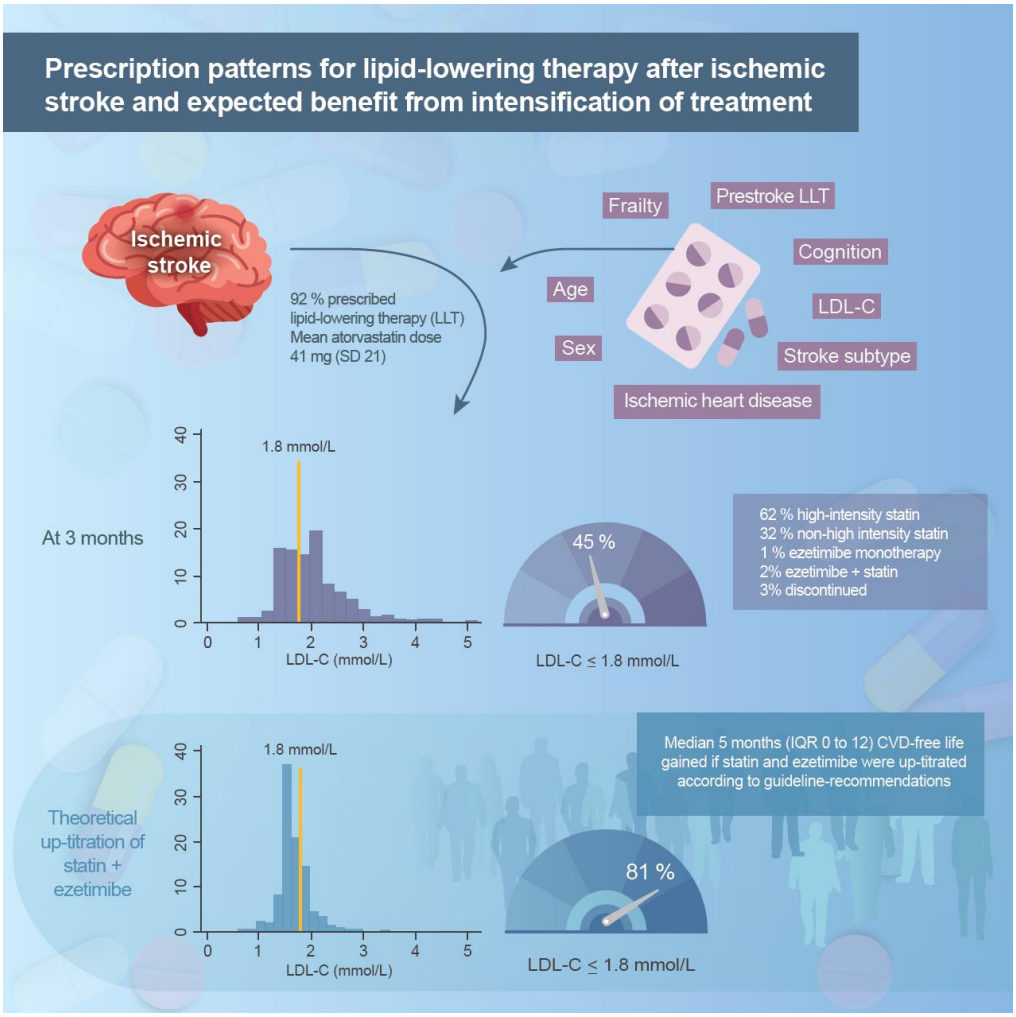
Paper III


Prescription patterns for lipid-lowering therapy after ischemic stroke and expected benefit from intensification of treatment
Ischemic stroke
92 % prescribed lipid-lowering therapy (LLT)
Mean atorvastatin dose 41 mg (SD 21)
Frailty
Prestroke LLT
Cognition
Age
LDL-C
Sex
Stroke subtype
Ischemic heart disease
At 3 months
1.8 mmol/L
LDL-C (mmol/L)
45 %
LDL-C ≤ 1.8 mmol/L
62 % high-intensity statin
32 % non-high intensity statin
1 % ezetimibe monotherapy
2% ezetimibe + statin
3% discontinued
Theoretical up-titration of statin + ezetimibe
1.8 mmol/L
LDL-C (mmol/L)
81 %
LDL-C ≤ 1.8 mmol/L
Median 5 months (IQR 0 to 12) CVD-free life gained if statin and ezetimibe were up-titrated according to guideline-recommendations

Prescription patterns for lipid-lowering therapy after ischemic stroke and expected benefit from intensification of treatment

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Abstract

Background: Elevated low-density lipoprotein cholesterol (LDL-C) increases the risk of recurrent cardiovascular disease (CVD) events. We examined prescription patterns for lipid-lowering therapy (LLT) following ischemic stroke, and estimated benefits from guideline-based up-titration of LLT.

Methods: The Norwegian COgnitive Impairment After STroke (Nor-COAST) study, a multicenter prospective cohort study, collected data on LLT use, dose intensity, and LDL-C levels for 462 home-dwelling patients with ischemic stroke. We used the SMART-REACH (Secondary Manifestations of Arterial Disease – Reduction of Atherothrombosis for Continued Health) model to estimate expected benefit of up-titrating LLT.

Results: At discharge, 92% received LLT (97% statin monotherapy). Patients with prestroke dementia and cardioembolic stroke etiology were less likely to receive LLT. Older patients (coefficient -3 mg atorvastatin per 10 years, 95% CI -6 to -0.5) and women (coefficient -5.1 mg atorvastatin, CI -9.2 to -0.9) received lower doses, while individuals with higher baseline LDL-C, ischemic heart disease, and large artery stroke etiology received higher dose intensity. At 3 months, 45% reached LDL-C ≤1.8 mmol/L, and we estimated that 81% could potentially reach the target with statin and ezetimibe, resulting in median 5 (interquartile range (IQR) 0 to 12) months of CVD-free life gain and median 2% 10-year absolute risk reduction (IQR 0 to 4) with large interindividual variation.

Conclusion: Potential for optimization of conventional LLT use exists in ischemic stroke patients. Awareness of groups at risk of undertreatment and objective estimates of the individual patient's benefit of intensification can help personalize treatment decisions and reduce residual cholesterol risk.

Introduction

Patients with ischemic stroke are at high risk of recurrent cardiovascular disease (CVD) events (1). Drugs lowering low-density lipoprotein cholesterol (LDL-C) concentrations reduce the risk of recurrent events (2-6) and statins are first-line lipid-lowering therapy (LLT) with the addition of ezetimibe or other novel drugs in patients with persistently elevated LDL-C levels or patients intolerant to statins (3, 7). Although the optimal LDL-C target after stroke remains unclear (3), recent studies indicate that lower treatment targets are more beneficial (5, 8, 9), especially in stroke patients with atherosclerotic disease.

There has been an increase in both statin use and dose over time (10, 11), but gaps still exist between recommendations in guidelines (3, 7, 12, 13) and current practice with suboptimal target achievement for LDL-C (3, 10, 14-16). Therefore, stroke patients may not gain the full potential benefit from use of LLT. This gap could be associated with both patient-related factors, such as poor adherence and persistence to prescribed treatment and perceived side-effects (6, 13, 14, 17), and physician-related factors like the choice of drug type and dose intensity (6, 13, 14, 17). Awareness of an individual patient's risk of CVD events, perceived risk of adverse effects and the expected harm-benefit ratio may also influence how LLT is prescribed and used (3, 6, 12, 13, 16, 18).

Little is known about current use of LLT among patients with a recent ischemic stroke and factors influencing prescribing patterns. Moreover, stroke patients show considerable interindividual variation in risk of recurrent events, competing risks and remaining life expectancy (1), with a corresponding variation in the net benefit from more intensive LLT (1, 19). Objective estimates of an individual patient's benefit of intensification of LLT might assist in making well-balanced decisions on whether to intensify treatment or not, in light of potential costs, adverse effects and remaining life-expectancy. Our study therefore aimed to address two sets of questions. First, how do current prescription patterns and achieved LDL-C reduction differ in subgroups of stroke patients? Next, what is the expected treatment benefit when theoretically up-titrating LLT according to guideline recommendations?

Methods

Study population

Home-dwelling patients from the Nor-COAST (Norwegian Cognitive Impairment After Stroke) study, a multicenter observational cohort study, were included (n=729**), Figure S1**. In Nor-COAST, patients admitted with acute ischemic stroke at five Norwegian stroke units were consecutively included between May 2015 and March 2017 (20). Patients were assessed with self-report questionnaires, clinical examinations, and blood sampling after 3 and 18 months at outpatient clinics. Patients unable to attend were assessed by telephone interview or by proxy information. Detailed information about definitions used and data collection in Nor-COAST can be found in **Supplementary Methods**. For all analyses, we excluded patients who died within the first 3 months poststroke (n = 29), patients living in nursing homes at 3 months poststroke (n = 36) and patients lacking information about medications at all time points (n = 3). Patients between 45 and 80 years (n=462) were included in the present analyses as we used a cardiovascular risk prediction model derived and validated in this age range (1, 19). All participants in Nor-COAST gave written informed consent or by proxy if the participant was unable to cooperate. The Norwegian Regional Committee for Medical and Health Research Ethics North (REC numbers 2015/171 and 2017/1462) approved the study.

Assessment of use of lipid-lowering therapy

Trained health professionals obtained information about medications in use by clinical interview of patients and caregivers at the index stay, 3 and 18 months. If information regarding medications was missing, we contacted general practitioners and / or home care services or used the electronic summary care record for safer healthcare in Norway. LLT was identified using the following Anatomical Therapeutic Chemical (ATC) classification system codes defined by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (21): C10AA (HMG-CoA reductase inhibitors (statins)), C10AC (bile acid sequestrants), C10AX (other lipid modifying agents) and C10B (combinations of lipid-lowering drugs). Statins included atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. We used the Defined Daily Doses (DDDs) (21), which are 20 mg for atorvastatin, 30 mg for simvastatin, 10 mg for rosuvastatin, 60 mg for fluvastatin and 30 mg for pravastatin, to convert the doses to atorvastatin equivalent doses by the following formula: (Dose of statin / DDD for that statin) x DDD for atorvastatin = atorvastatin equivalent dose. High-intensity statin (HIS) treatment was defined as drugs known to lower LDL-C by approximately 50%, which corresponds to ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day (3). Other statins were defined as non-high-intensity treatment. We measured medication adherence by the 4-item Morisky Medication Adherence Scale (MMAS4), where a score of 4 points was defined as high adherence (22).

LDL-C target achievement at 3 months and expected LDL-C levels with up-titration of LLT

LDL-C ≤1.8 mmol/L was defined as target attainment (7, 12) and 3-month levels were used as the basis for theoretical intensification as this timepoint roughly corresponds to the guideline recommended control after an acute event where risk factors should be examined and prevention intensified if indicated (7). Guidelines recommend statins at maximally tolerated dose as first-line therapy (**Step 1**) and use of ezetimibe (**Step 2**) in patients who are unable to achieve the LDL-C target with statins alone or are statin intolerant (3, 7, 12). While statins and ezetimibe are well-established treatments available at low costs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are more potent and expensive and mainly considered for patients still not reaching targets (**Step 3**) (3, 7).

We included patients receiving LLT at discharge in these analyses. When information of drug and dose was missing at 3 months (6%), we used the drug and dose prescribed at discharge (14). We estimated the effect of hypothetically up-titrating current LLT, defined as drug and dose used at the 3-month visit, using a stepwise approach (7). The mean percent reduction in LDL-C derived from randomized clinical trials, as previously presented and validated specifically for each drug and dose, was used (23) (**Supplementary Methods, Table S1**). First, all patients with LDL-C > 1.8 mmol/L not using HIS was up-titrated to HIS, assuming a 50.2% mean reduction in LDL-C corresponding to the effect of atorvastatin 80 mg (23). If the expected LDL-C then was > 1.8 mmol/L, ezetimibe was added on top, assuming a mean 22.7% reduction in LDL-C (23). We also estimated the effect of adding ezetimibe without increased statin doses, assuming that all patients already were on maximally tolerated statin dose and patients using ezetimibe monotherapy were statin intolerant.

Estimated potential benefit from up-titration of LLT

We estimated individual benefit of the abovementioned approach from a lifetime perspective expressed in terms of gain in months free of recurrent stroke, myocardial infarction or cardiovascular mortality (19) and as 10-year absolute risk reduction (ARR), by using the externally validated SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model (19). The model is a competing risk-adjusted lifetime risk model previously validated in Nor-COAST (1), which uses the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure, total cholesterol, serum creatinine concentration, number of locations of cardiovascular disease (coronary, cerebral and/or peripheral arterial disease), atrial fibrillation, and heart failure (**Supplementary Methods** and **Table S2**).

We first calculated the life expectancy without recurrent cardiovascular events based on 3-month levels of predictors in the model, defined as the median estimated survival without a recurrent event (19). We next estimated potential treatment benefit defined as the difference in CVD-free life expectancy with and without up-titration of LLT. CVD-free life expectancy with achieved LDL-C level after up-titration was calculated by incorporating a hazard ratio of 0.78 for major cardiovascular events per 1.0 mmol/L reduction in LDL-C (2) in the competing risk model. For 10-year ARRs, we first calculated the 10-year CVD risk based on 3-month LDL-C levels, and next, we calculated the 10-year CVD risk with achieved LDL-C levels after up-titration, where the difference corresponds to the individuals' ARRs. Patients were assigned to intensification only if they had not attained the LDL-C target. Since it is uncertain how well the SMART-REACH model performs in the subgroup with cardioembolic stroke (1) with otherwise low levels of atherosclerotic risk factors, we did additional analyses excluding patients with cardioembolic stroke etiology.

Statistical analysis

We report characteristics by LLT use and intensity at discharge by means with standard deviations (SD) and proportions as appropriate. We also reported descriptive statistics for patient characteristics in categories defined by quartiles of percent LDL-C reduction from discharge to 3 months. Logistic and linear regression was used with LLT prescription (yes/no) and atorvastatin equivalent dose (mg/d) as dependent variables, respectively, to identify variables predictive of LLT use and intensity. Potential predictors were selected a priori based on previous studies (10, 11, 17, 24) and clinical reasoning, leading to inclusion of the following covariates, first one at a time, and next, adjusted for age and sex: age, sex, LDL-C (measured the first day after admission), prestroke use of LLT, frailty by a modified version of the 5-item Fried criteria (14) as a continuous variable from 0 (robustness) to 5 (frail), the Global Deterioration Scale (GDS) as continuous variable from 1 (normal cognitive function) to 7 (severe dementia). A history of ischemic heart disease was included as a categorical variable (yes/no) and was defined as angina pectoris, myocardial infarction, and/or coronary revascularization (coronary bypass surgery or percutaneous coronary intervention). Stroke subtype was divided into five categories according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification: large artery disease, cardioembolic stroke, small vessel disease, other etiology, and undetermined strokes. As the subtype "other etiology" comprised a small number, it was grouped with "undetermined". We report coefficients or odds ratios (OR) with 95% confidence intervals (CI) where relevant. Two-sided p-values <0.05 were regarded as statistically significant. However, due to multiple comparisons, p-values between 0.01 and 0.05 should be interpreted with caution. Estimated CVD risks and benefits were reported as medians with interquartile ranges (IQRs). We visually compared distribution of estimated risk with current treatment and estimated risk after LLT intensification in histograms. Since an available case analysis might lead to bias and loss of power, we imputed missing data for LDL-C and covariates to predict

CVD risk by means of single imputation using predictive mean matching. The extent of missing data for relevant variables is described in **Table S2**. We included all variables to be used in the analyses in the imputation model. Data analysis was performed using Stata version 16 or R version 4.0.2.

Results

Baseline characteristics and prescription patterns at discharge

The analysis included 462 home-dwelling patients with mean age 69.0 years (SD 8.1), 38% were female, 24% were smoking and 27% were physically active. At hospital admission, 35% (n=161) were already using LLT in terms of statins (n=153), ezetimibe monotherapy (n=5) or combination (n=3). The mean atorvastatin equivalent dose was 34 mg (SD 22) and 37% used HIS.

At discharge, 92% (n=427) were prescribed LLT, of whom 422 received statins, either alone (n=414) or in combination with ezetimibe (n=8), whereas five patients were receiving ezetimibe alone. The most frequently prescribed statin was atorvastatin (77%), mean statin dose was 41 mg (SD 21) atorvastatin equivalent dose and 64% (n=276) received HIS. Type and doses of LLT are shown in **Table S3**. In total, 65% of those using LLT prestroke received the same LLT intensity at discharge.

Unadjusted and age- and sex-adjusted associations between patient characteristics and prescription of LLT (yes/no) at discharge are shown in **Table S4**. Prestroke cognitive impairment and cardioembolic stroke etiology were associated with no prescription**.** Patient characteristics associated with dose intensity at discharge are shown in **Table 2**. In analyses excluding cardioembolic stroke, the effect estimates were mostly the same as in Table 2, but there was no significant association between age and statin dose intensity (data not shown).

Achieved LDL-C levels and LLT at follow-up

For patients prescribed LLT at discharge (n=427), mean LDL-C decreased from 3.1 (SD 1.1) to 2.1 (SD 0.7) mmol/L from index stay to 3 months poststroke. For LLT naïve patients the corresponding decreases were from 3.5 (SD 1.0) to 2.0 (SD 0.7) mmol/L and for those receiving prestroke LLT from 2.4 (SD 1.0) to 2.1 (SD 0.7) mmol/L, respectively. In total, 45% (n=193) achieved the LDL-C target of ≤1.8 mmol/L and 33% of these had reached the target by receiving non-HIS, 62% by HIS, 1% by ezetimibe monotherapy, 2% by statin plus ezetimibe and 2% without LLT (discontinued). In total, 14 patients had discontinued statins between discharge and 3 months. For patients not at target, the mean distance to the target was 0.7 (SD 0.6) mmol/L. In total, 58% (n=249) had LDL-C ≤2.0 mmol/L, 11% (n=45) ≤1.4 mmol/L and 2% (n=10) ≤1.0 mmol/L and 78% reported high medication adherence.

Lipid profiles according to subgroups of stroke patients are shown in **Table S5,** where women, younger patients and patients with no prestroke LLT had higher LDL-C at admission. LLT for patients not reaching the target by subgroups of stroke patients is shown in **Table S6**. Target attainment in different subgroups of LLT regimens is shown in **Figure S2,** target attainment was observed in less than half of patients in all LLT intensity groups.

Table 3 shows characteristics in categories defined by quartiles of relative LDL-C reduction. Patients with the largest reduction were younger, had higher LDL-C at index stay, 82% were prescribed HIS and 86% reported optimal adherence. Among patients with the smallest LDL-C reduction, 78% had

prestroke LLT. In total, 28% had achieved ≥50% reduction in LDL-C, mean relative reduction in LDL-C for patients initiating HIS (with no prestroke LLT) was 42.5 % (SD 26).

In total, 73% of the 352 patients with available medication lists at 18 months reported high medication adherence and 11% (n=38) had discontinued statins (10% of men and 13% of women, p=0.337, 9% with HIS and 14% with non-HIS, p=0.229), of whom 4 had switched to ezetimibe monotherapy. Treatment patterns for those still persistent to statins are shown in **Figure S3**. Of patients with no LLT use at discharge or 3 months (n=26), six patients had started with LLT after more than 3 months.

Expected LDL-C levels when theoretically up-titrating LLT

Figure 1 shows LDL-C distribution after theoretically up-titrating LLT according to guidelines, proportions achieving the guideline target for each step and proportions at different LLT. Of the 55% (n=234) of patients not at target at 3 months, 63% (n=147) were already receiving HIS whereas 37% (n=87) could undergo up-titration to HIS **(Step 1), Supplementary Figure S4.** Up-titration in these 87 subjects would result in an additional 18% (n=43) achieving an LDL-C level ≤ 1.8 mmol/L (overall cohort with LDL-C ≤ 1.8 mmol/L, 55% at this stage). Of the remaining 45% (n=191) not at the LDL-C target, six patients were already receiving concomitant ezetimibe. Ezetimibe could be added to the remaining 44% (n=185) receiving HIS who were not at the target **(Step 2).** After this step, an additional 26% would have reached the target (total at target, 81% (n=347)).

After intensification, mean LDL-C changed from 2.1 mmol/L (SD 0.7) to 1.7 mmol/L (SD 0.4). Mean LDL-C for those not reaching the target after intensification (n=80) was 2.2 mmol/L (SD 0.4). Assuming all patients were already using maximally tolerated statin dose and only ezetimibe could be added to current treatment, 75% (n=319) could potentially reach the treatment target.

Expected benefit when theoretically up-titrating LLT

For all patients prescribed LLT (n=427), the median 10-year CVD risk was 42% (IQR 31 to 54%) and lifetime risk was 70% (IQR 64 to 76%). Median CVD-free life expectancy was 80.2 years (IQR 76.2 to 83.2). The median estimated lifetime benefit when up-titrating LLT for those not at target was 5 months (IQR 0 to 12). Median CVD-free life gain was < 6 months for 52% (n=220), 6 to 12 months for 27% (n=115) and > 12 months for 22% (n=92). Estimated median 10-year ARR was 2% (IQR 0 to 4%).

For patients with LDL-C above 1.8 mmol/L (n= 234), the median estimated lifetime benefit by up-titrating LLT was 11 months (IQR 7 to 17), with 39% having > 12 months of estimated CVD-free life gain (**Figure 2, panel D).** Characteristics for patients stratified by tertiles of months of gain in CVD-free life are shown in **Supplementary Table S7**. Estimated 10-year ARR for these patients was median 4% (IQR 3 to 5%), and the median 10-year risk level could be reduced from 40% (IQR 31 to 52%) to 35% (IQR 27 to 46%). Estimated lifetime benefit when excluding patients with cardioembolic stroke etiology (n=51) was 11 months (IQR 7 to 17) and median 10-year ARR was 4% (IQR 3 to 5%). Further up-titration to the LDL-C target 1.4 mmol/L would lead to median 17 months (IQR 11 to 25) of estimated lifetime benefit (**Supplementary Figure S5**). Two illustrative patient examples are shown in **Figure 3**.

Discussion

In this observational study of patients ≤80 years discharged home after relatively minor ischemic strokes, we showed high LLT prescription rates, and although LDL-C levels in many cases were not far from target, less than half of patients reached the target of 1.8 mmol/L. Age, sex, index stroke etiology and baseline LDL-C were related to LLT intensity prescribed; however, target attainment was observed in approximately 40-50% irrespective of age, sex, prestroke LLT, subtypes of stroke and LLT intensity subgroups. Younger patients, women and patients receiving HIS had larger % LDL-C reduction. We estimated that 81% could potentially reach the target with well-established low-cost drugs leading to median of 11 months CVD-free life-gain for patients with elevated LDL-C, but with large interindividual variation.

The prescription rates and mean statin doses were higher in the present study than in other studies (10, 15, 16, 24-27). In total, 63% of those not reaching the target reported using HIS, illustrating that many patients with established CVD do not reach treatment targets by the highest tolerated statin monotherapy dose (13, 15). However, a previous study has noted that LDL-C levels down to a mean of 1.4 mmol/L is possible to achieve if adherence to therapy is optimal and optimized dose of conventional LLT (including ezetimibe) is prescribed (28). Although the Nor-COAST study was conducted between 2015 and 2018 and most physicians were treating towards a target of LDL-C < 2.0 mmol/L (29) (reached by 58% of patients), most patients with dose adjustments had their dose reduced, in line with other studies (30), few used alternative LLT and although reason for discontinuation was not known, 11% discontinued statins within 18 months.

In a previous study also including patients > 80 years, female sex and younger age were associated with poor LDL-C control (14), while higher statin dose was associated with better LDL-C control. As shown in the current analyses, multiple factors might interfere with choice of dose intensity. As in other studies (10, 11, 24, 26, 30, 31), female sex and advanced age were associated with lower dose intensity and females also had higher LDL-C levels at admission. Other studies have shown that females less often receive evidence-based CVD drugs and often experience more adverse drug reactions than men and also more often have lower awareness of their CVD risk (12). Current prescription patterns in the elderly might be explained by the large heterogeneity in underlying health status and life-expectancy (3, 18, 32), as well as age and polypharmacy being risk factors for adverse effects and interactions (3). Although emerging evidence supports similar relative risk reductions for major CVD events regardless of age, including those ≥ 75 years (32), previous guidelines have been less concise in their recommendations. The absolute risk reduction with intensified LLT can be substantial in the elderly. At the same time, the actual increase in life-expectancy might be limited due to risk of both CVD events and competing risks (**Figure 3**) (3, 18, 32).

Cardioembolic stroke was associated with no LLT prescription, while large artery disease etiology was associated with higher dose intensity. Coexisting ischemic heart disease was associated with higher dose intensity. Evidence has historically been more robust for patients with ischemic heart disease and large artery disease (4, 5, 15, 16), and previous studies have reported that patients with ischemic heart disease receive LLT and HIS more often than patients with peripheral and cerebrovascular disease (15, 16). However, the large overlap between ischemic stroke subtypes and the high prevalence of atherosclerosis regardless of stroke etiology illustrate the need for optimal lipid control in all subtypes (33). Furthermore, consistent relative treatment effects across multiple subgroups of patients have been demonstrated in landmark meta-analyses (2, 3) and observational studies show reduced risk of CVD events and mortality with statins also in cardioembolic stroke (34, 35). Though, some of these patients might not have atherosclerosis and treating lipids less intensively might better harmonize with the individual patients' expected benefit.

Concordance with guidelines might not be the ultimate marker of successful treatment for all patients (36). However, not achieving targets might well be influenced by lack of familiarity with guidelines, physicians' and patients' preferences and uncertainty of clinical benefit of LLT which might lead to misinterpretations about the benefit-harm tradeoffs (13, 15-18, 30). Statin intolerance and narrow reimbursement criteria for PCSK9-inhibitors might also be important reasons (16, 17). Moreover, levels are often not far from targets; the physicians might then take a more pragmatic approach. When hypothetically up-titrating LLT, 81% was expected to reach LDL-C ≤1.8 mmol/L with safe, effective low-cost drugs, a proportion similar to large simulation studies (23, 37). Though, the efficiency of LLT is likely to be lower in real-life settings (**Supplementary Table S8**) and PCSK9 inhibitors would be required for a certain proportion especially if aiming for more stringent treatment targets (3, 13, 23). However, the estimated individual net benefit of a more intensive approach varies, depending on baseline CVD risk, level of LDL-C, remaining life-expectancy and competing risks (3, 12, 19). Benefit on group level was largest in younger patients with relatively high LDL-C levels, however, younger age also means longer treatment duration and thereby higher costs to achieve those benefits (**Figure 3**). The amount of benefit considered meaningful is also highly subjective and conditional on side effects, costs, and patient preferences (38). Furthermore, only estimating further up-titration for patients with LDL-C above 1.8 mmol/L underestimated the actual potential benefit of intensified LLT, since CVD risk is linearly related to LDL-C reduction (2, 3) (**Supplementary Figure S5**).

Strengths and limitations

The **strengths** of this study include prospective consecutively inclusion and assessing LLT intensity three time-points post an acute event (3, 7), whereas previous studies are hampered by retrospective design (10, 25) with data collected a long period after an event (10, 25, 30) or solely at discharge (11, 24, 26). We add knowledge about factors influencing LLT use in patients with stroke, which is a less studied group compared to i.e., ischemic heart disease (15). Although proportions with frailty and dementia were low, including detailed clinical information about these features and ischemic stroke etiology is a strength that previous studies lack or have based on registry data and diagnostic codes only (10, 11). Using a lifetime risk prediction model adjusted for competing risk avoids overestimating treatment benefit in older individuals and underestimation of benefit in younger individuals (19). The Nor-COAST study participants have characteristics comparable to patients in the Norwegian Stroke Registry (39) and generalization at least to Norwegian stroke patients and comparable populations is plausible, however, it should be noted that we excluded the oldest patients from these analyses.

Several **limitations** merit considerations. Self-reported use of LLT and medication adherence might overestimate the actual use and might lead to a conservative estimate of the expected LDL-C levels achieved with intensification of treatment in these analyses. We did not account for the large interindividual variations in percentage LDL-C reduction achieved with the same drug dose (3, 13). Whereas most variables only had limited missingness, there was considerable missing for LDL-C at 3 months (24%). In addition, the findings of the current study could further have improved if information regarding drug-related adverse effects or patient preferences was available, as these data might be the reason for non-adherence and reduction in dose intensity. Our cohort does by no means represent a randomized controlled trial setting, from which the LDL-C reductions and hazard ratio were retrieved. Although ischemic stroke has more heterogeneous etiology than, i.e., ischemic heart disease, we assumed all subtypes of stroke had the same relative benefit of LDL-C reduction. However, the SMART-REACH model may perform differently in patients with cardioembolic stroke etiology (1). Moreover, these results give an indication of the impact of conventional LLT but need to

be put into the perspective of a patient's estimated life-expectancy, multimorbidity, polypharmacy and functional impairments (12, 36).

In **conclusion**, in a cohort with recent ischemic stroke ≤ 80 years, almost all patients received LLT at discharge from hospital, but below half of the patients reached the guideline-based LDL-C treatment target. We show potential for improving LDL-C control and reducing residual cholesterol risk with safe, effective well-established low-cost lipid-lowering therapies. Awareness of patient groups at risk of undertreatment, like women, and awareness of an individual patient's risk of CVD events and the benefits of intensifying treatment might help avoid under- and overtreatment. To overcome uncertainties regarding individuals' clinical benefit of further intensification of treatment, the SMART-REACH model can be used to objectively estimate expected benefit. When benefits are known, these can be balanced against potential costs and perceived side-effects, to assist physicians and patients in well-informed treatment decisions.

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Conflict of interest

The authors declares that there is no conflict of interest in this work. IS have been investigator in Boehringer-Ingelheim 1346.0023.

Authors' contributions

MNG, SH, JD, OS, IS, FV and HE contributed to conception and design. MNG drafted the manuscript. MNG, HE and IS contributed to data acquisition. MNG, SH and SL contributed to analysis, and MNG, SH, JD, OS, SL, IS, FV and HE contributed to interpretation and critically revising the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Clinical characteristics at index stay by lipid-lowering therapy use at discharge

	Prescribed lipid-lowering therapy (n = 427)			Not prescribed lipid-lowering therapy (n = 35)	Total population (n = 462)
	Non-high intensity statin (n=146)	High-intensity statin[a] (n=276)	Any[b] (n=427)		
Demographics					
Age (years)	70.4 (8.0)	68.0 (8.0)	68.8 (8.1)	70.7 (8.2)	69.0 (8.1)
Sex, female	57 (39)	105 (38)	163 (38)	14 (40)	177 (38)
Education	12.3 (3.8)	12.6 (3.7)	12.6 (3.7)	11.5 (3.4)	12.5 (3.7)
Home care services	7 (5)	5 (3)	15 (4)	5 (14)	20 (4)
Cardiovascular characteristics					
Atrial fibrillation	38 (26)	46 (17)	84 (20)	16 (46)	100 (22)
Diabetes mellitus	32 (22)	50 (18)	84 (20)	6 (17)	90 (20)
History of hypertension	84 (58)	146 (53)	233 (55)	17 (49)	250 (54)
Prestroke lipid-lowering therapy	69 (47)	89 (32)	160 (37)	1 (3)	161 (35)
Previous cerebrovascular disease	41 (28)	52 (19)	97 (23)	10 (29)	107 (23)
Ischemic heart disease	30 (21)	46 (17)	77 (18)	2 (6)	79 (17)
Peripheral artery disease	15 (10)	19 (7)	34 (8)	0 (0)	34 (7)
Heart failure	2 (1)	6 (2)	8 (2)	3 (9)	11 (2)
Glomerular Filtration Rate (ml/min/1.73 m^2)	79 (15)	78 (16)	79 (16)	77 (21)	79 (16)
Body Mass Index (kg/m^2)	26.2 (4.2)	27.0 (4.3)	26.7 (4.2)	26.0 (3.7)	26.7 (4.2)
Current smoker	34 (23)	101 (37)	100 (24)	9 (26)	109 (24)
Physically active	36 (25)	77 (28)	115 (27)	8 (23)	123 (27)
Lipid levels at index stay					
Total cholesterol (mmol/L)	4.6 (1.2)	5.1 (1.3)	5.0 (1.3)	4.7 (1.4)	5.0 (1.3)
LDL cholesterol (mmol/L)	2.8 (0.9)	3.3 (1.1)	3.1 (1.1)	3.0 (1.3)	3.1 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.6)	1.4 (0.6)	1.4 (0.6)	1.3 (0.4)	1.4 (0.5)
Stroke characteristics and other comorbidities					
NIHSS discharge	1.4 (1.8)	1.7 (2.4)	1.6 (2.2)	2.0 (3.9)	1.7 (2.4)
Stroke subtype (n = 447)					
Large artery disease	10 (7)	38 (14)	48 (12)	1 (3)	49 (11)
Cardioembolic	34 (24)	54 (20)	88 (21)	15 (43)	103 (23)
Small vessel disease	35 (25)	62 (24)	99 (24)	5 (14)	104 (23)
Other cause	5 (4)	6 (2)	11 (3)	1 (3)	12 (3)
Undetermined or multiple causes	59 (41)	104 (39)	166 (40)	13 (37)	179 (40)
Charlson Comorbidity Index	3.8 (1.7)	4.3 (1.9)	3.6 (1.8)	4.1 (1.9)	3.6 (1.8)
Frail	14 (10)	16 (6)	30 (7)	2 (6)	32 (7)
Cognitive impairment	3 (2)	4 (2)	7 (2)	6 (17)	13 (3)
Independent functional status at discharge[c]	102 (70)	196 (71)	303 (71)	21 (60)	324 (70)
Other secondary preventive drugs at discharge					
Antithrombotic drugs	144 (99)	275 (100)	424 (99)	34 (97)	458 (99)
Antihypertensive drugs	113 (77)	205 (74)	321 (75)	25 (71)	346 (75)
Total number of medications	5.3 (2.6)	5.2 (2.4)	5.2 (2.5)	4.0 (3.0)	5.1 (2.6)

Values are n (%) or mean (standard deviation) (n observations). [a] Defined as ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day. [b]5 patients received ezetimibe monotherapy. [c]Defined as ≤2 on Modified Rankin Scale.

Abbreviations: LDL; Low density lipoprotein, HDL; High density lipoprotein; NIHSS, National Institutes of Health Stroke Scale. Detailed definitions in supplementary methods.

Table 2. Linear regression with statin dose intensity (mg) [a] as dependent variable, for participants prescribed statin monotherapy at discharge (n = 414)

		Unadjusted analysis		Age- and sex adjusted analysis	
	n	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Age, years	414	-0.30 (-0.55 to -0.05)	0.019	-0.26 (-0.51 to -0.01)	0.039
Sex, female	414	-5.1 (-9.2 to -0.9)	0.017	-4.5 (-8.6 to -0.3)	0.036
LDL-C[b], mmol/L	414	2.7 (0.9 to 4.5)	0.004	2.8 (0.9 to 4.6)	0.003
Prestroke use of LLT	414	-2.4 (-6.6 to 1.8)	0.268	-1.8 (-6.1 to 2.4)	0.402
Frailty[c]	414	0.2 (-2.0 to 2.3)	0.889	1.3 (-0.9 to 3.5)	0.249
Cognitive impairment[d]	408	0.2 (-3.0 to 3.4)	0.918	0.8 (-2.4 to 4.0)	0.626
Ischemic heart disease	414	6.1 (0.8 to 11.4)	0.024	6.7 (1.3 to 12.1)	0.016
Index stroke etiology[e]	399				
Large artery disease		Reference category		Reference category	
Cardioembolic stroke		-11.8 (-19.4 to -4.2)	0.002	-11.6 (-19.1 to -4.1)	0.003
Small vessel disease		-11.3 (-18.8 to -3.8)	0.003	-11.3 (-18.8 to -3.9)	0.003
Undetermined or multiple causes		-9.2 (-16.2 to -2.3)	0.010	-9.4 (-16.3 to -2.4)	0.008

[a]Atorvastatin equivalent dose. [b]Measured at first day after admission [c]Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail. [d]Prestroke, measured by Global deterioration scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia. [e]Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. Abbreviations: LDL-C, Low-density lipoprotein cholesterol.

Table 3. Characteristics in categories defined by quartiles of % LDL-cholesterol reduction from index stay to the 3-month visit for patients prescribed LLT at discharge (n=427)

	≤Q1 < 8% reduction (n=107)	Q1 to Q2 9 to 35% reduction (n=107)	Q2 to Q3 36 to 51% reduction (n=107)	Q3 >51% reduction (n=106)
Median % reduction (IQR)	-6 (-28 to 0)	23 (16 to 29)	44 (39 to 48)	57 (54 to 61)
Age, mean (SD)	70.3 (8.1)	69.3 (7.8)	68.9 (8.3)	66.9 (7.9)
Sex, female	28 (26)	42 (39)	44 (41)	49 (46)
Body Mass Index (kg/m^2), mean (SD)	26.7 (4.1)	26.6 (4.8)	26.5 (4.1)	27.0 (3.9)
Current smoker at admission	26 (24)	22 (21)	23 (22)	29 (27)
Hypertension	81 (76)	66 (62)	44 (41)	42 (40)
Prestroke use of LLT	83 (78)	51 (48)	18 (17)	8 (8)
Diabetes mellitus	28 (26)	20 (19)	19 (18)	17 (16)
History of ischemic heart disease	41 (28)	19 (18)	13 (12)	4 (4)
Prior stroke	45 (42)	29 (27)	11 (10)	12 (11)
Charlson Comorbidity Index	4.3 (1.8)	3.8 (2.0)	3.2 (1.4)	3.1 (1.8)
Frail	7 (7)	9 (8)	6 (6)	8 (8)
Cognitive impairment	4 (4)	3 (3)	0 (0)	0 (0)
Stroke subtype (n=412)				
Large artery disease	10 (9)	14 (14)	13 (12)	11 (11)
Cardioembolic stroke	33 (31)	24 (24)	18 (17)	13 (13)
Small vessel disease	19 (18)	24 (24)	27 (26)	29 (29)
Other	3 (3)	3 (3)	5 (5)	0 (0)
Undetermined	40 (38)	36 (35)	43 (41)	47 (47)
LDL-C at index stay, mean (SD)	2.1 (0.8)	2.8 (0.8)	3.5 (0.9)	4.0 (0.9)
LDL-C at 3 months, mean (SD)	2.4 (0.8)	2.1 (0.6)	2.0 (0.5)	1.7 (0.4)
10-year CVD risk (%)[a], median (IQR)	50 (38 to 63)	43 (33 to 54)	40 (30 to 52)	37 (29 to 49)
Discontinued statin between 0 and 3 months	7 (7)	6 (6)	1 (1)	0 (0)
Optimal medication adherence[b] (n=351)	70/87 (81)	67/87 (77)	69/90 (77)	75/87 (86)
Non-high intensity statin	50 (47)	37 (35)	37 (35)	19 (18)
High-intensity statin	50 (47)	64 (60)	69 (64)	87 (82)
At target at 3 months	29 (27)	41 (38)	47 (44)	76 (72)

Values are n/N (%) if other not specified. [a]Estimated by the SMART-REACH model. [b]Corresponding to score 4 on Morisky Medication Adherence Scale 4. Abbreviations: LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; LLT, lipid-lowering therapy; CVD, cardiovascular disease; SD, standard deviation; IQR, interquartile range. Detailed definitions of variables in Supplementary Methods.

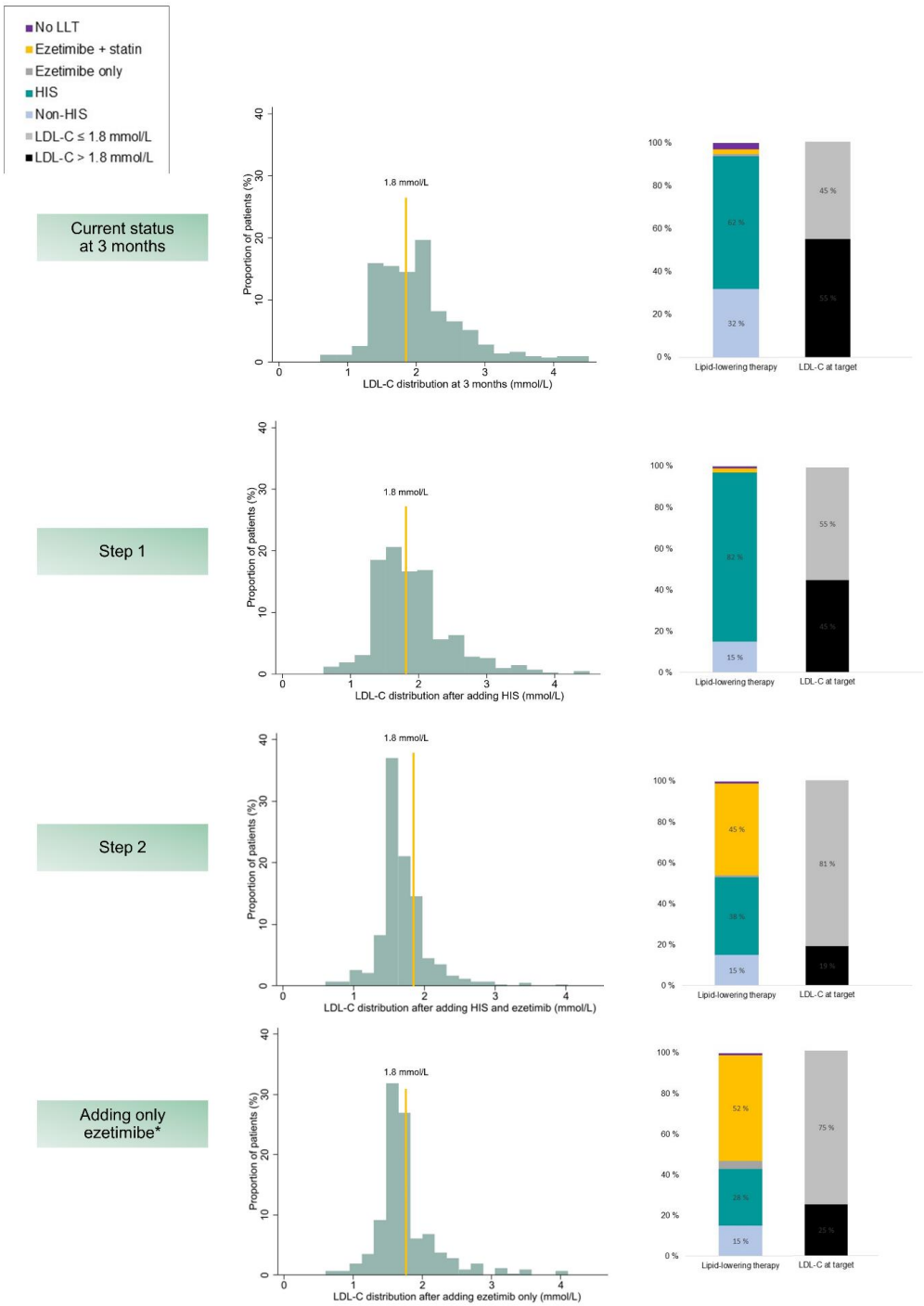

Figure 1. Distribution of LDL-C, proportions at target ≤1.8 mmol/L and LLT in use at 3 months and after hypothetically up-titrating LLT according to guideline-recommendations first (step 1) by

adding / up-titrating to high intensity statin, and next (step 2) by adding ezetimibe.*Assuming already on maximally tolerated statin dose. Proportions are n of the total population (n=427). Patients with no LLT, are patients who have discontinued prescribed LLT between discharge and 3 months. Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; HIS, high-intensity statin.

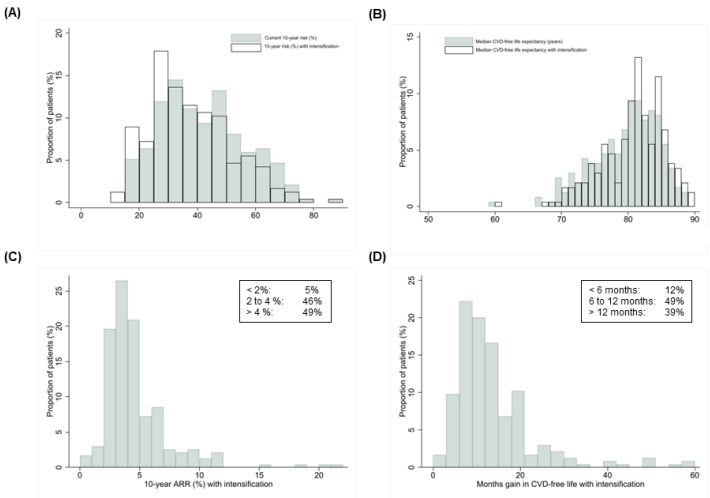

Figure 2. Estimated prognostic impact of intensification of lipid-lowering therapy according to the guideline-recommendations for patients with LDL-C above 1.8 mmol/L at 3 months (n=234). *The top row shows (A) the distribution of the estimated 10-year CVD before and after intensification and (B) estimated median life-expectancy free from CVD events before and after intensification. The bottom row shows (C) distribution of estimated 10-year ARRs with intensification and (D) distribution in gain in months free from CVD events with intensification.* Abbreviations: LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; ARR, absolute risk reduction

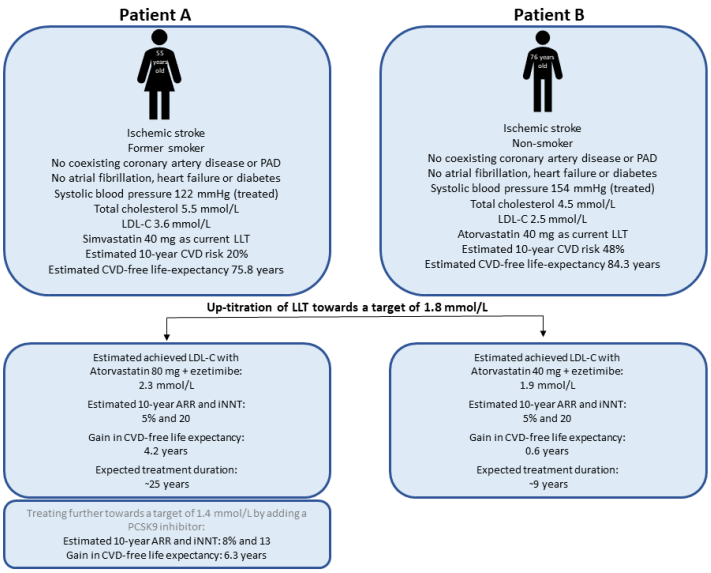

Figure 3. **Patient examples**. The benefit of intensification of current lipid-lowering therapy estimated by the SMART-REACH model for patients aged 55 years versus 76 years and expected treatment duration. Abbreviations: PAD, peripheral artery disease; LLT, lipid-lowering therapy; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ARR, absolute risk reduction; iNNT, individual number-needed-to-treat (1 divided by ARR); PCSK9, proprotein convertase subtilisin/kexin type 9.

Supplementary Paper III

SUPPLEMENTARY MATERIAL

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Supplementary methods

Data collection and definitions used in Nor-COAST

Atrial fibrillation was defined by self-report or documented on electrocardiogram or telemetry during admission. Prestroke diabetes mellitus was defined as self-reported diabetes or HbA1c ≥ 48 mmol/mol at index stay or prescribed antidiabetic drugs at admission. Hypertension was defined as self-reported hypertension or use of antihypertensive drugs. Prestroke use of lipid-lowering therapy was defined as use of ATC classes: C10AA, C10B, C10AC or C10AX. Prevalence of previous cerebrovascular disease and coronary heart disease was retrieved from hospital medical records. Estimated glomerular filtration rate was based on the CKD-EPI equation (1). Physically active was defined as self-reported adherence to physical activity guidelines defined as minimum 75 min per week of high-intensity exercise or minimum 150 min per week of moderate intensity exercise. Stroke severity was measured according to National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification by experienced stroke physicians (2). Frailty was measured by a modified version of the Fried frailty criteria (3), giving a score from 0 (robustness) to 5 (frail) based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss. Cognitive impairment was defined as score ≥ 3 on Global Deterioration Scale (4), a global measure of cognitive function and ability to perform daily life activities. Trained study nurses used all available information from interviews with caregivers during hospital stay to give a score from 1 (normal cognitive function) to 7 (severe dementia). Independent functional status was defined as Modified Rankin Scale ≤2.

Estimation of achievable LDL-C levels when up-titrating LLT according to guideline recommendations

We used the mean percentage change in LDL-C reduction with statins and ezetimibe as presented and validated by Cannon et al. (5) (as shown in **Supplementary table S1**) to estimate potentially achievable LDL-C levels when up-titrating therapy for those not already at the target at 3 months. For patients already using a high-intensity statin (HIS), achieved LDL-C levels at 3 months were used when calculating the effect of adding ezetimibe. For patients using non-high intensity statins, we calculated additional LDL-C reduction (based on LDL-C levels achieved at 3 months) by switching from non-high intensity statin to HIS, for example for switching from atorvastatin 10 mg (associated with 35.5% LDL-C reduction) to atorvastatin 80 mg (associated with 50.2% LDL-C reduction), the assumed additional LDL-C reduction was 23% (1-(1-0.502)/(1-0.355)) (5). After up-titrating all to a high-intensity statin, we assumed a mean 22.7% reduction in LDL-C when adding ezetimibe (5, 6).

Assessment of cardiovascular risk and benefit of LDL-C lowering by the SMART-REACH model

The SMART-REACH model is a Fine and Gray model consisting of two complementary competing-risk-adjusted cause specific hazard functions; one for vascular events, and one for non-vascular mortality, where age is used as the underlying time function (7). The model uses the following predictors: age, sex, current smoking, diabetes mellitus, systolic BP, history of heart failure, history of atrial fibrillation, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and

number of locations of vascular disease (cerebrovascular, coronary and peripheral artery disease). Since the model is intended for use in patients with stable cardiovascular disease, clinical measurements at the 3-month visit were used in the analysis. Detailed definition of the variables in the model have been previously published when validating the model in Nor-COAST (8). Missing data for the relevant variables and mean levels at 3 months are shown in **Supplementary Table S2.**

The SMART-REACH model was used to estimate life expectancy (years) without a recurrent cardiovascular event for individual patients and 10-year risk of CVD events by calculating the cumulative cause-specific event-risk truncated at 10 years after age at baseline (7, 9). To estimate the benefit of the guideline-recommended intensification of LLT, the cardiovascular risk was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month LDL-C levels, and next we estimated the risk with the achieved LDL-C levels after intensification. The difference between estimated 10-year risk and healthy life-expectancy with 3-month LDL-C levels and estimated risk after intensification corresponds to the individuals' absolute benefit.

The effect of LLT on CVD events depends on the estimated reduction in LDL-C compared to baseline. A hazard ratio of **0.78 was assumed per 1.0 mmol/L reduction in LDL-C** (10). The individuals' expected relative risk reduction was calculated by $0.78^{\text{LDL-C reduction in mmol/L}}$. LDL-C reduction in mmol/L was defined as the 3-month LDL-C level minus achieved LDL-C level after intensification.

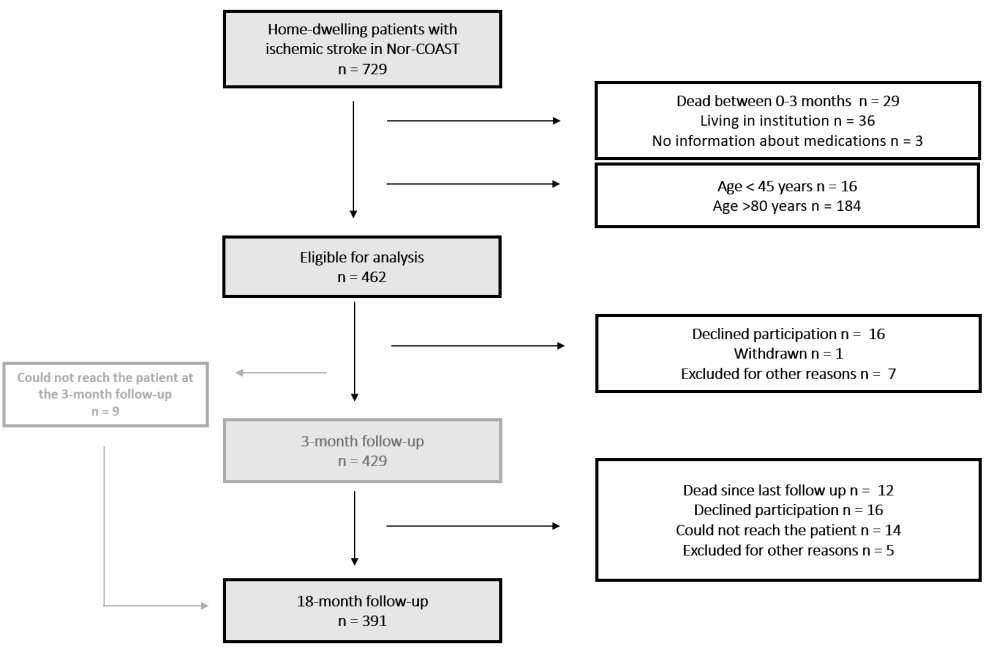


Figure S1. Flowchart of inclusion and exclusion of participants in current analysis

Table S1. Mean and standard deviation (SD) percentage change in LDL-C reduction with statins and ezetimibe, as presented and validated by Cannon et al. (5)			
Drug	**Dose, mg**	**Mean (reference)**	**SD (reference)**
Atorvastatin	10	35.5% (11)	10.6% (5, 12)
	20	41.4% (11)	13.5% (5, 12)
	40	46.2% (11)	12.5% (5, 12)
	80	50.2% (11)	13.8% (5, 12)
Fluvastatin	20	17.0% (12)	8.0% (12)
	40	23.0% (12)	10.0% (12)
	80	26.0% (12)	9.0% (12)
Lovastatin	10	21.0% (13)	10.1% (5)
	20	24.0% (14)	11.0% (14)
	40	30.0% (14)	11.0% (14)
	60	34.5% (5)	11.7% (5)
Pravastatin	10	20.0% (12)	11.0% (12)
	20	24.0% (12)	11.0% (12)
	40	30.0% (12)	13.0% (12)
	80	33.0% (13)	11.2% (5)
Rosuvastatin	5	38.8% (11)	13.2% (5)
	10	44.1% (11)	12.5% (5, 12)
	20	49.5% (11)	13.3% (5, 12)
	40	54.7% (11)	12.9% (5, 12)
Simvastatin	5	23.0% (13)	11.0% (5, 12)
	10	27.4% (11)	13.7% (5, 12)
	20	33.0% (11)	10.4% (5, 12)
	40	38.9% (11)	14.0% (5, 12)
	80	45.0% (11)	11.7% (5, 12)
Ezetimibe	10	22.7% (6)	16.5% (15)

Table S2. Levels of cardiovascular risk factors at 3 months for variables included in the SMART-REACH model (7) and n (%) missing for the relevant variables at 3 months (N=462)		
	Mean (SD) or n (%)	**n (%) missing at 3 months**
Age, years	69.0 (8.1)	0 (0%)
Sex, female	177 (38%)	0 (0%)
Current smoking[b]	54 (12%)	65 (14%)
Diabetes mellitus	90 (20%)	0 (0%)
Congestive heart failure	11 (2%)	0 (0%)
Atrial fibrillation	100 (22%)	0 (0%)
Systolic blood pressure (mmHg)	140 (19)	69 (15%)
Creatinine (µmol/L)	82 (22)	116 (25%)
Total cholesterol (mmol/L)	4.0 (0.9)	110 (24%)
LDL cholesterol (mmol/L)	2.1 (0.7)	112 (24%)
Cerebrovascular disease	462 (100%)	0 (0%)
History of ischemic heart disease	79 (17%)	0 (0%)
History of peripheral artery disease	34 (7%)	0 (0%)

Abbreviations: LDL, low-density lipoprotein

Table S3. Types and daily doses of statins and ezetimibe for patients using lipid lowering drugs at discharge and 18 months (n)		
	Discharge* (n = 427)	**18 months** (n = 321)**
Simvastatin n (%)	**80 (19%)**	**56 (17%)**
10 mg	3	4
20 mg	18	11
40 mg	56	33
80 mg	3	6
Unknown dose	0	2
Pravastatin n (%)	**6 (1%)**	**6 (2%)**
10 mg	1	**0**
20 mg	4	3
40 mg	0	2
80 mg	1	1
Atorvastatin n (%)	**328 (77%)**	**245 (76%)**
10 mg	5	17
20 mg	52	55
40 mg	191	121
60 mg	0	2
80 mg	80	48
Unknown dose	0	2
Rosuvastatin n (%)	**3 (1%)**	**4 (1%)**
5 mg	2	2
10 mg	0	1
20 mg	1	1
40 mg	0	0
Fluvastatin n (%)	**5 (1%)**	**3 1%)**
20 mg	2	0
40 mg	1	2
80 mg	2	1
Ezetimibe 10 mg monotherapy n (%)	**5 (1%)**	**7 (2%)**
Ezetimibe 10 mg in addition to statin n (%)	**8 (2%)**	**13 (4%)**

*In total, 412 were prescribed statins at discharge, while 10 patients received statins between 0-3 months, which was defined as statins at discharge. In addition, 5 patients received ezetimibe monotherapy. **Type and dose regardless of prescription at discharge or not. No patients used PCSK9-inhibitors.

Table S4. Logistic regression with prescription of lipid-lowering therapy at discharge as dependent variable (n= 462)

		Unadjusted analysis		Age- and sex adjusted analysis	
	n	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, years	462	0.97 (0.92 to 1.02)	0.185	0.97 (0.92 to 1.01)	0.191
Sex, female	462	0.93 (0.46 to 1.88)	0.831	1.00 (0.50 to 2.10)	0.989
LDL-C[a] (mmol/L)	462	1.13 (0.83 to 1.55)	0.439	1.09 (0.79 to 1.51)	0.584
Prestroke LLT	462	20.4 (2.76 to 150.30)	0.003	23.6 (3.18 to 175.39)	0.002
Frailty[b]	462	0.77 (0.56 to 1.07)	0.123	0.80 (0.57 to 1.13)	0.205
Cognitive impairment[c] prestroke	456	0.59 (0.43 to 0.80)	0.001	0.60 (0.44 to 0.83)	0.002
History of ischemic heart disease	462	3.63 (0.85 to 15.5)	0.081	4.30 (0.99 to 18.7)	0.051
Index stroke etiology[d]	447				
Cardio embolic stroke		Reference category		Reference category	
Large artery disease		8.18 (1.04 to 63.8)	0.045	8.09 (1.03 to 63.27)	0.046
Small vessel disease		3.38 (1.17 to 9.66)	0.023	3.24 (1.13 to 9.30)	0.029
Undetermined or multiple causes		2.16 (1.00 to 4.66)	0.051	2.06 (0.95 to 4.48)	0.068

[a]Measured at first day after admission [b]Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail. [c]Measured by Global deterioration scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia. [d]Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. There were no patients with large artery disease as stroke etiology not receiving lipid-lowering therapy at discharge. Abbreviations: OR, odds ratio; LDL-C, Low-density lipoprotein cholesterol.

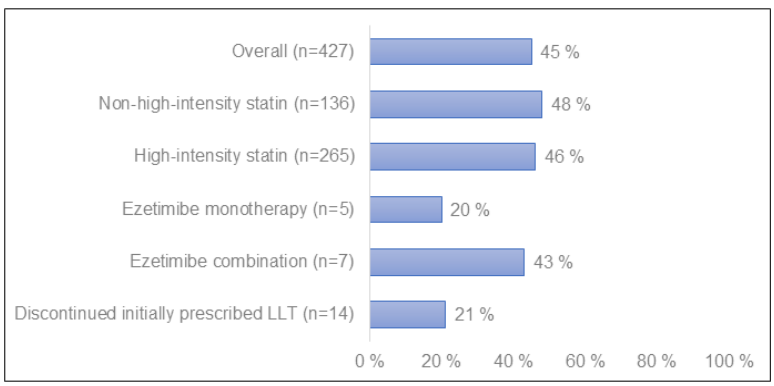
Table S5. Lipid profile according to subgroups of stroke patients at index stay and 3 months follow-up (n=427)

	Index stay				3-month follow-up				
	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Mean distance from target[c]
All (n=427)	5.0 (1.3)	3.1 (1.1)	1.4 (0.6)	53 (12%)	4.0 (0.8)	2.1 (0.7)	1.5 (0.5)	193 (45%)	0.7 (0.6)
Men (n=264)	4.7 (1.2)	3.0 (1.1)	1.3 (0.5)	39 (15%)	3.8 (0.8)	2.1 (0.7)	1.4 (0.5)	115 (44%)	0.7 (0.6)
Women (n=163)	5.3 (1.3)	3.3 (1.1)	1.6 (0.6)	14 (9%)	4.2 (0.8)	2.1 (0.6)	1.7 (0.5)	78 (48%)	0.7 (0.6)
Age groups									
45 – 59 years (n=61)	5.2 (1.2)	3.3 (1.0)	1.4 (0.5)	6 (10%)	3.9 (0.8)	2.1 (0.7)	1.5 (0.5)	25 (41%)	0.8 (0.6)
60 – 69 years (n=135)	5.2 (1.3)	3.4 (1.2)	1.4 (0.5)	9 (7%)	3.9 (0.8)	2.1 (0.7)	1.4 (0.6)	60 (44%)	0.7 (0.6)
70 – 80 years (n=231)	4.7 (1.2)	2.9 (1.0)	1.5 (0.6)	38 (17%)	4.0 (0.8)	2.0 (0.6)	1.6 (0.5)	108 (47%)	0.7 (0.6)
No prestroke LLT (n=267)	5.4 (1.1)	3.5 (1.0)	1.5 (0.5)	9 (3%)	3.9 (0.8)	2.0 (0.7)	1.6 (0.5)	122 (46%)	0.7 (0.6)
Prestroke LLT (n=160)[a]	4.2 (1.1)	2.4 (1.0)	1.4 (0.6)	44 (28%)	4.0 (0.8)	2.1 (0.7)	1.4 (0.5)	71 (44%)	0.7 (0.8)
Stroke subtype									
Large artery disease (n=48)	5.0 (1.2)	3.1 (1.1)	1.4 (0.7)	5 (10%)	3.8 (0.8)	2.0 (0.6)	1.5 (0.4)	25 (52%)	0.6 (0.4)
Cardioembolic stroke (n=88)	4.7 (1.2)	2.9 (1.1)	1.4 (0.4)	15 (17%)	4.0 (0.8)	2.2 (0.8)	1.4 (0.4)	37 (42%)	0.8 (0.7)
Small vessel disease (n=99)	5.1 (1.3)	3.2 (1.2)	1.6 (0.6)	12 (12%)	4.0 (0.8)	2.0 (0.7)	1.6 (0.7)	48 (49%)	0.7 (0.6)
Undetermined or other (n=177)	5.1 (1.2)	3.2 (1.1)	1.4 (0.5)	19 (11%)	4.0 (0.80)	2.1 (0.6)	1.5 (0.5)	77 (44%)	0.6 (0.6)

Values are mean (SD) or n (%). [a]39% of men were using LLT at admission and 34% of women. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]Mean (SD) distance (mmol/L) from the LDL-C target 1.8 mmol/L for patients not at target. Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

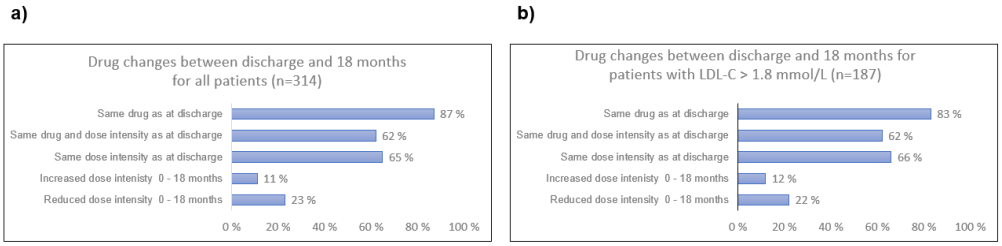
Table S6. Lipid-lowering therapy (LLT) at 3 months for patients prescribed LLT at discharge not reaching the target (n=234) by subgroups of stroke patients					
	Discontinued LLT[a]	Non-HIS	HIS	Ezetimibe monotherapy	Ezetimibe + statin[c]
All	11 (5%)	71 (30%)	144 (61%)	4 (2%)	4 (2%)
Men (n=149)	8 (5%)	46 (31%)	87 (58%)	4 (3%)	4 (3%)
Women (n=85)	3 (4%)	25 (29%)	57 (67%)	0 (0%)	0 (0%)
Age groups (years)					
<60 (n=36)	2 (6%)	9 (25%)	25 (69%)	0 (0%)	0 (0%)
60 – 69 (n=75)	4 (5%)	19 (25%)	50 (67%)	1 (1%)	1 (1%)
70 – 80 (n=123)	5 (4%)	43 (35%)	60 (56%)	3 (3%)	3 (2%)
Stroke subtype[b]					
Large artery disease (n=23)	0 (0%)	4 (17%)	17 (74%)	0 (0%)	2 (9%)
Cardioembolic stroke (n=51)	3 (6%)	19 (37%)	29 (57%)	0 (0%)	0 (0%)
Small vessel disease (n=51)	7 (8%)	22 (43%)	24 (47%)	1 (2%)	0 (0%)
Undetermined or other (n=100)	4 (4%)	25 (25%)	66 (66%)	3 (3%)	2 (2%)

[a]Discontinued LLT between discharge and 3 months. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]3 out of 4 received high-intensity statin. Abbreviations: LLT, lipid-lowering therapy; HIS, high-intensity statin; LDL-c, low-density lipoprotein cholesterol



Supplementary figure S2. Proportions at LDL-C target at 3 months in subgroups of lipid-lowering therapy regimen.

Abbreviations: LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol



Supplementary Figure S3. Statin drug type and dose intensity at 18 months follow-up compared to discharge

For a) all patients with information on medications in use and persistent to statins at 18 months (n=314) and b) patients still not reaching the LDL-C target ≤1.8 mmol/L at 18 months (n=187). A total of 352 patients prescribed statins at discharge had medication lists at 18 months follow-up (18% missing).

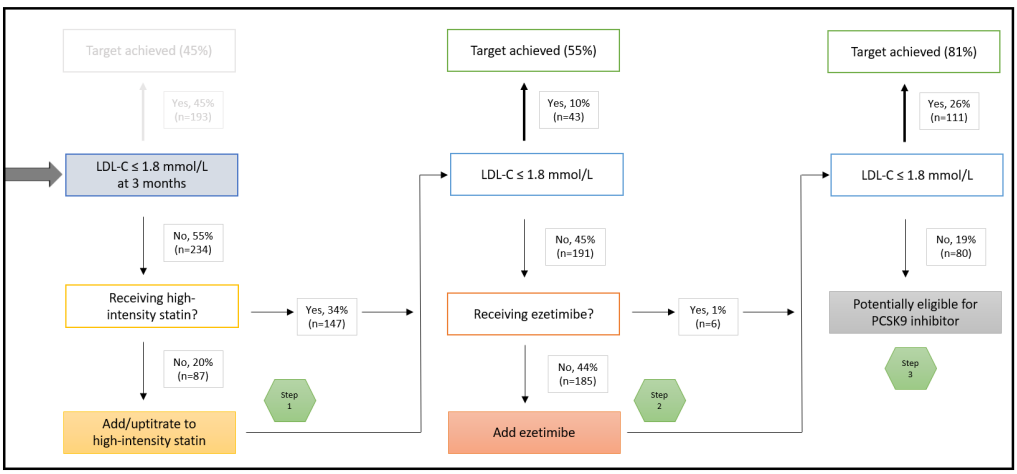


Figure S4. Estimation of effect of up-titration of lipid lowering treatment according to guideline recommendations and proportion of patients reaching LDL-C ≤1.8 mmol/L

With Step 1; Adding / up-titrating to high intensity statin, Step 2; Adding ezetimibe. Proportions are n of the total population (n=427). Abbreviations: LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Table S7. Characteristics for patients according to tertiles (T1 to T3) of months gain in CVD-free life by up-titrating lipid-lowering therapies according to the stepwise guideline-recommendation for patients with LDL-C above the guideline recommended target 1.8 mmol/L (n=234)

	T1 (n=79)	T2 (n=79)	T3 (n=76)
Median CVD-free life months (IQR)	**6.0 (4.8 to 7.2)**	**10.8 (9.6 to 12)**	**18.6 (16.8 to 25.8)**
Age, y	73.1 (5.6)	69.1 (6.8)	63.2 (9.5)
Sex, female	19 (24%)	36 (46%)	30 (39%)
Diabetes mellitus	26 (33%)	12 (15%)	7 (9%)
≥ 2 vascular areas[a] involved	31 (39%)	13 (16%)	8 (11%)
Current smoker at 3 months	12 (15%)	6 (8%)	7 (9%)
Systolic blood pressure (mmHg)[b]	141 (22)	142 (15)	141 (18)
Total Cholesterol [b], mmol/L	4.0 (0.5)	4.3 (0.6)	4.8 (0.8)
HDL Cholesterol [b], mmol/L	1.5 (0.7)	1.5 (0.4)	1.4 (0.4)
LDL Cholesterol [b], mmol/L	2.1 (0.3)	2.4 (0.4)	2.9 (0.7)
Estimated GFR (ml/min/1.73 m²) [b, c]	70 (16)	78 (16)	85 (16)
High sensitive CRP (mg/L) [b]	3.3 (7.3)	3.1 (4.1)	3.7 (8.0)
Frail[d]	2 (3%)	6 (8%)	2 (3%)
Prestroke dementia[e]	4 (5%)	1 (1%)	0 (0%)
Ischemic stroke subtype			
Large artery disease	9 / 75 (12%)	10 / 75 (13%)	4 / 75 (5%)
Cardioembolic stroke	18 / 75 (24%)	16 / 75 (21%)	17 / 75 (23%)
Small vessel disease	20 / 75 (27%)	10 / 75 (13%)	21 / 75 (28%)
Other, undetermined or unknown	28 / 75 (37%)	39 / 75 (52%)	33 / 75 (44%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; HDL, High density lipoprotein; GFR, Glomerular Filtration Rate; CRP, C-reactive protein.

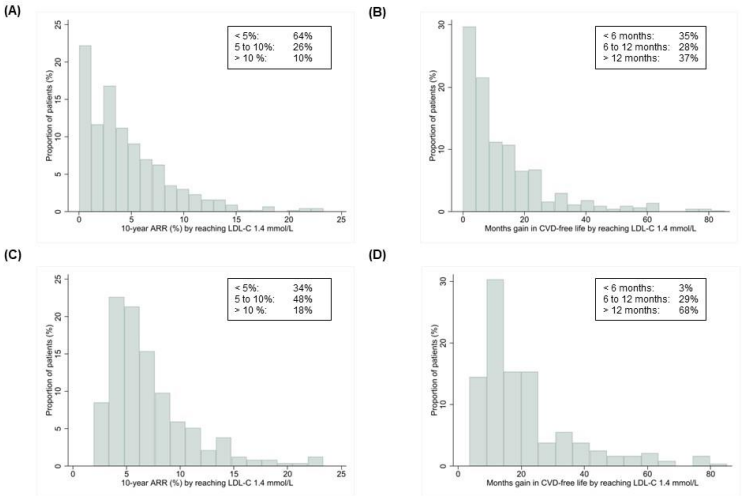


Figure S5. Estimated prognostic impact of reaching an LDL-C level of 1.4 mmol/L

The top row shows (A) distribution of estimated 10-year ARRs (B) distribution in gain in months free from CVD events for all patients prescribed LLT (n=427) when reacing LDL-C 1.4 mmol/L. The bottom row shows (C) distribution of estimated 10-year ARRs and (D) distribution in gain in months free from CVD events for patients with LDL-C above 1.8 mmol/L at 3 months (n=234) when reaching LDL-C 1.4 mmol/L. Abbreviations: LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; ARR, absolute risk reduction.

Table S8. Sensitivity analysis using other effect estimates for % LDL-C reduction when intensifying LLT

	% estimated at target at 3 months with HIS only	Mean LDL-C (mmol/L) (SD) obtained after adding HIS	% estimated at target when adding ezetimibe	Mean LDL-C (mmol/L) (SD) obtained after adding HIS and ezetimib
Main analysis	55%	1.9 (0.6)	81%	1.7 (0.4)
Using LDL-C values at index stay	58%	1.9 (0.7)	84%	1.7 (0.4)
Using % reduction obtained by Rosuvastatin 40 mg[c]	58%	1.9 (0.6)	82%	1.7 (0.4)
Using mean % reduction obtained in Nor-COAST[a]	49%	2.0 (0.6)	68%	1.8 (0.5)
Using % reduction obtained in SWEDEHEART (16)[b]	48%	2.0 (0.6)	66%	1.8 (0.5)

[a]Mean % reduction for patients prescribed HIS at discharge not at LLT prestroke (n=181) was 42.5% (SD 26), for ezetimibe naïve (n=5) the mean % reduction was 16.2%. [b]Mean % reduction in LDL-C obtained with high-intensity statin in SWEDEHEART was 39.7% (SD 15.7) (16), when adding ezetimibe 14.7% (SD 21.3). [c]Rosuvastatin 40 mg is assumed to reduce LDL-C by 54.7% and ezetimibe 22.7%. Abbreviations: HIS, high-intensity statin; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

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