JIM Original Article

doi: 10.1111/joim.13161

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*; 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

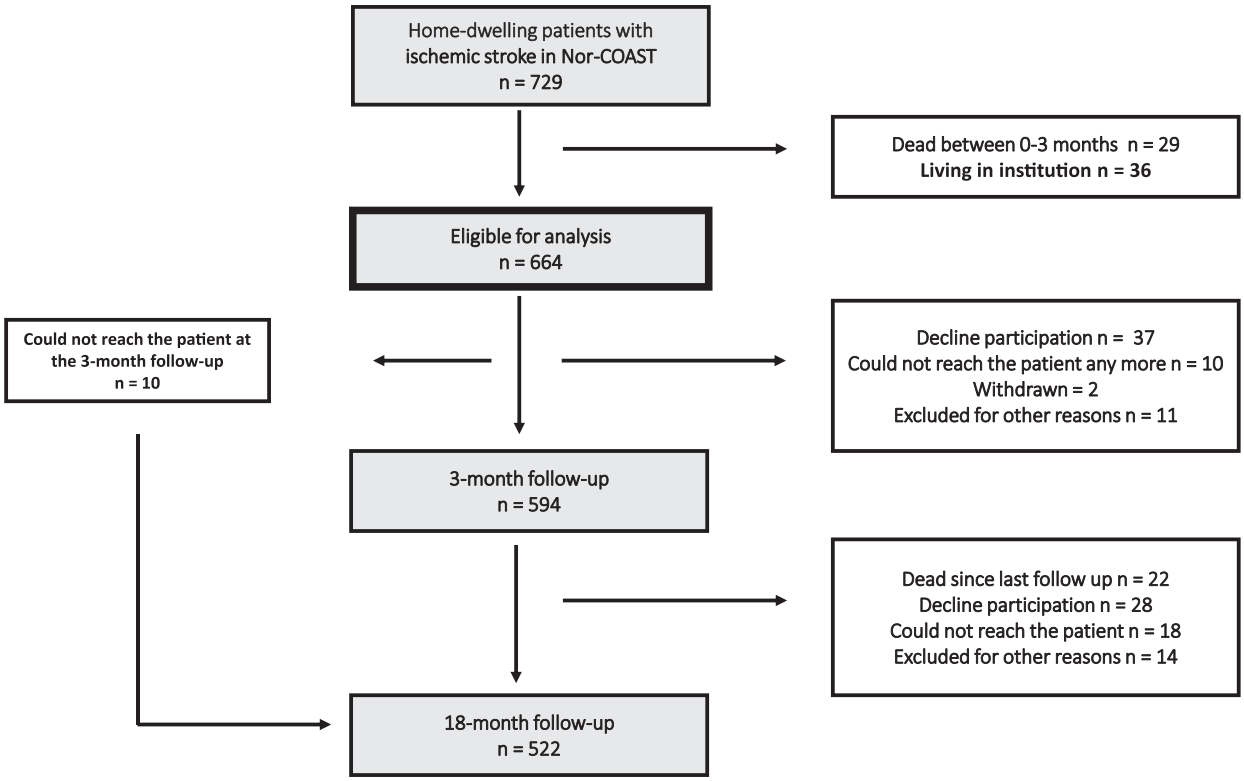

Fig. 1 *Flow chart of inclusion and exclusion of participants in current analysis.*

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].

Acknowledgements

We thank all study participants for their contribution to the study and the research staff at all the participating hospitals. MMAS Research Morisky Widget Software U.S. Copyright Office Number TX 8-816-517 is protected by U.S. Copyright laws. Permission for use is required. A license agreement was made between St. Olav University Hospital and MMAS Research LLC. A license is available from: MMAS Research LLC. E-mail: strubow@-morisky.org

Funding

The Nor-COAST study is funded by the Norwegian Health Association, and additional funding was provided by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, Norwegian University of Science and Technology. The work by Mari Nordbø Gynnild was funded by Dam Foundation and from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU).

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 (%).

