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Investigating the prevalence, predictors and prognosis of suboptimal statin use early after a non-ST elevation acute coronary syndrome

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Abstract

Background High potency statin therapy is recommended in the secondary prevention of cardiovascular disease but discontinuation, dose reduction, statin switching and/or non-adherence occur in practice.

Objectives To determine the prevalence and predictors of deviation from high potency statin use early after a non-ST elevation acute coronary syndrome (NSTE-ACS), and its association with subsequent major adverse cardiovascular events (MACE) and all-cause mortality (ACM).

Methods 1,005 patients from a UK-based prospective NSTE-ACS cohort study discharged on high potency statin therapy (atorvastatin 80mg, rosuvastatin 20mg or 40mg daily) were included. At one month, patients were divided into constant high potency statin users, and suboptimal users incorporating statin discontinuation, dose reduction, switching statin to a lower equivalent potency and/or statin non-adherence. Follow up was a median 16 months.

Results There were 156 suboptimal (~15.5%) and 849 constant statin users. Factors associated in multivariable analysis with suboptimal statin occurrence included female sex (odds ratio (OR) 1.75, 95% confidence interval (CI) 1.14-2.68) and muscular symptoms (OR 4.28, 95% CI 1.30-14.08). Suboptimal statin use was associated with increased adjusted risks of time to MACE (hazard ratio (HR) 2.10, 95% CI 1.25-3.53, p=0.005) and ACM (HR 2.46, 95% CI 1.38-4.39, p=0.003). Subgroup analysis confirmed that the increased MACE/ACM risks were principally attributable to statin discontinuation/non-adherence.

Conclusion Conversion to suboptimal statin use is common early after NSTE-ACS, and is partly related to muscular symptoms. Statin discontinuation/non-adherence carries an adverse prognosis. Interventions that preserve and enhance statin utilisation could improve post NSTE-ACS outcomes.

Key words

Statin, cardiovascular, mortality, discontinuation, non-adherence, muscular symptoms

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide[1, 2]. In the US and the UK, CVD accounts for the largest and second largest proportions of healthcare expenditure of any disease category, respectively[3-5]. Although an acute coronary syndrome (ACS) is a sudden event, most of the morbidity and mortality accrues later, following hospital discharge. Statins are 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors that reduce circulating low-density lipoprotein-cholesterol (LDL-C). Following an ACS, high potency statin therapy, prescribed as atorvastatin 80mg daily, is indicated because it has been demonstrated in randomized controlled trials (RCTs) to be highly effective and superior to both placebo and moderate statin therapy for reducing cardiovascular events[6-8]. However, the effectiveness of drugs in RCTs can be undermined in clinical practice by several factors including poor adherence, discontinuation, and switching prescriptions to a lower equivalent potency. Poor statin adherence has been reported in up to 50% of patients[9], statin discontinuation rates vary from 15%[10] to 60-75%[11, 12] and changing to lower potency statin therapy has been noted in ~1%[13] to 42%[14] of patients.

It is important to understand the clinical consequences of deviating from recommended high potency statin therapy in high-risk patients who have had at least one cardiovascular event. The adverse effects of statin non-adherence and discontinuation on cardiovascular clinical outcomes have been investigated previously[15-17], but relatively little is known about the impact of statin dose reductions and/or switching to a statin of lower equivalent potency in real world secondary prevention[14]. The collective extent to which statin discontinuation, dose reduction, switching and/or non-adherence occur early in secondary prevention is also under-reported. Furthermore, few real world statin adherence studies have focussed exclusively on non-ST elevation ACS (NSTE-ACS) patients, which as a group are often older, have more comorbidities, are more likely to receive non-interventional medical management and have a worse long term prognosis than patients suffering an ST-elevation myocardial infarction (STEMI)[18-20] and so may be more susceptible to insufficient statin therapy.

Therefore, the aims of this study were to investigate: i) the prevalence of, ii) the risk factors for, and iii) the clinical consequences associated with conversion from high potency to 'suboptimal' statin use due to statin discontinuation, dose reduction, switching to an alternative statin of lower equivalent potency and/or statin non-adherence, early after an NSTE-ACS in a contemporary prospective cardiovascular cohort.

Material and methods

Prospective study outline

This investigation utilises a prospective CVD observational study that was conducted at 16 different UK hospital sites between 2008-2013, entitled the Pharmacogenetics of Acute Coronary Syndrome (PhACS). 1470 patients hospitalised with an NSTE-ACS (both non-ST elevation myocardial infarction (NSTEMI) and unstable angina) were eligible for inclusion in PhACS. Patients were followed up at one (visit 2 (V2)) and 12 months (visit 3 (V3)) post recruitment, and annually thereafter until all participants had been followed up for at least 12 months. Further study information is provided in the Supplement.

The protocol was approved by the Liverpool (adult) research Ethics Committee, UK; site-specific approval was granted at all sites involved and local informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki.

Cohort Selection

Patients were eligible for inclusion in the current study if they were discharged on a high potency statin from their index hospital NSTE-ACS admission. High potency statin therapy was: atorvastatin 80mg daily, the equivalently potent rosuvastatin 20mg, and rosuvastatin 40mg daily (see eTable 1 in the Supplement for relative potency information). All other statins and doses were considered non-high potency statin therapy. Patients were excluded if they died within 30 days of discharge, because this prevented assessment of suboptimal statin status during follow up (see below). Patients were excluded if their V2 occurred during a prolonged index hospital admission or did not actually occur until >180 days after

index admission (as ~85% of muscular symptoms occur within 180 days[21]), or they were lost to follow up following V2.

Assessment of statin adherence

At V2, cardiac medication adherence was assessed using the Brief Medication Questionnaire (BMQ) (eFigure 1 in the Supplement)[22]. The BMQ incorporates three screens: a regimen screen, belief screen and a recall screen. The BMQ has been compared to the Medication Events Monitoring System.[22] The regimen screen had a sensitivity of 80% for detecting repetitive non-adherence and did not classify any adherent patients as non-adherent. However, it had 0% sensitivity for detecting sporadic non-adherence, and so its overall accuracy was 95%[22]. Further information about the BMQ is available in the Supplement. For the main analysis, assessment of adherence utilised the regimen screen; patients were classed statin non-adherent if they reported missing at least one statin pill over the past week.

Classification of suboptimal statin use

Patients were designated 'suboptimal statin users' if, by V2, they had discontinued, reduced their statin dose, switched to an alternative statin of lower equivalent potency and/or were statin non-adherent. Patients that were on high potency statin therapy at baseline and V2 and were statin adherent represented 'constant statin users'.

Outcomes

i) Suboptimal statin use at V2 was itself the outcome for investigating clinical factors associated with its occurrence.

ii) For investigating potential sequelae of suboptimal statin use, the primary endpoint was time to first major adverse cardiovascular event (MACE): a composite of death from a CVD (or no known) cause, or non-fatal myocardial infarction or ischaemic stroke. Time to all-cause mortality (ACM) was the secondary endpoint.

Covariates

The following were considered for investigating factors associated with suboptimal statin occurrence: age≥75, sex, body mass index (BMI)≥30, hypertension, hyperlipidaemia, diabetes mellitus, smoking (current or previous versus non-smokers), chronic kidney disease, chronic obstructive pulmonary disease (COPD), prior CVD (previous MI, stroke, transient ischaemic attack (TIA) or peripheral artery disease (PAD)), statin use prior to index admission, raised index troponin, high potency statin discharged on (atorvastatin/rosuvastatin), treatment with PCI or CABG surgery during or within 30 days following discharge from index admission, New York Heart Association (NYHA) functional class at V2, reported use at V2 of aspirin, a $P2Y_{12}$ inhibitor, a beta blocker, an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker (ACEI/ARB), warfarin, or a proton pump inhibitor (PPI), concomitant use of levothyroxine (a surrogate for hypothyroidism) or a drug(s) that inhibits cytochrome P450 3A4 (CYP3A4) (listed in the Supplement), and muscular symptoms recorded at V2 (bothersome muscular pains/cramps/aches/weakness whilst on statin therapy recorded in the BMQ).

For the analyses investigating the risks of MACE and ACM, all of the above covariates were included except muscular symptoms, levothyroxine, CYP3A4-inhibiting drugs, and type of high potency statin discharged on. Follow up commenced from the date of V2.

Subgroup analyses

Suboptimal statin use was divided into those who had discontinued or were statin non-adherent, and those who had reduced statin dose or switched statin (but were statin adherent), and the risks of time to MACE and ACM were analysed for both subgroups, compared to constant statin users.

Statistical analysis

Overall, 4.3% of data were missing, but 28.6% of cases had at least one missing value. This missing data were handled as follows. First, missing V2 dates were imputed by adding 30 days to baseline discharge date, because 30 days represented the median duration of the non-missing data. Second, V2 drug data were manually imputed where possible by comparison of baseline and V3 drug data. Missing V2 muscular symptoms were also manually imputed as 'no symptoms', because only 1.2% of patients openly reported symptoms. Lastly, multiple imputation was used: all remaining missing values were sampled using a fully conditional specification method, which uses an iterative Markov chain Monte Carlo procedure, and ten imputation datasets were generated. See the Supplement for further details.

i) **Investigating factors associated with suboptimal statin use**

Following imputation, the null hypothesis of no association with suboptimal statin occurrence (compared to constant statin use) was tested for each variable using the Wald test, because it generates a pooled value from the ten datasets. Those covariates with univariate $p<0.1$ were entered into a multivariable logistic regression model, using forwards stepwise (likelihood ratio) selection. Odds ratios (OR) and p-values are pooled from the ten imputed datasets; $p<0.05$ indicated significance.

ii) **Investigating risks of MACE and ACM associated with suboptimal statin use**

A univariate Cox proportional hazard model was fitted for each covariate to test its association with time to MACE; the same was performed for time to ACM. For each covariate, the Cox proportional hazards assumption was assessed by visual inspection of Kaplan-Meier curves. If a covariate did not meet the proportional hazards assumption, it was excluded from the main analyses (see sensitivity analyses D1 and D2). Covariates meeting the proportional hazards assumption and p-value<0.1 in univariate analysis were taken forwards into multivariable Cox proportional hazards modelling, with the final multivariable model covariates chosen by forwards stepwise (likelihood ratio) selection. After the covariate model had been fitted for both time to MACE and time to ACM, suboptimal statin use was introduced into both models to test its adjusted association with risk of MACE, or ACM. The hazard ratios (HR) and p-values provided in the results section are pooled results across all imputed datasets, except in the complete cases sensitivity analyses.

As two outcomes (MACE, ACM) were investigated here, a Bonferroni correction was used to adjust the significance threshold to $p \leq 0.025$. This threshold was also applied to all sensitivity analyses that further examined the risks of MACE or ACM associated with suboptimal statin use (see below).

Sensitivity Analyses

To investigate result robustness, sensitivity analyses were undertaken (see the Supplement for details). Firstly, a subcohort consisting of all cases with complete data ('complete cases') assessed whether missing data impacted either the factors associated with suboptimal statin occurrence or the associations between suboptimal statin use and risk of MACE/ACM. Additional sensitivity analyses evaluated the robustness of the associations between suboptimal statin use and MACE/ACM further by: expanding the statin non-adherence definition, considering covariates that did not meet the proportional hazards assumption for full follow up duration, including all variables that differed significantly between suboptimal and constant statin user groups at V2, and examining the potential for healthy user bias by considering PPI prescription changes between baseline discharge and V2.

The expanded statin non-adherence definition was: patients that missed at least one statin pill (BMQ Qu. 1e), took a statin for six or fewer days (Qu. 1b) (both from regimen screen), reported that the statin did not work well for them or they did not know (Qu. 1g), found that the statin bothered them at least a little (Qu. 2) (both from belief screen) and those that found it at least somewhat hard to remember to take all of their pills (Qu. 3c the recall screen).

All analyses were performed using IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

Results

Figure 1 outlines the cohort selection process for this study. 1,005 patients discharged on a high potency statin were included; >99% were prescribed atorvastatin 80mg daily. 156 patients (15.5%) were suboptimal statin users by V2; 849 (84.5%) remained on and adherent to high potency statin therapy, constituting constant statin users.

Of 1005 eligible patients discharged from hospital with a diagnosis of non-ST elevation acute coronary syndrome on recommended high potency statin therapy, 156 (15.5%) had inadequate statin utilisation by a median of one month following hospital discharge; 849 (84.5%) patients remained on and adherent to high potency statin therapy at V2.

Factors associated with suboptimal statin occurrence

Suboptimal and constant statin users were broadly similar (Table 1). However, in multivariable logistic regression, being female (p=0.010), not on either a $P2Y_{12}$ inhibitor (p=0.007) or beta blocker at V2 (p=0.036), and being bothered by muscular symptoms (p=0.017) were all associated with an increased adjusted risk of suboptimal statin occurrence (Table 2).

Table 1 Characteristics of suboptimal and constant statin users

Variable	Suboptimal Statin therapy	Constant Statin users	Unadjusted p-value
Patients (%)	156 (15.6)	849 (84.4)	
Median follow up from V2 (months)	16	15	0.52
Demographics			
Age ≥ 75, n (%)	39 (25.0)	161 (19.0)	0.13
Men, n (%)	102 (65.4)	660 (77.4)	0.004
BMI ≥ 30, n (%)	54 (34.6)	292 (33.4)	0.92
Medical History, n (%)			
Hypertension	93 (59.6)	490 (57.7)	0.63
Hyperlipidaemia	75 (48.1)	455 (53.6)	0.27
Diabetes mellitus	43 (27.6)	43 (27.6)	0.091
Ever smoked	113 (72.4)	588 (69.3)	0.42
CKD (Cr>150μmol/L)	13 (8.3)	48 (5.7)	0.28
COPD	13 (8.3)	74 (8.7)	0.89
Prior CVD[1]	51 (32.7)	287 (33.8)	0.82
On Statin prior to index admission	79 (50.6)	387 (45.6)	0.30
Diagnosis, n (%)[2]			
Troponin-raised NSTE-ACS	149 (95.5)	828 (97.5)	0.16
Normal troponin NSTE-ACS	7 (4.5)	21 (2.5)	-
Treatment, n (%)			
PCI/CABG	72 (46.2)	401 (47.2)	0.80
Discharged on Atorvastatin 80mg daily	155 (99.4)	843 (99.3)	0.91
NYHA Functional Classification at Visit 2, n (%)			
Class I	82 (52.6)	457 (53.8)	0.61
Class II	56 (35.9)	314 (37.0)	
Class III	18 (11.5)	70 (8.3)	
Class IV	0 (0.0)	8 (0.9)	
Drugs at Visit 2, n (%)			
Aspirin	142 (91.0)	795 (93.6)	0.36
$P2Y_{12}$ inhibitor	122 (78.2)	738 (86.9)	0.006
Beta blocker	119 (76.3)	725 (85.4)	0.016
ACEI/ARB	121 (77.6)	706 (83.2)	0.11
Warfarin	6 (3.9)	41 (4.8)	0.57
Proton pump inhibitor	67 (43.0)	358 (42.2)	0.89
CYP3A4-inhibitors	19 (12.2)	66 (7.8)	0.080

Levothyroxine	6 (3.8)	39 (4.6)	0.67
Muscular symptoms at V2, n (%)	5 (3.2)	7 (0.8)	0.020

ACEI = angiotensin converting enzyme inhibitor; ARA = aldosterone receptor antagonist; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; Cr = creatinine; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4 drug-metabolising enzyme; LD = loop diuretic; NSTE-ACS = non-ST elevation acute coronary syndrome; PCI = percutaneous coronary intervention; V2 = Visit two.

[1] = Prior CVD encompasses past MI, stroke, TIA or PAD; [2] = raised troponin taken to indicate non-ST elevation myocardial infarction (NSTEMI), and a normal troponin unstable angina.

Table 2 Adjusted factors associated with suboptimal statin occurrence

Risk factor	**Suboptimal Statin therapy, n (%)**	**Constant Statin users, n (%)**	**Multivariable analysis**	
			OR (95% CI)	**p-value**
Muscular symptoms	5 (3.2)	7 (0.8)	4.28 (1.30-14.08)	0.017
Sex (F vs M)	M: 102 (65.4)	M: 660 (77.4)	1.75 (1.14-2.68)	0.010
$P2Y_{12}$ inhibitor at V2	122 (78.2)	738 (86.9)	0.53 (0.34-0.84)	0.007
Beta blocker at V2	119 (76.3)	725 (85.4)	0.59 (0.36-0.96)	0.036

Covariates with univariate p<0.1 were entered into multivariable logistic regression modelling using a forwards likelihood ratio method to select the multivariable model presented here.

Risks of MACE and ACM associated with suboptimal statin use

The median study duration after V2 was 16 months, and there were 113 MACE and 79 ACM events; 33% of ACM deaths were non-cardiovascular. Table 3 shows the results of the univariate analyses of association between time to MACE, or time to ACM, and each variable considered. Of patients with suboptimal statin use, 32 and 25 suffered MACE and ACM, respectively. In multivariable analysis, suboptimal statin use was a risk for both time to MACE (HR 2.10, 95% confidence interval (CI) 1.25-3.53, p=0.005) and time to ACM (HR 2.46, 95% CI 1.38-4.39, p=0.003), after adjusting for age≥ 75, prior CVD, PCI/CABG treatment, NYHA class, and either diabetes mellitus (time to MACE) or chronic kidney disease (time to ACM) (Table 4). The adjusted survival curves, stratified by suboptimal statin status, are illustrated in Figures 2A and 2B, and demonstrate early separation of hazard risk after V2.

Table 3 Univariate Cox regression analysis results for association with time to MACE or time to ACM.

Variable	Time to MACE (n=113)		Time to ACM (n=79)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Demographics				
Age ≥ 75	3.02 (2.07-4.40)	<0.001	5.17 (3.31-8.07)	<0.001
Sex (F vs M)	1.31 (0.87-1.97)	NS (p=0.19)	*	*
BMI ≥ 30	1.30 (0.89-1.90)	NS (p=0.18)	1.40 (0.89-2.20)	NS (p=0.14)
Medical History				
Hypertension	1.82 (1.21-2.71)	0.004	2.12 (1.29-3.49)	0.003
Hyperlipidaemia	1.56 (1.06-2.27)	0.023	1.90 (1.20-3.02)	0.007
Diabetes mellitus	2.56 (1.76-3.74)	<0.001	2.77 (1.78-4.33)	<0.001
Ever smoked	1.22 (0.80-1.86)	NS (p=0.35)	1.33 (0.80-2.21)	NS (p=0.27)
CKD (Cr>150)	2.72 (1.65-4.47)	<0.001	3.93 (2.34-6.61)	<0.001
COPD	1.39 (0.79-2.43)	0.26	1.88 (1.03-3.42)	0.039
Prior CVD	3.06 (2.09-4.48)	<0.001	4.25 (2.64-6.87)	<0.001
On statin prior to index admission	1.66 (1.14-2.42)	0.009	2.01 (1.26-3.21)	0.003
Diagnosis				
Raised vs normal troponin NSTE-ACS	0.84 (0.34-2.09)	NS (p=0.71)	1.47 (0.36-6.01)	NS (p=0.59)
Treatment				
PCI/CABG	0.42 (0.28-0.63)	<0.001	0.31 (0.18-0.53)	<0.001
Functional statin at V2				
NYHA	1.89 (1.51-2.37)	<0.001	2.07 (1.60-2.70)	<0.001
Drugs at V2				
Suboptimal Statin therapy	2.18 (1.40-3.40)	0.001	2.54 (1.56-4.14)	<0.001
Aspirin	0.49 (0.28-0.86)	0.013	0.23 (0.13-0.38)	<0.001
$P2Y_{12}$ inhibitor	*	*	0.66 (0.39-1.12)	NS (p=0.12)
Beta blocker	0.86 (0.53-1.42)	NS (p=0.56)	0.76 (0.43-1.34)	NS (p=0.34)
ACEI/ARB	1.46 (0.84-2.55)	NS (p=0.18)	1.16 (0.63-2.13)	NS (p=0.63)
Warfarin	2.23 (1.13-4.42)	0.022	2.94 (1.41-6.13)	0.004
Proton pump inhibitor	0.97 (0.67-1.42)	NS (p=0.89)	1.40 (0.90-2.18)	NS (p=0.14)

* = Visit two $P2Y_{12}$ status did not meet the proportional hazards assumption for MACE, and patient sex did not meet the proportional hazards assumption for ACM; these variables were considered in sensitivity analyses (see eTables 5, 8, 9 in the Supplement).

Table 4 Multivariable adjusted Cox regression results for risk of time to MACE or ACM

Variable	Time to MACE		Time to ACM	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Suboptimal Statin therapy	**2.10 (1.25-3.53)**	**0.005**	**2.46 (1.38-4.39)**	**0.003**
Age ≥ 75	2.05 (1.36-3.09)	0.001	3.47 (2.12-5.68)	<0.001
NYHA	1.48 (1.12-1.96)	0.006	1.62 (1.16-2.27)	0.005
Treatment with PCI/CABG	0.56 (0.37-0.86)	0.008	0.49 (0.28-0.85)	0.011
Prior CVD	2.00 (1.31-3.04)	0.001	2.43 (1.45-4.08)	0.001
Diabetes mellitus	1.52 (1.002-2.30)	0.049	-	-
Chronic kidney disease	-	-	1.65 (0.93-2.93)	0.089

Covariates with p<0.1 in univariate Cox analysis were entered into multivariable Cox regression modelling using the forwards likelihood ratio method to select the covariate model (variables not in bold font). After these time to MACE or ACM covariate models were selected, the suboptimal statin therapy variable was entered into both models to produce the presented results.

Sub-group analyses

The subgroup of suboptimal statin users that had discontinued/were non-adherent (n=95) had significantly increased risks of MACE (HR 2.74 (1.49-5.04, p=0.001) and ACM (HR 3.50 (1.69-7.23, p=0.001), compared to constant statin users (Table 5). The smaller subgroup of patients with reduced statin dose/switched statin (n=61), did not have significantly increased risks of MACE (p=0.24) or ACM (p=0.22) (Table 5).

Sensitivity Analyses Complete cases subcohort sensitivity analyses reinforce that muscular symptoms, female sex and beta blocker use were associated with suboptimal statin occurrence (eTables 2, 3 in the Supplement). Suboptimal statin use was robustly associated with risks of MACE, and ACM, irrespective of adherence definition (Table 5), missing data imputation (Table 5, and eTable 5 in the Supplement), variables that did not meet the proportional hazards assumption ($P2Y_{12}$ use for MACE and sex for ACM) and after inclusion of all variables associated with suboptimal statin occurrence (eTables 5-9 in the Supplement). There was no substantive healthy user effect (eTables 5, 10, 11 in the Supplement).

Table 5 Summary of main results for the adjusted risks of time to MACE or ACM associated with suboptimal statin use

Analysis	Statin use, n (%)		Time to MACE		Time to ACM	
	Suboptimal	Constant	HR (95% CI)	p-value	HR (95% CI)	p-value
Main Analysis	156 (15.5)	849 (84.5)	2.10 (1.25-3.53)[1]	0.005	2.46 (1.38-4.39)[2]	0.003
Subgroup analyses:						
Statin discontinuation/ non-adherence only	95 (10.1)	849 (89.9)	2.74 (1.49-5.04)[3]	0.001	3.50 (1.69-7.23)[4]	0.001
Statin dose reduction/ switch only	61 (6.7)	849 (93.3)	1.55 (0.75-3.20)[5]	0.24	1.71 (0.72-4.04)[6]	0.22
Main Sensitivity analyses:						
Including expanded non-adherence definition	272 (27.1)	733 (72.9)	1.75 (1.17-2.63)[7]	0.007	1.75 (1.06-2.89)[8]	0.030
Complete cases analysis	89 (12.3)	635 (87.7)	2.60 (1.58-4.28)[9]	<0.001	3.41 (1.91-6.06)[10]	<0.001

For each analysis (main, subgroup and sensitivity analyses for both time to MACE and time to ACM), a multivariable covariate model was fitted before the suboptimal statin variable was added. Covariates with univariate $p<0.1$ were entered into multivariable Cox proportional hazards modelling, with the final multivariable covariate model for each analysis chosen by forwards stepwise (likelihood ratio) selection. All analyses selected to adjust for age ≥ 75, prior cardiovascular disease (previous myocardial infarction, stroke, transient ischaemic attack or peripheral artery disease), New York Heart Association functional class at Visit 2 and treatment with percutaneous coronary intervention or coronary artery bypass grafting surgery during baseline admission or within 30 days of discharge. Other covariates adjusted for in specific analyses were: diabetes mellitus (analyses 1, 6, 7, 9, 10); chronic kidney disease (analyses 2, 3, 4, 8).

Discussion

The main findings of this study are firstly, by a median of one month after admission for NSTE-ACS in patients discharged on high potency statin therapy, ~15% have suboptimal statin utilisation. Expanding the non-adherence definition increased this to 27% (Table 5). Secondly, suboptimal statin occurrence was associated with muscular symptoms, female sex, and reduced use of beta blockers and $P2Y_{12}$ inhibitors. Thirdly, suboptimal statin use was associated with increased adjusted risks of times to both MACE and ACM, although this was largely attributable to statin discontinuation/non-adherence early after NSTE-ACS rather than statin dose reduction/statin switching.

This study is novel because it considered all components of attenuated statin therapy (discontinuation, non-adherence, switching and dose reduction), both collectively and in subgroups. To date, the majority of adherence studies have assessed medication availability (e.g. proportion of days covered) via electronic data sources[23-25]. Although this approach allows assessment of average adherence over time, it is difficult for healthcare professionals to easily measure and act upon in practice. Importantly, the pragmatic approach used in this study highlights the importance of assessing statin usage early after hospital discharge in CVD secondary prevention patients. Furthermore, the assessment of statin utilisation used in this study is relatively straightforward and so is potentially actionable.

Overall, there were few differences at V2 between suboptimal and constant statin users. However interestingly, females[23, 24, 26, 27] and a lower rate of beta blocker[23, 28] and antiplatelet[29] drug use have all previously been associated with poorer statin adherence. In this study, suboptimal statin users were more likely to have not been prescribed $P2Y_{12}$ therapy at hospital discharge and to have stopped the beta blocker they were discharged on (data not shown). This study also found that muscular symptoms were a risk factor for suboptimal statin use. Very few other statin utilisation studies have included potential adverse events, although a cross-sectional internet-based survey previously determined that muscular symptoms are reported more frequently in patients that have discontinued, switched statin or are non-adherent, compared to non-switching statin adherent participants[27]. Overall, there was no evidence that these differences altered the multivariable increased risks of time to MACE or ACM associated with suboptimal statin use (eTables 8 and 9 in the Supplement).

Statins are associated with increased myotoxicity, incident diabetes mellitus and probably haemorrhagic stroke[30]. Statin-associated muscular symptoms are reported in ~1.5-3% of statin users in RCTs[31] and in ~7-29% of patients in observational studies[32]. However, whilst rare statin-induced severe myopathy/rhabdomyolysis is incontrovertible, the contribution of statins to milder muscle symptoms remains controversial. One informative estimate for the extent of muscular symptoms *attributable* to statin therapy is ~5%[33], which is derived from a

blinded RCT that compared rates of stringently defined myalgia in healthy volunteers receiving either atorvastatin 80mg daily or placebo for six months (p=0.05)[33]. The reported rate of bothersome muscular symptoms in our observational study was low (~1.2%) (Table 1). This may be a reflection of muscular symptoms not being explicitly asked about, and/or because patients who experienced muscular symptoms shortly after discharge had amended their statin therapy by V2, with potential symptomatic resolution. There is currently no unifying mechanistic explanation for statin-induced myotoxicity. However, several factors increase risk including female sex, advanced age, hypothyroidism, chronic kidney disease, exercise, drug-drug interactions, and for simvastatin myopathy specifically a genetic variant (*SCLO1B1* rs4149056) is a risk factor[34].

The largest type of suboptimal statin users in this study was statin non-adherent patients. The aetiology of statin non-adherence is multifactorial and incompletely understood; predictors beyond those identified in this study include age, low income and increased non-cardiovascular medications[35]. Health beliefs and knowledge affect both perceptions of need for a treatment, and counteracting perceptions of potential treatment adverse effects, are influenced by factors such as patient satisfaction with physician treatment explanations, and likely also modulate non-adherence[36]. Therefore, irrespective of the exact underlying aetiology of mild muscular symptoms, the attribution of these symptoms to statin therapy by a patient will potentially reduce statin utilisation.

Another potential reason for the statin discontinuation/dose reductions/statin switching observed in this study early after an NSTE-ACS is a communication breakdown leading to the high potency statin hospital discharge prescription not being transferred and incorporated into a patient's repeat outpatient prescription drug list. Transfer of medical information from secondary to primary care is often incomplete and untimely[37, 38], although further research is required to evaluate the extent of its potential impact on early post-ACS suboptimal statin therapy.

Previous secondary prevention cohorts have reported elevated risk estimates for statin non-adherence or discontinuation/persistence of 1.01-5.26 for MACE and 1.25-5.00 for

mortality, with the majority reporting statistically significant results[39]. Our study results of increased adjusted risks of time to MACE or ACM associated with both suboptimal statin use and the statin non-adherence/discontinuation subgroup in particular are in keeping with these findings. This emphasises the generalizability of these clinically relevant findings across secondary prevention populations, settings and study designs.

In this study of NSTE-ACS patients, the statin dose reduction/switching statin subgroup was not significantly associated with increased risks of time to MACE or ACM. One other prospective study has investigated statin dose reduction/switching following ACS, but included both NSTE-ACS and ST-elevation ACS patients, and reported a significantly increased risk for adverse clinical outcomes (HR 2.7, 95% CI 1.7-5.1)[14]. Our smaller number of dose reduction/switching cases (n=61) may have accounted for this subgroup only showing a non-significant trend for increased risk. Two other observational studies have investigated the influence of switching from atorvastatin to simvastatin[40, 41] on cardiovascular events, using mixed primary/secondary prevention populations identified using electronic healthcare databases. The UK-based study found a modestly increased cardiovascular event risk (HR 1.30, 95% CI 1.02-1.64)[40], whilst the US-based study found no association[41]. However in both of these studies the majority of patients were on atorvastatin ≤20mg/day, and it has been noted that the proportion of switches from atorvastatin to a lower rather than equivalently potent simvastatin regimen increases as the initial atorvastatin dose increases[41]. This is particularly relevant in post-ACS patients, as practically all switches from atorvastatin 80mg/day are to another statin of lower equivalent potency. Overall, persistent adherence to high potency statin therapy after an ACS appears optimal; however, if necessary, reducing the dose or switching statin appears preferable to statin non-adherence or complete discontinuation.

Recently, several interventions have been proposed that attempt to reduce non-adherence/discontinuation and improve statin therapeutic effectiveness, including improving CVD and statin literacy, co-payment reduction, using fixed-dose 'polypill' combinations and behaviour-modification interventions[17]. For example, brief pharmacist-led face-to-face counselling sessions have been shown to improve statin adherence[42]. There is also increasing interest in utilising mobile technology applications (apps) to remind patients to

take their medications, and patients are being involved in medication-related app development[43]. It is thus plausible that an intervention based on reminders (e.g. apps and/or posted letters) and face-to-face contact could be targeted to patients early after a CVD event to both screen for and address suboptimal statin utilisation, although further research is required.

Our study has limitations. It is a *post hoc* assessment of the PhACS study. The exact reasons for statin prescription changes and the cause(s) for patient non-adherence were not recorded. The data are observational and therefore we cannot confirm causality due to the potential for confounding influences by unmeasured variables, such as cardiac rehabilitation attendance. Although we cannot definitively exclude any healthy user effect, our assessment of PPI utilisation (eTables 10 and 11 in the Supplement) is in keeping with the lack of healthy user effect reported in other statin utilisation studies[23, 24, 44], and so makes a prominent contribution of this type of influence unlikely. It is acknowledged that both the assessment of statin adherence at a single time point and basing the primary assessment on the number of pills missed over the preceding week will limit detection of sporadic non-adherence[22]. However, the expanded non-adherence definition (Table 5) includes all components of the BMQ and the BMQ recall screen (enquiring about how hard the patient finds it to remember to take all the pills) has a sensitivity of 90% for sporadic non-adherence, albeit with a reduced specificity of 80%[22]. The assessment of statin utilisation at one month is also unlikely long enough to capture full stabilisation of drug use. However, median statin discontinuation in secondary prevention appears to occur at 30-37 days after discharge[14, 45], and our approach does not preclude follow up adherence assessments. Overall, this investigation used a prospective multicentre study with event validation rather than electronic diagnostic codes, and the several sensitivity analyses confer robustness to the main findings.

In conclusion, patients with an NSTE-ACS are at high risk of subsequent MACE and ACM. Following discharge on high potency statin therapy, the intensity of statin therapy is already reduced for a sizeable proportion of patients by one month back in the community, and self-reported muscular symptoms appear to increase the risk for suboptimal statin utilisation. Early statin discontinuation/non-adherence correlates with increased risks of subsequent

MACE and ACM. Physicians, pharmacists and cardiac rehabilitation programmes are encouraged to discuss statin therapy with ACS patients early after discharge, reaffirm the benefits of statins, and explore barriers to their effective use in order to maintain and enhance statin utilisation and so potentially improve post NSTE-ACS outcomes.

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Author Contributions:

Prospective Study and design: Pirmohamed, FitzGerald, Hanson, Jorgensen, Stables.

Acquisition, analysis, or interpretation of data: All authors.

Statistical analysis: Turner, Jorgensen, Morris, Yin.

Drafting of manuscript: Turner.

Critical revision of the manuscript: All authors.

All authors have approved the final manuscript.

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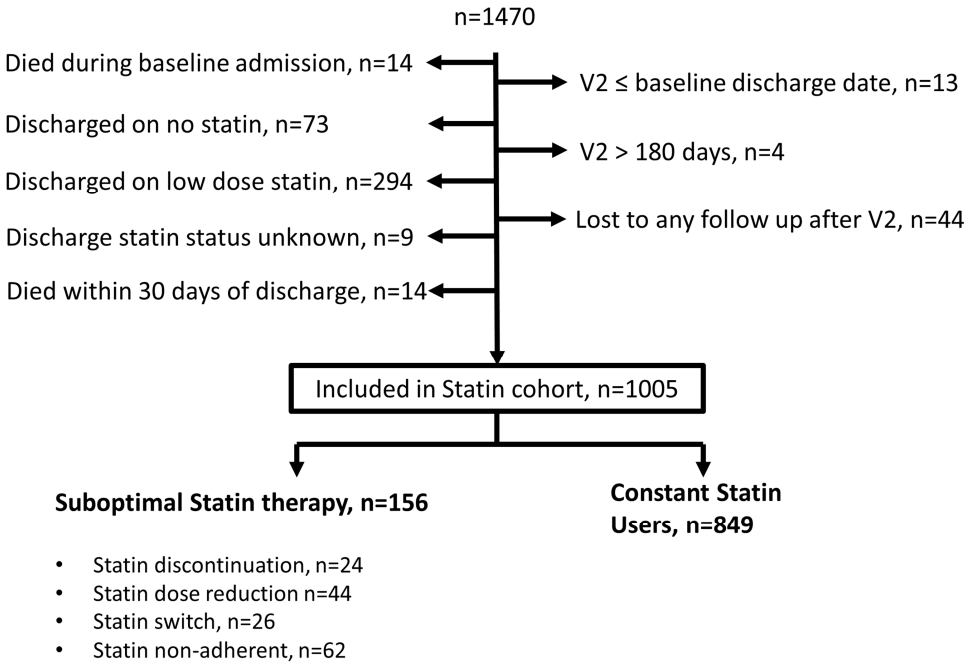
Figure legends

Figure 1 A schematic of the study selection process.

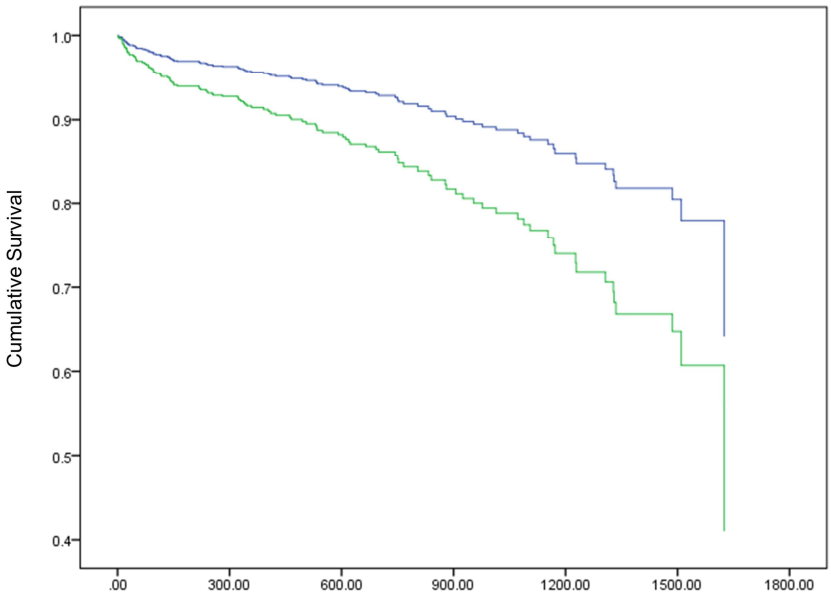
Figure 2 Cumulative survival curves

The cumulative survival curves compared suboptimal statin (green) and constant statin use (blue) group survival free from; **A)** major adverse cardiovascular events (MACE) and; **B)** all-cause mortality (ACM). Survival curves plotted until last event occurrence.



- Statin discontinuation, n=24
- Statin dose reduction n=44
- Statin switch, n=26
- Statin non-adherent, n=62

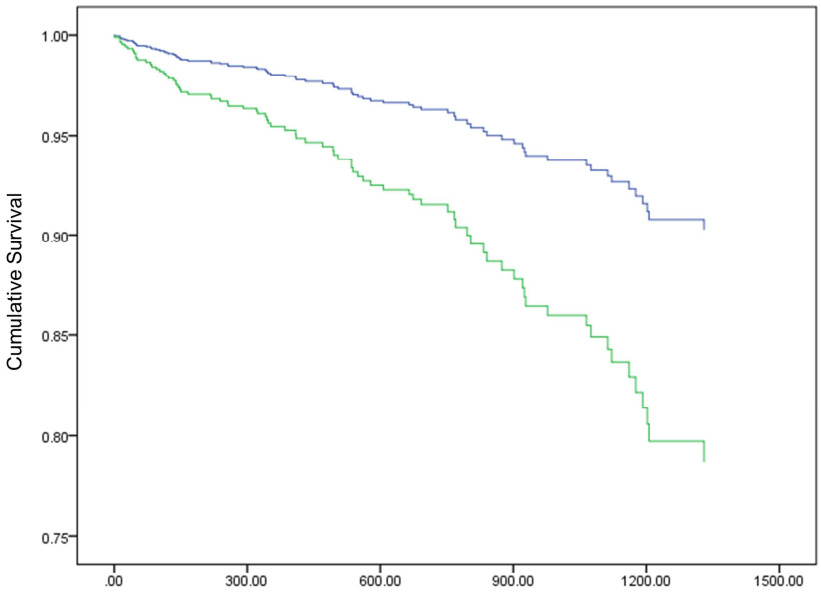
A)



Number at risk — Follow up (days)

All	**1005**	**926**	**442**	**177**	**81**	**26**
Suboptimal Statin	156	129	65	29	13	4
Constant Users	849	797	377	148	68	22

B)



Number at risk — Follow up (days)

All	**1005**	**948**	**461**	**191**	**90**	**28**
Suboptimal Statin	156	137	71	32	14	4
Constant Users	849	812	390	159	76	24

Highlights

- Deviation from high potency statin therapy is common early in secondary prevention
- Deviation can be by discontinuation, dose reduction, switching or non-adherence
- Muscular symptoms are associated with suboptimal statin use
- Statin discontinuation/non-adherence is associated with increased adverse outcomes
- Interventions to enhance statin use could improve secondary prevention outcomes