Article:
Hale, M, Zaman, H, Mehdizadeh, D et al. (4 more authors) (2020) Association between Statins Prescribed for Primary and Secondary Prevention and Major Adverse Cardiac Events among Older Adults with Frailty: A Systematic Review. Drugs & Aging, 37 (11). pp. 787-799. ISSN 1170-229X

https://doi.org/10.1007/s40266-020-00798-3

Association between statins prescribed for primary and secondary prevention and major adverse cardiac events among older adults with frailty: A systematic review

Authors:

Matthew Hale[1,2*], Hadar Zaman[3], David Mehdizadeh[3,4], Oliver Todd[1], Harriet Callaghan[1,2], Chris P Gale[5,6,7], Andrew Clegg[1,2]

Affiliations:

1. Academic Unit for Ageing and Stroke Research, University of Leeds, UK
2. Bradford Teaching Hospitals NHS Foundation Trust
3. School of Pharmacy and Medical Sciences, University of Bradford, UK.
4. NIHR Yorkshire and Humber Patient Safety Translational Research Centre (YHPSTRC), UK
5. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK
6. Leeds Institute for Data Analytics, University of Leeds, UK
7. Department of Cardiology, Leeds Teaching Hospitals NHS Trust, UK

* Corresponding author: Dr Matthew Hale, ORCID ID: 0000-0003-4056-0304
Email: m.hale@doctors.org.uk
Address: Dr M Hale, Department of Geriatrics, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, BD9 6RJ

Running head: Association between statins and MACE among older adults with frailty

Acknowledgements

The authors would like to thank Deirdre Andre, research librarian at the University of Leeds, for her assistance with developing the search strategy and conducting the searches.

ABSTRACT

Background

Statins reduce the risk of major adverse cardiovascular events (MACE), however, their clinical benefit for primary and secondary prevention among older adults with frailty is uncertain. This review investigates whether statins prescribed for primary and secondary prevention are associated with reduced MACE among adults aged ≥65 years with frailty.

Methods

Systematic review of studies published between 01.01.1952 and 01.01.2019 in MEDLINE, Embase, Scopus, Web of Science, Cochrane Library and the International Pharmaceutical Abstracts. Studies that investigated the effect of statins on MACE among adults ≥65 years with a validated frailty assessment were included. Data were extracted from the papers as per a pre-published protocol, PROSPERO: CRD42019127486. Risk of bias was assessed using the Cochrane Risk of Bias in non-randomised studies of interventions.

Finding

Six cohort studies fulfilled the inclusion criteria. There were no randomised clinical trials. Of studies involving statins for primary and secondary prevention (n=6), one found statins were associated with reduced mortality (hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.37-0.93) and another found they were not (p=0.73). One study of statins used for secondary prevention found they were associated with reduced mortality (HR 0.28, 95%CI 0.21-0.39). No studies investigated the effect of statins for primary prevention or the effect of statins on the frequency of MACE.

Discussion

This review identified only observational evidence that, among older people with frailty, statins are associated with reduced mortality when prescribed for secondary prevention, and an absence of evidence evaluating statin therapy for primary prevention. Randomised trial data are needed to better inform the use of statins among older adults living with frailty.

Key points:

- Only observational evidence supports statins reducing mortality for secondary prevention among older people with frailty
- There is an absence of evidence evaluating statin therapy for primary prevention for older adults with frailty
- Randomised trial data are needed to better inform the use of statins among older adults living with frailty.

DECLARATIONS

Funding:

MH is funded by an Academic Clinical Fellowship from the National Institute for Health Research

OT funded by a doctoral fellowship from the Dunhill Medical Trust, UK [RTF107/0117]

AC is part-funded by the National Institute for Health Research Applied Research Collaboration, Yorkshire & Humber. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care

Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare.

Availability of data and material: The search strategy utilised is published in Online Resource 2

Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Matthew Hale, Hadar Zaman, David Mehdizadeh, Oliver Todd and Harriet Callaghan. The first draft of the manuscript was written by Matthew Hale and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: Not applicable

Consent to participate: Not applicable

Consent for publication: All authors have consented for publication of the manuscript in its present form

1. INTRODUCTION

There is robust evidence that HMG Co-A reductase inhibitors (statins) reduce the frequency of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular death, known as major adverse cardiovascular events (MACE)[1]. However, the evidence-base for statins is largely derived from randomised controlled trials (RCTs) that included middle aged and healthy older adults, with trial eligibility criteria potentially excluding older people with multiple long-term conditions and frailty[2-4]. Additionally, RCTs of statins were, on average, around four years in duration – a time horizon that may be irrelevant for some older people with advancing frailty who are entering the terminal stage of life[5]. There is, therefore, uncertainty as to whether statins reduce MACE among older adults with frailty. Consequently, there is variation in clinical practice of prescribing statins for this group, with some clinicians advocating aggressive statin therapy for all older people[6] and others suggesting the deprescription of statins among older people with frailty[7].

Frailty is a spectrum disorder that is estimated to affect 10% of community dwelling over 65 year olds in the UK[8] and 15% of community dwelling over 65 year olds in the United States of America[9].. Ranging from mild to severe, frailty is characterised by an increased vulnerability to stressors[10]. Older adults with frailty may be less likely to experience benefit from medications prescribed for primary or secondary prevention, but are typically more likely to experience side effects and treatment burden from medications than people without frailty[11]. It is important that clinical practice guidelines account for advancing frailty, where the treatment burden from statins may outweigh the currently unclear benefit. Current United Kingdom, European and American cardiovascular risk reduction guidelines do not consider this[2-4].

This review evaluates the current evidence for the association between statins and reduced MACE among adults aged 65 years and over with frailty.

121

2. METHODS

A systematic review was conducted using a pre-published protocol, PROSPERO: CRD42019127486[12]. This review followed methodology Mand was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Online Resource 1)[13].

2.1 Eligibility Criteria

Randomised controlled trials or observational studies assessing the effect of statins (any statin, at any dose), with a mean study population age of ≥65 years, including a validated frailty assessment and reporting outcomes of mortality, frequency of MACE or statin deprescribing with follow up of at least one year were eligible for inclusion.

2.2 Information sources

We searched MEDLINE, Embase, Scopus, Web of Science, Cochrane Library: Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, and International Pharmaceutical Abstracts Database between 01.01.1952 and 01.01.2019. Where abstracts were written in a non-English language, Google translate was used to enable assessment for inclusion. Backwards citation searching of subsequently included manuscripts was performed to identify further articles of interest. The MEDLINE search strategy is provided in Online Resource 2.

2.3 Study Selection

The title and abstract of all studies were screened using Rayyan QCRI software[14] by MH to assess for eligibility, 60% (11 330 of 18 794 abstracts) of studies were additionally

146 screened by a second reviewer (HC, OT or HZ). Two independent reviewers screened (MH
147 and DM or HZ) all full-text manuscripts of potentially eligible studies.

148

149 **2.4 Data collection process**

150 Data were extracted from published reports using a pre-piloted pro-forma (MH and HZ or
151 DM). Manuscript lead authors were contacted where additional information was required.

152

153 **2.5 Data items**

154 The following data were extracted: study design, study duration, use of randomisation or
155 blinding, funding sources, reported conflicts of interest, total number of participants,
156 participant age and sex, country of study, method and definition for assessing frailty,
157 healthcare setting, indication for starting statin treatment and which statin at which dose was
158 given. For each outcome measure, data were collected regarding the number of participants
159 in each treatment group, number of events per group and treatment effect (unadjusted,
160 adjusted for age and sex and adjusted according to the optimum co-variables according to
161 the original author).

162

163 **2.6 Outcomes**

164 The primary outcomes studied were: mortality from any cause, MACE (including how this
165 was defined) and statin discontinuation. The secondary outcomes studied were: coronary
166 revascularisation, angina, peripheral vascular disease, elevated hepatic transaminases,
167 myalgia/myositis, thrombocytopenia, new-onset diabetes, change in quality of life, change in
168 mobility, change in ability to perform activities of daily living, change in frailty state,

admission to hospital, admission to long-term care, evaluation of treatment burden and evaluation of treatment acceptability to study participants.

2.7 Risk of bias

The risk of bias for each study was assessed by two reviewers according to the Cochrane Collaboration Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool[15] (MH and DM or HZ).

2.8 Summary measures

The principal summary measures were hazard ratios (HR) and associated 95% confidence intervals (CI) for time-to-event data. For dichotomous event data, Risk Ratios (RR) were extracted with their 95% confidence intervals (CI). Where RRs were not presented, odds ratios (OR) were extracted. Summary measures adjusted for confounding were prioritised and reported throughout.

2.9 Synthesis of results

In addition to descriptive statistics, we planned to perform a meta-analysis to estimate the effect of statins on mortality between treatment groups using generic inverse variance random effects modelling and report the I^2 statistic, as a measure of statistical heterogeneity, using RevMan software version 5.3[16]. However, the clinical heterogeneity of the populations and interventions studied precluded meta-analysis.

2.10 Risk of bias across studies

We planned to perform a funnel plot to evaluate for publication bias, however, due to the low number of studies identified for inclusion within the review, this was not possible.

2.11 Role of the funding source

There was no funding source for this study

3. RESULTS

3.1 Study selection

18 794 abstracts were identified for screening following de-duplication. From these, 30 articles were identified for full-text review. Backwards citation searching of these articles yielded a further four articles of interest, resulting in 34 manuscripts undergoing full text review. A PRISMA flow diagram summarising the review process is provided (Fig. 1).

3.2 Study characteristics

Six observational studies fulfilled the eligibility criteria (Table 1). No randomised controlled trials were identified.

Among the six studies included[17-22], three were prospective cohort studies and three were retrospective cohort studies[17-22]. No studies assessed the effect of statins on clinical outcomes when prescribed for primary prevention of mortality or MACE. One study assessed the effect of statins on clinical outcomes when prescribed for secondary prevention[20]. Four studies assessed the effect of statins on mixed cohorts including individuals prescribed statins for primary and secondary prevention[17-19, 21]. One study evaluated the effect of statins for both primary and secondary prevention separately[22]. Two studies were conducted in Australia[18, 21], one in Canada[17], one in Italy[20], one in Ireland[22] and one in the United Kingdom[19].

Two studies used patient cohorts from long-term care facilities[17, 21], one evaluated community dwelling older adults excluding long term care facilities[18], one selected community dwelling adults recently discharged from hospital[20], one recruited older adults through hospital admissions or attendance at outpatient clinics[22] and one studied an unselected primary care population[19].

3.3 Study participant characteristics

In total, this study reports the analysis of 153 082 older adults with frailty from the eligible studies. Of the three studies which reported the mean age of their participants, the mean (range) age was 83 years (range 76.9 years to 87.5 years)[18, 20, 21]. Two studies reported ages as ≥76 years[17] or ≥80 years[19] and the remaining study reported the mean age (standard deviation) by treatment group for patients statin naïve: 73.4 years (15.6 years), for patients prescribed a statin prior to their first stroke 70.9 years (11.5 years) and for patients prescribed a statin immediately after their first stroke 69.9 years (13.1 years)[22].

3.4 Measuring frailty

Three studies utilised a frailty phenotype classification; Frailty in the Nursing Home Scale (FRAIL-NH)[21], modified Rankin[22] and Fried[18]. Two studies used a cumulative deficit model, the electronic Frailty Index[19] and 72 Resident Assessment Instrument–Minimum Data Set version 2.0 (RAI-MDS)[17]. One study used a combination of physical factors and combined social and functional scores: Multidimensional Prognostic Index based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons (MPI-SVaMA)[20].

3.5 Primary outcomes

The findings for the primary outcomes of the review are summarised in Table 2.

3.5.1 All-cause mortality

One study of statins for both primary and secondary prevention for long term care residents evaluated a comparison between high dose and intermediate dose statins for older adults with frailty, without a separate control arm, and reported no difference in mortality (propensity score adjusted HR:0.93, 95%CI:0.85 to 1.03)[17]. A second study, with limited statistical power (0.31), reported no difference in mortality for older adults with frailty who received statin treatment compared to control (propensity score adjusted p=0.73[18], no estimate of effect size reported).

One study which evaluated statins for secondary prevention among patients recently discharged following a hospital admission for coronary artery disease reported reduced mortality for people with frailty prescribed statin treatment (propensity score adjusted HR:0.28, 95%CI:0.21 to 0.39)[20]. A second study evaluated statins versus no treatment within a cohort of mixed primary and secondary prevention among nursing home residents, and reported reduced mortality for people with frailty treated with statins (propensity score adjusted HR:0.58, 95%CI:0.37 to 0.93)[20].

One study found that statins, when prescribed for primary prevention, were not associated with a difference in one-year mortality following first stroke in older people with frailty (confounder adjusted OR:0.48, 95%CI:0.23 to 1.01). However, commencement of statins at the time of participants' first stroke was associated with a significant reduction of the one year mortality rate of the study participants (OR:0.26, 95%CI:0.12 to 0.55)[22]. This study was at high risk of bias from non-randomised treatment group allocation, which favoured the experimental arm.

3.5.2 MACE

One study including a mixed primary and secondary prevention community-dwelling older cohort of 2 458 patients in each treatment arm reported the effect of high dose statin therapy versus intermediate dose statin therapy on the frequency of MACE. The study reported no

difference in MACE outcomes between treatments for older people with frailty (propensity score adjusted HR:1.01, 95%CI: 0.85 to 1.20[17]). No studies evaluated the effect of statins versus no statin treatment among older adults with frailty.

3.5.3 Statin discontinuation

One study reported the annual rate of deprescribing (defined as discontinuing a regular statin prescription) and initiation (newly starting a regular prescription) of statin drugs among a mixed primary and secondary prevention cohort[19]. This was reported stratified by frailty level[19]. There was a small increase in the annual rate of deprescribing with increasing frailty, from 5% (95%CI:4.35 to 5.65) among fit patients to 7.1% (95%CI:6.44 to 7.76) among those with severe frailty[19]. Annual deprescribing rates were slightly higher among those on statins for primary prevention (6.45%, 95%CI:6.01 to 9.89%) compared to those taking statins for secondary prevention (5.15%, 95%CI:4.85 to 5.44%)[19]. The reasons for deprescribing were not detailed within the study.

The annual incidence of starting statins increased with progression from fit (1.94%, 95%CI:1.59 to 2.30%) to mild frailty (2.57%, 95%CI:2.23 to 2.91%) to moderate frailty (2.75%, 95%CI:2.29 to 3.21%), reducing only in those with severe frailty (2.06%, 95%CI:1.42 to 2.70%)[19].

3.6 Secondary outcomes

The findings for the secondary outcomes of the review are summarised in Table 3.

3.6.1 Change in ability to perform activities of daily living

One study assessed the association between statin prescribing and good functional outcome (modified Rankin scale of 0-2[23, 24]) at one year post-stroke[22]. This study reported no difference in the number of patients progressing to a good functional outcome between those who had received statin therapy prior to having a stroke (confounder adjusted OR:1.41, 95%CI:0.67 to 2.96) or those who received statin therapy within 72 hours after stroke (confounder adjusted OR:1.69, 95%CI:0.84 to 3.39), compared with patients who did not receive statin treatment.

3.6.2 Hospitalisation

One study found that older adults with frailty prescribed statins had significantly fewer admissions to hospital resulting in an overnight stay compared to patients not prescribed statins (propensity score adjusted HR 0.67, 95%CI 0.46 to 0.98)[21]. The reasons for hospital admission were not collected (communication from the corresponding author).

3.6.3 Admission to long-term care

One study reported no difference in the number of admissions to long-term care among older adults with frailty prescribed statins compared with those who were not, p=0.40, in a propensity adjusted model[18].

3.6.4 Secondary outcomes not reported

No studies of older adults with frailty investigated the association between statin prescribing and the frequency of coronary revascularisation, new diagnoses of angina or peripheral vascular disease, the frequency of statin related adverse drug events, change in quality life, mobility or frailty state, or evaluation of treatment burden or treatment acceptability.

317

318 **3.7 Risk of bias within studies**

319 Overall, five studies were determined to be at low risk of bias[17-21] and one at high risk of
320 bias in the domains of confounding and selection of participants (Fig. 2)[22].

321

4. DISCUSSION

4.1 Key findings

This systematic review has summarised data from six observational studies, including 153 082 older adults living with frailty. We did not identify any RCTs of statin treatment for primary or secondary prevention of cardiovascular disease in older people that included a validated measure of frailty.

Review findings from adjusted analyses of observational study data indicate that prescribing statin drugs for secondary prevention of cardiovascular disease is associated with lower mortality among older adults with frailty. No published studies have evaluated if statins are associated with reduced mortality when given specifically for primary prevention for older people with frailty. There is insufficient evidence to state with any certainty whether statin prescribing is associated with a reduced risk of MACE among older adults with frailty. Limited evidence from one study indicated that statin prescribing was not associated with a change in functional outcome following first event of stroke[22] or in the frequency of admission to long term care[18] but was associated with a reduced frequency of admission to hospital[21]. Statins were more frequently deprescribed among older adults with frailty than older adults without frailty, however, the effect of deprescribing on patient mortality and MACE was not reported[19]. No studies evaluated the effect of statins on individuals' treatment burden or quality of life.

4.2 Strength of the review

Given its broad inclusion criteria, the search strategy is able to robustly capture the current evidence regarding the benefit of statins for older adults with frailty. Furthermore, this review is novel in that it is, to the authors' knowledge, the first systematic review to focus on the

evidence of an association between statin drugs and reduced MACE among older adults with frailty.

4.3 Limitations of the review

The main limitation of the review is that we did not identify any RCTs, with included evidence limited to observational studies. The findings must therefore be interpreted with caution, due mainly to the potential for unmeasured confounding when comparing treatment outcomes in observational studies. The possibility of clinician treatment selection bias due to the proximity of individual participants to death is a particular concern.

Furthermore, due to the lack of studies dedicated to evaluating statins for primary prevention only, the review was unable to specifically evaluate statins for this purpose. However, the lack of randomised controlled trials and dedicated studies evaluating statins for primary prevention identifies an important evidence gap for future research.

Over 18,000 potentially eligible studies were identified by the search strategy and, due to the volume of studies screened, it was not possible to double screen all abstracts. Despite this, the review provides a contemporary synthesis of the international literature evaluating statins for the prevention of MACE among older adults with frailty to guide the direction of future research.

4.4 Implications for clinical practice and research

The findings of this review have multiple implications for clinical practice and research. Firstly, the lack of evidence investigating statins for the purpose of primary prevention among adults aged 65 years and over living with frailty suggests that the current UK, EU and US clinical guidelines for statins for cardiovascular risk reduction should be interpreted with

caution and implemented pragmatically in this group[2-4].{Savarese, 2013 #1938} We recommend treatment decisions should be made on an individual patient basis according to treatment goals and priorities. Secondly, this review highlights that, among older adults with frailty, future research is needed to identify whether statins reduce MACE when given for primary prevention. Clinical trials to date have typically included fitter individuals, under-represented those with frailty and stratified their analysis according to participant age rather than frailty. Treatment stratification based on age alone may result in patients of a younger age, but higher frailty, receiving treatments from which they may not benefit. Additionally, older patients without frailty may be denied a potentially lifesaving treatment if age-based treatment decisions are made. It is vital that older adults with frailty are specifically targeted for future trial recruitment to inform treatment decisions within this patient group.

4.5 Conclusion

This systematic review has identified limited evidence from observational research to indicate that prescribing statins for secondary prevention of cardiovascular disease in older people with frailty is associated with reduced mortality. However, there is an absence of evidence on the benefit of statin treatment for primary prevention of cardiovascular disease in older people with frailty. Future observational research using carefully matched, real-world populations to investigate associations between statins for primary and secondary prevention of cardiovascular disease in frailty will help inform some of the evidence gaps identified, as well as refine target populations for clinical trials. Randomised trials to evaluate the effects of statins on MACE for older people with frailty will help address residual concerns regarding unmeasured confounding in observational research, particularly regarding clinician treatment selection bias.

396

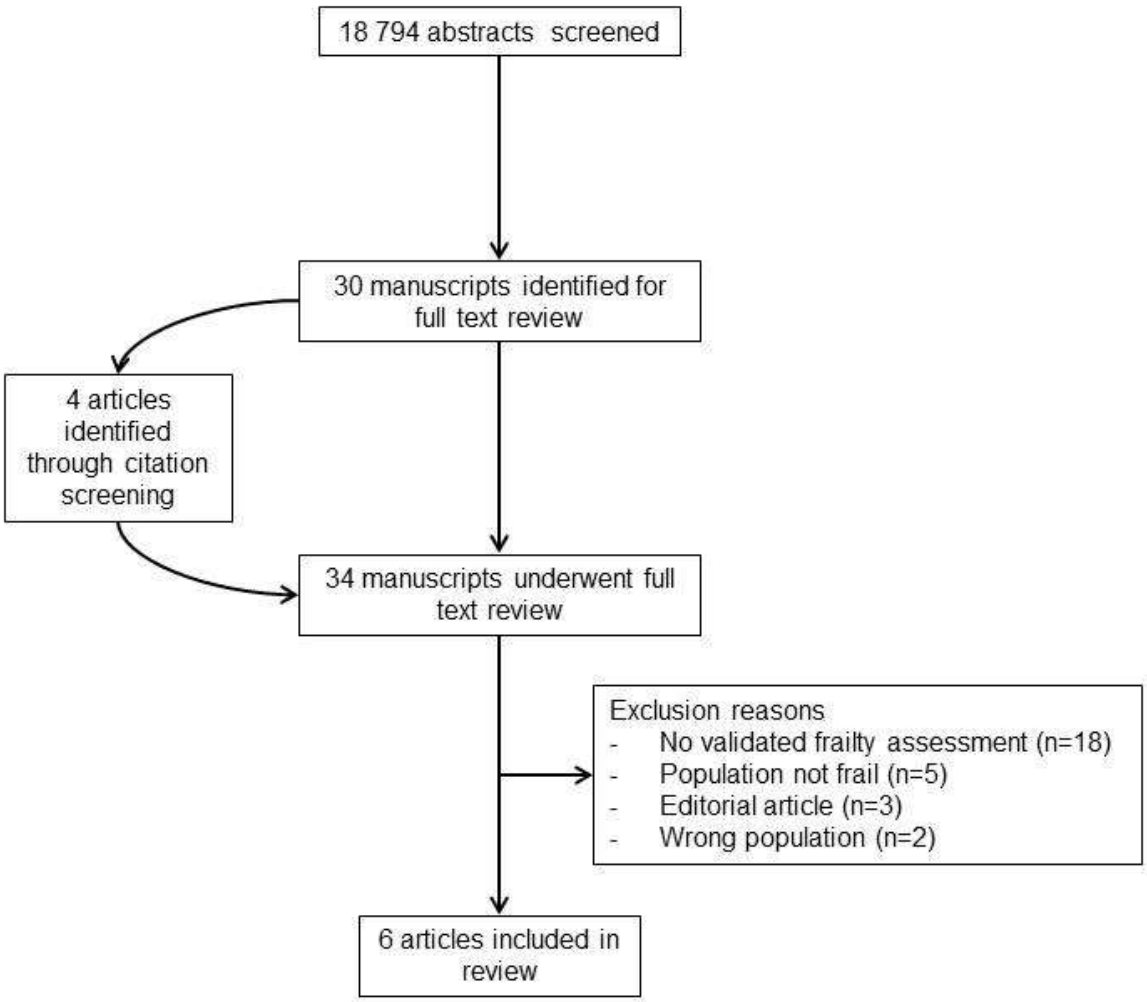
397

398

399

400 **FIGURES**

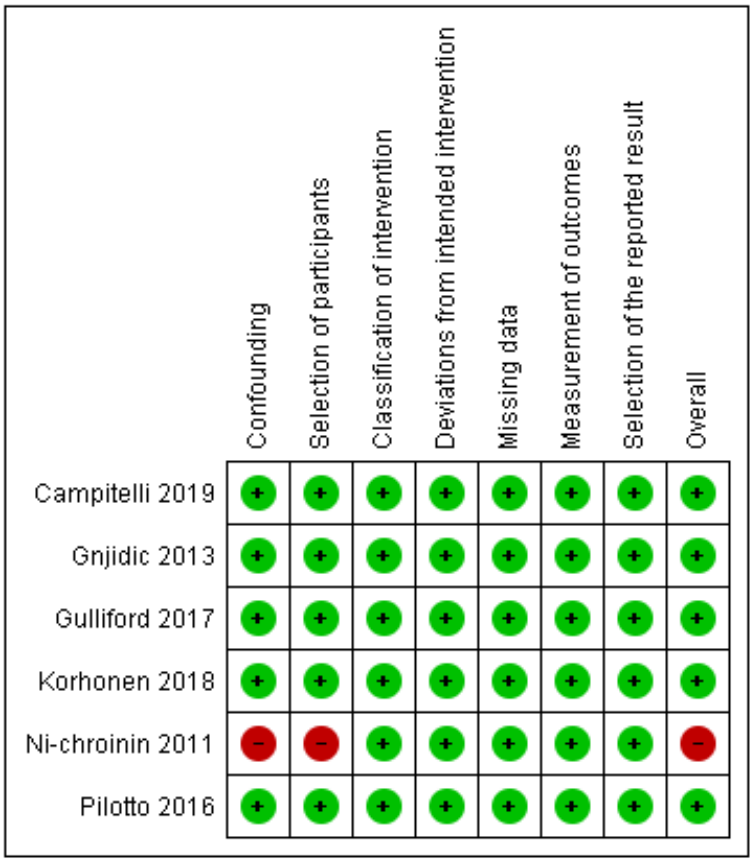
401



402

403 **Fig. 1. A PRISMA diagram reporting the identification of studies included within the**
404 **review**

405



406

407 **Fig. 2. A summary of the risk of bias of the studies included within the review.**

408

409

410 **TABLES**

Study Author	Year	Study design.	Primary/ secondary prevention	Study duration	Total number of participants	Mean age (years)	Percent who were male	Country of study	Method of assessment of frailty	Healthcare setting (community, RH, NH)	overall risk of bias
Campitelli [17]	2019	retrospective cohort	mixed	1 year	67,208	≥76y	39%	Canada	RAI-MDS[25]	Long-term care residents	Low
Gnjidic [18]	2013	prospective cohort	mixed	6.79 years (average 4 years)	1665	76.9	100%	Australia	Fried frailty index [26]	community (excluding care homes)	Low
Pilotto [20]	2016	retrospective cohort	secondary	mean (SD) 2.1 +/-2.2 years	2,597	83.9	45%	Italy	MPI-SVaMA [27]	community, discharged from hospital	High
Ni Chroinin [22]	2011	prospective cohort	effect on outcome of first CV event	1 year	567	71	50%	Ireland	pre-stroke modified Rankin scale [23, 24]	recruitment from hospital and outpatient attendance	High
Gulliford [19]	2017	retrospective cohort	mixed	15 year look back	212,566	≥80	32%	UK	electronic Frailty Index [10]	non-selected	Low
Korhonen [21]	2018	prospective cohort	mixed	1 year	383	87.5	23%	South Australia	FRAIL-NH [28]	Long-term care residents	Low

Table 1. A summary of the studies included within the review. Abbreviations: SD: standard deviation; RAI-MDS: Resident Assessment Instrument–Minimum Data set version 2.0; MPI-SVaMA: Multidimensional Prognostic Index based on the Standardized Multidimensional Assessment Schedule for Adults and Aged Persons; FRAIL-NH: Frailty in the Nursing Home Scale.

Primary outcomes

	Study	Control group	Intervention group (s)	Effect Estimate	Method of adjustment / controlling for confounding
Mortality	Campitelli[17]	low intensity statin: 2458	high intensity statin: 2458	HR: 0.93 (95%CI:0.85 to 1.03) (adjusted for propensity score)	Factors included in propensity score formation: age, sex, time in nursing home, total number of health conditions, dependency in performance of activities of daily living, cognitive performance, diabetes, congestive heart failure, hypertension, atherosclerotic heart disease, peripheral vascular disease, deep vein thrombosis, cardiac dysrhythmia, dementia, cancer, chronic lung disease, depression, arthritis, Parkinson's disease, hospitalisation due to atherosclerotic disease (heart attack, angina, stroke, peripheral artery disease), prior hospital attendance in past year, number of concurrent medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blocker, calcium channel blocker, oral anti-glycaemics, antipsychotics, benzodiazepines, antibiotics, opioids antidepressants and cholinesterase inhibitors
	Gnjidic[18]	never had statin:94	statin for primary or secondary prevention: 53	p=0.73 (adjusted for propensity score)	Factors included in propensity score formation: age, marital status, years in education, country of birth, alcohol consumption, smoking status, cardiovascular disease, number of self-reported comorbidities, polypharmacy, self-rated health, visual acuity, Body Mass Index, depressive symptoms, cognitive impairment, ability to perform activities of daily living, ability to perform instrumental activities of daily living, frailty, total cholesterol level, high density lipoprotein-cholesterol level, triglycerides level
	Pilotto[20]	never had statin:457	statin for secondary prevention: 259	HR 0.28 (95%CI:0.21-0.39) <0.001 (adjusted for propensity score))	Factors included in propensity score formation: age, gender, nursing care needs, cognitive status, pressure sores risk, activities of daily living, Barthel Index, social support requirement, the previous fractures, cancer, dementia, stroke, hypokinetic syndrome, and cardiovascular, respiratory, neurologic, or other diseases, and medications
	Ni Chroinin[22]	never had statin:112	statin for primary prevention: 134	confounder adjusted OR: 0.48 (95%CI:0.23 to 1.01)	Confounders adjusted for: age, prestroke modified Rankin Score score, National Institutes of Health Stroke Scale score, hypertension, acute aspirin, prestroke statin, and new acute poststroke statin treatment
		never had statin:112	statin therapy within 72 hours post stroke: 189	confounder adjusted OR:0.26 (95%CI:0.12 to 0.55)	
	Korhonen[21]	never had statin:234	statin for primary or secondary prevention: 152	HR:0.58 (95%CI:0.37–0.93) (adjusted for propensity score)	Factors included in propensity score formation: number of medications, independence with activities of daily living, polypharmacy, frailty, age, Charleston comorbidity index, sex, hypertension, dementia, diabetes, heart attack, previous facture, kidney disease, falls, gout, peripheral vascular disease, insomnia, chronic pain, depression, chronic obstructive airways disease, chronic heart failure, connective tissue disease, osteoporosis, arthritis, atrial fibrillation, urinary incontinence, anxiety, stroke disease, cancer, beta-blockers, anti-diabetes medications, drugs acting on the renin-angiotensin system, nitrates, aspirin, oral anticoagulants, diuretics, calcium channel blockers, sedatives, proton pump inhibitors, anti-dementia medications, opioids and antidepressants
Major Adverse Cardiovascular Events	Campitelli[17]	low intensity statin: 2458	high intensity statin: 2458	HR:1.01 (95%CI:0.85 to 1.20) (adjusted for propensity score)	Factors included in propensity score formation: age, sex, time in nursing home, total number of health conditions, dependency in performance of activities of daily living, cognitive performance, diabetes, congestive heart failure, hypertension, atherosclerotic heart disease, peripheral vascular disease, deep vein thrombosis, cardiac dysrhythmia, dementia, cancer, chronic lung disease, depression, arthritis, Parkinson's disease, hospitalisation due to atherosclerotic disease (heart attack, angina, stroke, peripheral artery disease), prior hospital attendance in past year, number of concurrent medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blocker, calcium channel blocker, oral anti-glycaemics, antipsychotics, benzodiazepines, antibiotics, opioids antidepressants and cholinesterase inhibitors
Discontinuation	Guillford[19]	statin for primary or secondary prevention:	No intervention	Proportion of patients deprescribed statins per year (95%CI) - Fit 5% (4.35-5.65) - Mild frailty 5.12% (4.74-5.50) - Moderate frailty 5.61% (5.18-6.04) - Severe frailty 7.10% (6.44-7.76)	No adjustment

Table 2. A summary of the primary outcomes reported within the studies included in this systematic review. Abbreviations: HR: Hazard Ratio; OR: Odds Ratio; CI: Confidence Interval.

Secondary outcomes

	Study	Control group	Intervention group (s)	Effect Estimate	Method of adjustment / controlling for confounding
Change in ability to perform activities of daily living	Ni Chroinin[22]	never had statin:112	primary prevention: 134	confounder adjusted OR: 1.41 (95%CI: 0.67 to 2.96 p=0.37)	Confounders adjusted for: age, prestroke modified Rankin Score score, National Institutes of Health Stroke Scale score, hypertension, acute aspirin, prestroke statin, and new acute poststroke statin treatment
		never had statin:112	statin therapy within 72 hours after stroke: 189	confounder adjusted OR: 1.69 (95%CI: 0.84 to 3.39 p=0.14)	
Hospital admission	Korhonen[21]	never had statin:234	statin for primary or secondary prevention: 152	HR: 0.67 (95%CI:0.46 to 0.98) (adjusted for propensity score)	Factors included in propensity score formation: number of medications, independence with activities of daily living, polypharmacy, frailty, age, Charleston comorbidity index, sex, hypertension, dementia, diabetes, heart attack, previous facture, kidney disease, falls, gout, peripheral vascular disease, insomnia, chronic pain, depression, chronic obstructive airways disease, chronic heart failure, connective tissue disease, osteoporosis, arthritis, atrial fibrillation, urinary incontinence, anxiety, stroke disease, cancer, beta-blockers, anti-diabetes medications, drugs acting on the renin-angiotensin system, nitrates, aspirin, oral anticoagulants, diuretics, calcium channel blockers, sedatives, proton pump inhibitors, anti-dementia medications, opioids and antidepressants
Admission to long term care	Gnjidic[18]	never had statin:94	statin for primary or secondary prevention: 53	p=0.04 (adjusted for propensity score)	Factors included in propensity score formation: age, marital status, years in education, country of birth, alcohol consumption, smoking status, cardiovascular disease, number of self-reported comorbidities, polypharmacy, self-rated health, visual acuity, Body Mass Index, depressive symptoms, cognitive impairment, ability to perform activities of daily living, ability to perform instrumental activities of daily living, frailty, total cholesterol level, high density lipoprotein-cholesterol level, triglycerides level

Table 3. A summary of the secondary outcomes reported within the studies included in this systematic review. Abbreviations: HR: Hazard Ratio; OR: Odds Ratio; CI: Confidence Interval.

References

1. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019 Feb 2;393(10170):407-15.
2. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.
3. Sussman JB, Wiitala WL, Zawistowski M, Hofer TP, Bentley D, Hayward RA. The Veterans Affairs Cardiac Risk Score: Recalibrating the Atherosclerotic Cardiovascular Disease Score for Applied Use. Medical care. 2017;55(9):864-70.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal. 2016;37(29):2315-81.
5. Savarese G, Gotto AM, Jr., Paolillo S, D'Amore C, Losco T, Musella F, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. Journal of the American College of Cardiology. 2013 Dec 3;62(22):2090-9.
6. Yandrapalli S, Gupta S, Andries G, Cooper HA, Aronow WS. Drug Therapy of Dyslipidemia in the Elderly. Drugs & aging. 2019 Apr;36(4):321-40.
7. Banach M, Serban M-C. Discussion around statin discontinuation in older adults and patients with wasting diseases. J Cachexia Sarcopenia Muscle. 2016;7(4):396-9.
8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.
9. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. The journals of gerontology Series A, Biological sciences and medical sciences. 2015;70(11):1427-34.
10. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and Ageing. 2016;45(3):353-60.
11. Hilmer SN, Gnjidic D. Prescribing for frail older people. Australian prescriber. 2017;40(5):174-8.
12. Hale MD. What is the association between statins, when prescribed for primary or secondary prevention of cardiovascular disease, and key outcomes for community dwelling older adults living with frailty?. PROSPERO 2019 CRD42019127486 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019127486. 2019 [cited; Available from:
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210-.
15. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
16. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration; 2014.
17. Campitelli MA, Maxwell CJ, Maclagan LC, Ko DT, Bell CM, Jeffs L, et al. One-year survival and admission to hospital for cardiovascular events among older residents of long-term care facilities who were prescribed intensive- and moderate-dose statins. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2019 Jan 14;191(2):E32-E9.

18. Gnjidic D, Le Couteur DG, Blyth FM, Travison T, Rogers K, Naganathan V, et al. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ open. 2013 Mar 9;3(3).
19. Gulliford M, Ravindrarajah R, Hamada S, Jackson S, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study. Age and Ageing. 2017;46(6):1001-5.
20. Pilotto A, Gallina P, Panza F, Copetti M, Cella A, Cruz-Jentoft A, et al. Relation of Statin Use and Mortality in Community-Dwelling Frail Older Patients With Coronary Artery Disease. The American journal of cardiology. 2016 Dec 1;118(11):1624-30.
21. Korhonen MJ, Ilomaki J, Sluggett JK, Brookhart MA, Visvanathan R, Cooper T, et al. Selective prescribing of statins and the risk of mortality, hospitalizations, and falls in aged care services. Journal of clinical lipidology. 2018 May - Jun;12(3):652-61.
22. Ni Chroinin D, Callaly EL, Duggan J, Merwick A, Hannon N, Sheehan O, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. Stroke. 2011 Apr;42(4):1021-9.
23. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. Journal of Neurology, Neurosurgery & Psychiatry. 1991;54(12):1044.
24. Rankin J. Cerebral Vascular Accidents in Patients over the Age of 60: II. Prognosis. Scottish Medical Journal. 1957 1957/05/01;2(5):200-15.
25. Campitelli MA, Bronskill SE, Hogan DB, Diong C, Amuah JE, Gill S, et al. The prevalence and health consequences of frailty in a population-based older home care cohort: a comparison of different measures. BMC geriatrics. 2016;16:133-.
26. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001 Mar;56(3):M146-56.
27. Pilotto A, Gallina P, Fontana A, Sancarlo D, Bazzano S, Copetti M, et al. Development and Validation of a Multidimensional Prognostic Index for Mortality Based on a Standardized Multidimensional Assessment Schedule (MPI-SVaMA) in Community-Dwelling Older Subjects. Journal of the American Medical Directors Association. 2013 2013/04/01/;14(4):287-92.
28. Kaehr E, Visvanathan R, Malmstrom TK, Morley JE. Frailty in nursing homes: the FRAIL-NH Scale. Journal of the American Medical Directors Association. 2015 Feb;16(2):87-9.