Statin use is not associated with future long-term care admission - extended follow-up of two randomised controlled trials

Statin use is not associated with future long-term care admission - extended follow-up of two randomised controlled trials

Running title: Statins and long-term care

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Abstract

Background: Statins have been associated with later life long-term care admission in observational studies. However, by preventing vascular events, statins may also prevent or delay admission. We wished to determine statin and long-term care admission associations in a randomised controlled trial context and describe associations between long-term care admission and other clinical and demographic factors

Methods: We used extended follow-up of two randomised trial populations, using national data to assign the long-term care admission outcome. We included individuals screened or recruited to two large randomised trials of pravastatin 40mg daily: the West of Scotland Coronary Prevention Study (WOSCOPS) and Pravastatin in elderly individuals at risk of vascular disease (PROSPER). We described univariable and multivariable analyses of potential predictors of long-term care admission with corresponding survival curves of incident long-term care admission and analyses adjusted for competing risk

Results: In total 11,015 (10%) of the trial participants were admitted to long-term care. There was no difference between the participants in the statin or placebo arm of either trial regarding admissions to long-term care. On multivariable analyses, independent associations with incident long-term care admission in PROSPER trial were, age (HR:1.06 per year [95%CI:1.03-1.09]) and male sex (HR:0.72 [95%CI:0.53-0.99]). In the WOSCOPS age (HR:1.12 per year [95%CI:1.10-1.13]) and increasing social deprivation (HR:1.05 [95%CI:1.03-1.08]) were associated with incident long-term care admission.

Conclusion: We did not demonstrate association between historical statin use and future long-term care admission. The strongest associations with incident long-term care admission were non-modifiable factors of age, sex and socioeconomic deprivation.

Keywords: long-term care; statin; data linkage; outcome; predictor

Key points:

Long-term care admission is an important event for older adults and a potentially useful outcome measure for trials.

Routinely collected health and social care can be used to assign long term care admission status.

Statin use in mid or late adult life is not associated with subsequent long-term care admission.

1 Introduction

The benefits of statins (HMG-CoA reductase inhibitors) for reducing cardiovascular events and mortality are well described for older adults.(1) Statins have pleiotropic effects and various non-cardiovascular benefits of statins have been demonstrated.(2) The potential for statins to influence common syndromes of older age, such as functional or cognitive decline, has also been postulated.(3) These statin effects in older age may not necessarily be beneficial and observational data have suggested possible adverse events in relation to physical and cognitive function.(4)

Arguably the outcomes of greatest relevance to older adults are not mortality or incident vascular events but maintaining functional independence. In other research areas, older adults have expressed that the most desired effect of an intervention is not to prolong life per se but to maintain cognitive and functional ability.(5) The complex construct of independence can be difficult to measure robustly at a population level.(6) However, admission to institutional long-term care could be viewed as an inversely related measure of independence, where care needs exceed those which can be met in the community. Acre-home admission would be especially relevant to older adults, many of whom have stated that institutionalisation would be a 'fate worse than death'.(7) Admission to long-term care is relatively common, affecting 2-5% of the adult population worldwide,(8) and so has potential as a clinical trial outcome of relevance to older adults, physicians and policy makers.

Utilising extended follow-up data from existing statin trial cohorts, allows evaluation of the effects of risk modification on later life and allows capture of novel outcomes not collected during the initial study period.

1.1 Aims

Our aim was to describe associations with long-term care admission using populations from randomised controlled trials (RCTs) of statins. Our primary hypothesis was that statin exposure in mid to older age would be associated with later long-term care admission. A secondary aim was to assess the feasibility of using admission to long-term care as a trial outcome surrogate for functional decline.

2 Methods

We conducted extended follow-up of the participants and screenees from two large RCTs of the statin Pravastatin: the West of Scotland Coronary Prevention Study (WOSCOPS)(8) and Pravastatin in elderly individuals at risk of vascular disease (PROSPER).(9)

2.1 Trial data sources

WOSCOPS was a primary prevention trial conducted in Scotland, UK between the years of 1989 and 1991 and included male participants aged 45-64 with raised plasma cholesterol levels.(9) PROSPER was an international trial conducted between 1997 and 1999 for men and women aged 70-82 who had elevated vascular risk or existing vascular disease.(10) Both evaluated the use of Pravastatin, at a dose of 40mg nocte, in a randomised placebo-controlled design. Comprehensive description of baseline characteristics have been published.(11,12) Mean duration of in-trial statin exposure was 4.9 years for WOSCOPS(13) and 3.2 years for PROSER.(10) Only participants recruited at the Scottish site of PROSPER were included, as outcome ascertainment relied on residency in Scotland. All participants and screenees were eligible for inclusion, using baseline data collected at the time of study evaluation and recruitment and linked to data collected through national health and social care services.

2.2 Definition of covariates

Basic demographic information was available for the entire cohort including age, sex and socioeconomic status and there were also some common cardiovascular risk factors. Other clinical and demographic data collected at baseline differed between the studies and so the two datasets were not combined. Full details on how the covariates were operationalised are available from the published protocols for the two studies.(14, 15) Socioeconomic status was evaluated using the Carstairs index,(14) an area-based measure of deprivation, based on postcode of residence. The measure has seven categories, with an increase in category indicative of greater material deprivation.(17) Both sets of trial participants were categorised based on whether they were randomised to the statin arm of the trial in which they participated.

2.3 Outcomes

The outcomes of interest were admission to long-term care and death. Long-term care admission was defined as being recorded as residing in long-term care at any point during the period 2012-2015. To assign the outcomes we used a variety of nationally (Scottish) collected data sources.(18) To ensure that the long-term care data were robust we triangulated three datasets: The Prescribing Information System (which indicates if a drug prescription was issued to a patient registered in a long-term care facility); the Scottish mortality registers (which indicate if a patient attending secondary care was discharged to a long-term care facility); the care-home census (a national annual census of long-term care residents). We described mortality following study completion using National Records Scotland Death Registrations data.

2.4 Data linkage

Identifiers for screenees and participants in the clinical trials were securely supplied for linkage with national centrally-held routine data sources including names, date of birth, full address and postcode. Each individual was then assigned to a national unique identifier that is used in Scotland, the community health index (CHI), where available. The CHI is also used within all the routine data sources of interest and this allows individual patient level linkage of datasets.

For our initial study we were interested in the care home status at specific time points. To this end, given the differences in coverage, it was necessary to harmonise the four possible data sources to analysis. To allow harmonisation across data sources with differing temporal coverage, we focussed on care home resident status for the period 2012 onwards. Event based reports (eg from PIS, SMR, NRS) were not considered if out with the time window of interest.

Following linkage, all identifiable information was removed before the data were made available to the research team through a secured network (safe haven). Data management and analysis was performed at the Robertson Centre for Biostatistics, University of Glasgow.

2.5 Statistical methods

We described univariable and multivariable adjusted associations with care-home residence for PROSPER and WOSCOPS separately. For our primary analysis of statin exposure, we ran 'survival' curves using the Kaplan-Meier method and Time to Event Analysis using Cox proportional hazards models to analyse for association of predictors individually and in multiple regression analyses, censoring on death. Subsequently competing risk models for residence in a long-term care facility or death were created for participants in the two trials.

2.6 Approvals

All participants from WOSCOPS and PROSPER consented to the use of their medical records for follow-up. An ethics application was made using the Integrated Research Application System and approved by NHS Greater Glasgow & Clyde Health Board (NHS GG&C Board Approval) and the Public Benefit and Privacy Panel provided permission to link these data to national health and social care data (eDRIS: 1516-0130). The funding source (Chief Scientist Office, Scotland) played no part in the analyses or interpretation of the data.

3 Results

A total of 106,242 participants from the original screened population of 117,166 (91%) were indexed and linked to national health and care records. At March 2015, 56,090 (53%) of participants had died. Between 2012-2015, 11,015 (10%) were identified in routine data sources as having been admitted to long-term care. There were 608/6574 (9%) WOSCOPS participants admitted to long-term care and from PROPSER 482/2033 (24%).

There was no association between in-trial statin exposure and incident long-term care admission. Long-term care residents from the PROSPER participants had higher baseline age, were more likely to be female, had higher diastolic blood pressure, higher total cholesterol, were more likely to be smokers, and were more likely to have a history of hypertension, myocardial infarction, peripheral arterial disease and claudication.(Table 1) Long-term care residents from WOSCOPS had higher baseline age, systolic blood pressure, had lower socioeconomic status based on Carstairs category and were more likely to be current smokers.(Table 2)

On multivariable analyses, independent associations with incident long-term care admission in the PROSPER cohort were, age (HR:1.06 per year [95%CI:1.03-1.09]) and a lower risk for those of male sex (HR:0.72 [95%CI:0.53-0.99]). In the WOSCOPS cohort independent associations were age (HR:1.12 per year [95%CI:1.10-1.13]); increasing social deprivation (HR:1.05 [95%CI:1.03-1.08]) and smoking, with current smokers having fewer long-term care admissions (HR:0.76 [95%CI:0.62-0.95]). There was no difference between statin and placebo groups in terms of time to long-term care.(Figure 1) Using competing risk models for death and admission to long-term care there were no between group differences.(Figures 2 & 3)

4 Discussion

We did not show a difference in long-term care admission between those prescribed statin or placebo during the two large RCTS. Admission to long-term care can be considered a proxy for frailty and functional decline, our data would suggest no legacy effect of mid to later life statin prescribing on these important outcomes. This is aligned with other data describing statins and functional decline.(3, 4) An alternative interpretation of our results is that we did not demonstrate any statin related harm. Previous studies have suggested the possibility of statins increasing rates of institutionalisation for certain patient groups.(19) The potency and dose of statin used in the two RCTs is modest by contemporary standards and it remains possible that high dose potent statins may have effects on patterns of admission to long-term care.

The strongest, independent associations for incident care-home admission were age, sex, socio-economic status and smoking. The association of smoking with reduced care-home

status seems counter intuitive and not in keeping with our understanding of the effect on smoking in older age.(20) This finding is likely a result of survival bias and emphasises the importance of competing risks analyses in this field of research. A recent systematic review of associations with care-home admission from hospital also reported the importance of age and sex.(21) Other factors in this review with strong association including dementia and disability could not be assessed in our study as these were exclusion criteria for the included studies. In reviews looking at long-term care admission from community settings, dementia and factors relating to support networks and carer burden seem to be associated with this decision.(22) These findings highlight that admission to long-term care is a multi-faceted decision and only certain aspects of this process could plausibly be influenced by statin prescribing.

There are several strengths to our approach. We used multi-modal data to assign care-home status following best practice in 'big data' research.(23) The ability to link data from clinical trial cohorts to routinely collected health and social care data offers the potential to economically ascertain longer-term outcomes than would be possible within the primary study. Our results suggest that is feasible to use routinely collected health and social care data to assign outcomes that may be of greatest relevance to older adults – in this case, using admission to long—term care as a surrogate for cognitive and functional decline. By using data from RCTS we have large numbers of study quality data. Baseline randomisation should avoid those biases associated with observational data on statins (for example, confounding by indication; healthy user bias; healthy tolerater bias). Our previous work on the long-term follow-up of the WOSCOPS and PROSPER trials has demonstrated the additional scientific value of extended follow-up of these clinical trial populations and of record linkage to national datasets.(1)

However, there are limitations to our methodology. For our analysis of statins we have not corrected for life course statin exposure. Ideally we would have corrected our analyses with individual patient level data regarding treatment modification, adherence and achieved levels of LDL cholesterol. In population based analyses this level of granularity is not possible. However, we know from other studies that adherence and persistence are important issues particularly in the older adult population.(24) We also recognise that we may have missed incident care-home admission if it occurred early after trial and the patient was no longer resident during the time periods we selected for analyses.

The majority of older adults are now prescribed statins at some point (25) and it seems likely that many in the placebo arm of the original trials will have eventually been prescribed statin. This cross-over may weaken the power of our analysis to demonstrate a modest statin effect. Thus, our analysis can only tell us about a potential legacy effect of previous statin administration. Describing the future effects of earlier life statin exposure remains a valid question. In other longer term follow-up studies of statin trials a persisting benefit from earlier treatment is consistently observed.(26,27). For example, after the end of the WoSCOPS trial, use of lipid-lowering therapy during the first 5 years of extended follow-up was monitored by review of case records (in the original pravastatin and placebo groups respectively proportions on statin therapy were 28.6% and 24.3% at 1 year post-trial, 33.6% and 29.4% at 3 years and 38.7% and 35.2% at 5 years).(1) That the initial treatment arm continues to show differential cardiovascular and other outcomes speaks to the legacy effect of statin exposure earlier in life. Our analysis had a specific focus around functional decline and we recognise that, despite the increasing numbers of large trials of statin in older adults, many questions remain around statins in older age.(28)

We did not demonstrate association between several years of statin use in mid or later life and future long-term care admission and a direct link between statins and admission to long-term care seems unlikely. The strongest associations with incident long-term care admission were non-modifiable factors of age and sex and socioeconomic deprivation.

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Conflict of Interest

The authors Burton; Papworth; Haig; McCowan; Ford and Quinn declare that they have no relevant conflicts of interest that may be relevant to this manuscript.

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Author Contributions

JKB, drafted manuscript RP, CH, CM, IF handled data management and analyses, DJS, TJQ created protocol, awarded funding. All authors contributed to interpretation of data and final manuscript.

Sponsor's Role

The sponsors played no part in the design, conduct or analysis of this study.

References

1. Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007;357(15):1477-86.

2. Davies JT, Delfino SF, Feinberg CE, et al. Current and Emerging Uses of Statins in Clinical Therapeutics: A Review. Lipid insights. 2016;9:13-29.

3. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016(1):Cd003160.

4. Scott D, Blizzard L, Fell J, Jones G. Statin therapy, muscle function and falls risk in community-dwelling older adults. QJM. 2009;102(9):625-33.

5. Salkeld G, Cameron ID, Cumming RG et al Quality of life related to fear of falling an dhip fracture in older women: a time trade off study. BMJ.2000; 320:241-6.

6. Quinn TJ, McArthur K, Ellis G, Stott DJ. Functional assessment in older people. BMJ. 2011;343:d4681.

7. Rubin EB, Buehler AE, Halpern SD. States Worse Than Death Among Hospitalized Patients With Serious Illnesses JAMA Internal Medicine.2016;176:1557-9.

8. Ribbe MW, Ljunggren G, Steel K, et al. Nursing homes in 10 nations: a comparison between countries and settings. Age Ageing. 1997;26 Suppl 2:3-12.

9. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7.

10. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623-30.

11. WoSCOPS study group. Screening experience and baseline characteristics in the West of Scotland Coronary Prevention Study. Am J Cardiol. 1995; 76:485-91.

12. Ford I, Blauw GJ, Murphy MB et al A prospective study of pravastatin in the elderly at risk (PROSPER) Screening experience and baseline characteristics. Curr Control Trials Cardiovasc Med.2002; 3:8

13. Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation. 2016;133(11):1073-80.

14. The West of Scotland Coronary Prevention Study Group. A coronary primary prevention study of Scottish men aged 45-64 years: trial design. . J Clin Epidemiol. 1992;45(8):849-60.

15. Shepherd J, Blauw GJ, Murphy MB, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol. 1999;84(10):1192-7.

16. Carstairs V, Morris R. Deprivation and health in Scotland. Health Bull (Edinb). 1990;48(4):162-75.

17. McLoone P, Boddy FA. Deprivation and mortality in Scotland, 1981 and 1991. BMJ. 1994;309(6967):1465-70.

18. Barry SJ, Dinnett E, Kean S, et al. Are routinely collected NHS administrative records suitable for endpoint identification in clinical trials? Evidence from the West of Scotland Coronary Prevention Study. PLoS One. 2013;8(9):e75379.

19. Gnjidic D, Le Couteur DG, Blyth FM, et al. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ Open. 2013;3(3).

20. Pruchno R, Hahn S, Wilson-Genderson M. Cigarette smokers, never-smokers, and transitions: implications for successful aging. International journal of aging & human development. 2012;74(3):193-209.

21. Harrison JK, Walesby KE, Hamilton L, et al. Predicting discharge to institutional long-term care following acute hospitalisation: a systematic review & meta-analysis. Age Ageing. 2017.

22. Luppa M, Luck T, Weyerer S, et al. Prediction of institutionalization in the elderly. A systematic review. Age Ageing. 2010;39(1):31-8.

23. Doubal FN, Ali M, Batty GD, et al. Big data and data repurposing - using existing data to answer new questions in vascular dementia research. BMC neurology. 2017;17(1):72.

24. Ruscica M, Macchi C, Pavanelo C, Corsini A, Sahebkar A, Sirtoni CR. Appropriateness of statin prescription in the ederly. Eur J Intern Med. 2018;50:33-40.

25. Murphy C, Bennett K, Fahey T, et al. Statin use in adults at high risk of cardiovascular disease mortality: cross-sectional analysis of baseline data from The Irish Longitudinal Study on Ageing (TILDA). BMJ Open. 2015;5(7):e008017.

26. Lloyd SM, Stott DJ, de Craen AJ et alLong-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).PLoS One. 2013 Sep 2;8(9):e72642. doi: 10.1371/journal.pone.0072642. eCollection 2013.

27. Sever PS, Chang CL, Gupta AK et al The Anglo-Scandinavian Cardiac Outcomes Trial: 11 year mortality follow-up of the lipid lowering arm in the UK. Eur Heart J. 2011; 32:2525-32.

28. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly. Circulaton.2017;135:1979-81.

Tables

Table 1: Characteristics of PROSPER subjects

Variable		All subjects N=2033	No care-home N=1551	Care-home N=482	P-value
Age (years)	Mean (SD)	75.8 (3.3)	75.6 (3.3)	76.4 (3.4)	< 0.001
Female	N (%)	1155 (56.8%)	843 (54.4%)	312 (64.7%)	< 0.001
Randomised to statin	N (%)	1027 (50.5%)	786 (50.7%)	241 (50.0%)	0.835
SBP (mmHg)	Mean (SD)	153.6 (21.2)	153.4 (21.0)	154.3 (21.9)	0.455
DBP (mmHg)	Mean (SD)	82.6 (10.6)	82.3 (10.6)	83.4 (10.4)	0.038
Total cholesterol (mmol/L)	Mean (SD)	5.7 (1.0)	5.7 (1.0)	5.8 (1.0)	0.025
LDL cholesterol (mmol/L)	Mean (SD)	3.9 (0.8)	3.8 (0.8)	3.9 (0.8)	0.063
HDL cholesterol (mmol/L)	Mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.3)	0.063
Triglycerides (mmol/L)	Mean (SD)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	0.907

Variable		All subjects N=2033	No care-home N=1551	Care-home N=482	P-value
Height (cm)	Mean (SD)	162.9 (9.3)	163.3 (9.4)]	161.9 (9.1)	0.004
Weight (kg)	Mean (SD)	71.1 (13.1)	71.3 (13.1)	70.2 (12.9)	0.095
BMI (kgm2)	Mean (SD)	26.7 (4.3)	26.7 (4.3)	26.8 (4.4)	0.890
Barthel index score	Median (IQR)	20.0 (20.0, 20.0)	20.0 (20.0, 20.0)	20.0 (20.0, 20.0)	0.883
Instrumental activities of daily living	Median (IQR)	14.0 (14.0, 14.0)	14.0 (14.0, 14.0)	14.0 (14.0, 14.0)	0.843
MMSE	Mean (SD)	28.1 (1.5)	28.2 (1.5)	28.1 (1.6)	0.152
Number of concomitant drugs	Median (IQR)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	0.468
History of vascular disease	N (%)	1010 (49.7%)	789 (50.9%)	221 (45.9%)	0.060
Current Smoker Ex Smoker	N (%) N (%)	545 (26.8%) 824 (40.5%)	436 (28.1%) 641 (41.3%)	109 (22.6%) 183 (38.0%)	0.001
History of hypertension	N (%)	1187 (58.4%)	886 (57.1%)	301 (62.4%)	0.039
History of diabetes	N (%)	178 (8.8%)	132 (8.5%)	46 (9.5%)	0.518

Variable		All subjects N=2033	No care-home N=1551	Care-home N=482	P-value
History of myocardial infarction	N (%)	297 (14.6%)	242 (15.6%)	55 (11.4%)	0.022
History of angina	N (%)	657 (32.3%)	513 (33.1%)	144 (29.9%)	0.200
History of claudication	N (%)	192 (9.4%)	163 (10.5%)	29 (6.0%)	0.003
History of PAD surgery	N (%)	45 (2.2%)	41 (2.6%)	4 (0.8%)	0.020
History of stroke or TIA	N (%)	222 (10.9%)	163 (10.5%)	59 (12.2%)	0.316
History of CABG	N (%)	45 (2.2%)	35 (2.3%)	10 (2.1%)	1.000
History of PCI	N (%)	73 (3.6%)	57 (3.7%)	16 (3.3%)	0.781

SBP=Systolic blood pressure; DBP=diastolic blood pressure; LDL=Low density lipoprotein; HDL=high density lipoprotein; BMI=body mass index; MMSE=mini mental state examination; PAD=Peripheral Arterial Disease; TIA=transient ischaemic attack; CABG=coronary arterial bypass grafting; PCI=Percutaneous Coronary Intervention

Table 2: Characteristics of WOSCOPS subjects

Variable		All subjects N=6574	No care-home N=5966	Care-home N=608	P-value
Age (years)	Mean (SD)	55.2 (5.5)	54.9 (5.5)	58.3 (4.6)	< 0.001
Randomised to statin	N (%)	3294 (50.1%)	2984 (50.0%)	310 (51.0%)	0.670
SBP (mmHg)	Mean (SD)	135.5 (17.3)	135.2 (17.2)	138.1 (18.1)	< 0.001
DBP (mmHg)	Mean (SD	83.9 (10.3)	83.9 (10.3)	84.1 (10.4)	0.588
Total chol (mmol/L)	Mean (SD)	7.0 (0.6)	7.0 (0.6)	7.0 (0.6)	0.743
HDL cholesterol (mmol/L)	Mean (SD)	1.1 (0.2)	1.1 (0.2)	1.2 (0.2)	0.223
BMI (kgm2)	Mean (SD)	26.0 (3.2)	26.0 (3.2)	25.8 (3.1)	0.194
Mean Carstairs score	Mean (SD)	0.7 (3.5)	0.6 (3.5)	1.3 (3.8)	< 0.001
Former smoker	N (%)	2254 (34.3%)	2029 (34.0%)	225 (37.0%)	0.039
Current smoker	N (%)	2902 (44.1%)	2663 (44.6%)	239 (39.3%)	
History of hypertension	N (%)	1034 (15.7%)	934 (15.7%)	100 (16.4%)	0.599
History of diabetes	N (%)	75 (1.1%)	66 (1.1%)	9 (1.5%)	0.419

History of angina	N (%)	337 (5.1%)	299 (5.0%)	38 (6.2%)	0.209

Nobs=Number of observations; Nmiss=Number with missing data

SBP=Systolic blood pressure; DBP=diastolic blood pressure; LDL=Low density lipoprotein; HDL=high density lipoprotein; BMI=body mass index; Carstairs=socioeconomic deprivation score

Legends

Figure 1: Kaplan Meier curve for admission to a care-home for trial participants

Figure 2: Competing risks model for death or admission to a care-home for PROSPER trial participants

Figure 3: Competing risks model for death or admission to a care-home for WOSCOPS trial participants