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)

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ABSTRACT

Objectives: This study aims to examine the extent to which statins are used by adults at high risk of cardiovascular disease (CVD) compared to European clinical guidelines. The high-risk groups examined are those with (1) known CVD, (2) known diabetes and (3) a high or very high risk (≥5%) of CVD mortality based on Systematic Coronary Risk Evaluation (SCORE).

Design: This study is cross-sectional in design using data from the first wave (2009–2011) of The Irish Longitudinal Study on Ageing (TILDA).

Setting and participants: The sample (n=3372) is representative of community living adults aged 50–64 years in Ireland.

Results: Statins were used by 68.6% (95% CI 61.5% to 75.8%) of those with known CVD, 57.4% (95% CI 49.1% to 65.7%) of those with known diabetes and by 19.7% (95% CI 13.0% to 26.3%) of adults with a SCORE risk ≥5%. Over a third (38.5%, 95% CI 31.0% to 46.0%) of those with known CVD, 46.8% (95% CI 38.4% to 55.1%) of those with known diabetes and 85.2% (95% CI 79.3% to 91.1%) of those with a SCORE risk ≥5% were at or above the low-density lipoprotein cholesterol (LDL-C) target of 2.5 mmol/L specified in the 2007 European guidelines.

Conclusions: Despite strong evidence and clinical guidelines recommending the use of statins for secondary prevention, a gap exists between guidelines and practice in this cohort. It is also of concern that a low proportion of adults with a SCORE risk ≥5% were taking statins. A policy response that strengthens secondary prevention, and improves risk assessment and shared decision-making in the primary prevention of CVD is required.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality globally and accounts for about a third of all deaths in Ireland. Dyslipidaemia, especially hypercholesterolaemia, plays a major role in the development of CVD.
CVD.8–11 Statins also play a role in the primary prevention of CVD for adults at high risk of CVD. This includes those with diabetes,8–10 those with familial hypercholesterolaemia12 and those with a high or very high (≥5%) Systematic CORonary Risk Evaluation (SCORE) in combination with defined LDL-C threshold levels.3 European guidelines on CVD prevention in clinical practice, including the management of dyslipidaemia, were published in 200712 and updated in 2012.3

This study aims to examine the extent to which statins are used by adults (50–64 years) at high risk of CVD morbidity and mortality in Ireland compared to European clinical guidelines. The high-risk groups examined include those with: (1) known CVD, (b) known diabetes and (3) a high or very high risk (≥5%) of CVD mortality based on SCORE.13

METHODS
Design and data collection
The study uses cross-sectional data from a nationally representative sample of community living adults aged 50 years and older in Ireland. The sample was recruited based on a national directory of residential addresses using the RANSAM system.14 The data were collected as part of the first wave of the Irish Longitudinal Study on Ageing (TILDA). All participants provided written informed consent.

Data were collected between October 2009 and July 2011. Participants took part in a face-to-face computer-assisted personal interview in their home followed by a health assessment in a designated centre or in their home. Further details are available elsewhere on the health assessment element of this study.15

Measurements
Participants were asked “Has a doctor ever told you that you have any of the following conditions?” CVD (angina, myocardial infarction, coronary artery bypass surgery, stroke or transient ischaemic attack (TIA)) and diabetes (types I and II) classification were based on participant responses to this question or a self-report of having undergone an angioplasty or stent insertion procedure. Information on current smoking status was collected during the interview.

Current medication use, including statin therapy, was recorded by the interviewer during the home-based interview and cross-checked using medication labels. Good agreement has been demonstrated in this cohort between self-report and pharmacy dispensing records for lipid-modifying agents (κ=0.73, 95% CI 0.69 to 0.77).16 Medication was classified according to the WHO Anatomical Therapeutic Chemical classification system. All 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)-reductase inhibitors (statins) were coded as C10AA, and those in combination with other lipid-modifying agents and with other combinations, coded as C10B, were combined to create a single statin variable.

Blood pressure was measured during the health assessment by a nurse according to a standard protocol. A digital automated oscillometric blood pressure monitor (Omron M10-IT, Omron Inc, Kyoto, Japan) was used to measure blood pressure while the respondent was seated comfortably in an upright position after a period of rest. Blood pressure was recorded twice while seated with a timed interval of 1 min between readings. The mean systolic blood pressure obtained from these two measurements was used in SCORE.

Non-fasting venous blood was drawn to estimate total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides. LDL-C was estimated based on the Friedewald equation.17 Total cholesterol and LDL-C were grouped according to targets set in the 200712 guidelines and threshold categories for drug intervention in the 20123 guidelines.

High-risk groups
SCORE estimates the 10-year risk of first fatal atherothrombotic event in those aged 40–64 years.13 The youngest TILDA participants were 50 years old; therefore, this study is limited to those aged 50–64 years. SCORE was developed to provide a risk scoring system for use in the clinical management of cardiovascular risk in participants without known CVD in European clinical practice. It includes the following risk factors: age, sex, systolic blood pressure, total cholesterol and smoking status. Risk equations have been developed for ‘low risk’ and ‘high risk’ countries3 based on cut-off points for CVD and diabetes mortality in men and women in 2008. Ireland was classified as ‘low risk’; therefore, the corresponding risk equations were applied to the TILDA data in this study.

Those with known CVD, diabetes mellitus and familial hypercholesterolaemia are considered to be at high risk.3 12 Those with familial hypercholesterolaemia (LDL-C >6 mmol/L, n=13) were not analysed in this study due to the small number found. The remainder of the sample was grouped into four categories according to the SCORE protocol: low risk (<1%), moderate risk (1% and <5%), high risk (≥5% and <10%) and very high risk (≥10%) of CVD mortality. The high-risk and very high risk groups were collapsed into a single SCORE ≥5% high-risk group.

Covariates
Demographic covariates included age, sex and highest educational attainment (primary, secondary and tertiary). Access to primary healthcare was assessed using entitlement to a means tested medical card which provides free access to general practitioner (GP) care and heavily subsidised prescribed medicines. Frequency of GP visits was recorded as the number of visits to the GP in the previous 12 months.
Statistical analysis
We calculated the prevalence and 95% CIs for CVD, diabetes, and high or very high SCORE risk in the age group of 50–64 years. Respondent groups were compared using \( \chi^2 \) tests for categorical variables and t tests for continuous variables. Generalised linear models with binomial distribution, log link function and robust standard errors were used to determine the association between medical card status and statin utilisation in the three groups at high risk of CVD mortality, adjusting for age, sex, level of education and frequency of GP visits. Unadjusted and adjusted risk ratios (RRs) and 95% CIs are presented.

Estimates of the absolute number of individuals suboptimally treated with statins in the high-risk groups were calculated based on the 2012 guidelines \(^3\) and using population data from Census 2011. \(^18\) Survey weights based on age, sex and educational attainment were applied to reduce non-response bias to the interview stage of the survey. Additional weights based on health and demographic factors were applied to increase the representativeness of the sample used in the analysis. Statistical significance was set at \( p<0.05 \). The statistical software Stata/MP V.12.1 was used to conduct the analyses.

RESULTS
The overall household response rate was 62%. In total, 8175 respondents completed the home-based interview, 57.1% (n=4668) of these respondents were aged 50–64 years (figure 1). Of these, 75.3% (n=3517) completed a health assessment (91.6% in a health assessment centre, 8.4% in the respondent’s home). Owing to small numbers, the high-risk group with LDL-C >6 mmol/L (n=13) were excluded from the analysis as were those with missing data (n=132). The final sample size for analysis consisted of 3372 individuals with full risk factor data available.

Characteristics of the sample by sex are provided in table 1. The mean age of the sample was 56.7 (SD=4.2) years and 45% were men. Almost one-fifth were current smokers (18.3%), and smoking was equally distributed between men and women. Total cholesterol, LDL-C and HDL-C levels were higher in women compared to men. In contrast, triglycerides, systolic and diastolic blood pressure levels were higher in men compared to women.

High-risk groups
Three high-risk groups for CVD mortality were identified: those with known CVD, those with known diabetes and those at high or very high (\( \geq 5\% \)) SCORE risk. Of those aged 50–64 years, 4.9% (95% CI 4.1% to 5.6%) (n=166) had known CVD, including 23 with diabetes. A further 4.2% (95% CI 3.5% to 4.8%) (n=141) had self-reported diabetes without CVD (figure 1).

SCORE 10-year risk of CVD mortality was estimated in those without evidence of CVD or diabetes (n=3065). The majority were classified as low risk (40.9%, 95% CI 30.9% to 50.4%). The high-risk group with SCORE risk scores of \( 5\% \) or higher included 4.2% (95% CI 3.5% to 4.8%) (n=132) who had incomplete risk factor profile.

![Figure 1](https://example.com/figure1.png)

**Table 1**: Sample characteristics by sex.

Murphy C, et al. BMJ Open 2015;5:e008017. doi:10.1136/bmjopen-2015-008017
Bivariate and multivariable models were used to examine the relationship between statin utilisation and medical card status in each of the three groups at high risk (table 3). No association was found between medical card status and statin utilisation in those with known CVD or in those with known diabetes. In the group with SCORE risk ≥5%, those with a medical card were twice as likely to be taking statins (adjusted RR=2.20, 95% CI 1.13 to 4.26) compared to those without a medical card (table 3).

### Lipid profiles in high-risk groups compared to guideline targets in 2007

Over a third (38.5%, 95% CI 31.0% to 46.0%) of those with known CVD, 46.8% (95% CI 38.4% to 55.1%) of those with known diabetes and 85.2% (79.3%-91.1%) of those with a SCORE risk ≥5% were at or above the LDL-C target of 2.5 mmol/L specified in the 2007 European guidelines. Close to half (45.7%, 95% CI 38.1% to 53.4%) of those with known CVD, 50.3% (95% CI 42.0% to 58.7%) of those with known diabetes and 90.8% (95% CI 86.0% to 95.6%) of those with a SCORE risk ≥5% were at or above the total cholesterol target of 4.5 mmol/L (table 2).

### Lipid profiles in high-risk groups compared to guideline targets in 2012

The target LDL-C for those with CVD was reduced to <1.8 mmol/L in the 2012 guidelines. Just over a quarter (27.7%, n=46) were at the recommended target LDL-C level for secondary prevention populations using the updated guidelines published within a year of data collection completion (not shown). These updated guidelines recommend immediate drug intervention at the LDL-C threshold of ≥1.8 mmol/L in those with a very high (≥10%) SCORE risk and a threshold of ≥2.5 mmol/L in those with a high (≥5% and <10%) SCORE risk. Using these cut-off, 87% (n=123) of those with a SCORE risk ≥5% were identified as requiring immediate drug intervention based on these recent guidelines.

Population data from Census 2011 were used to calculate the absolute difference between the observed number of high-risk individuals in the age group of 50–64 years on statin therapy and the expected number based on the 2012 guidelines (table 4). In a total population (50–64 years) of 737 694, we estimate that 51 885 individuals were on suboptimal statin treatment compared to the guidelines. This includes 11 715 with known CVD, 13 398 with known diabetes and 26 772 with a SCORE risk ≥5%.

### DISCUSSION

**Statement of the principal findings**

The main finding in this study was that statin utilisation for secondary prevention in those aged 50–64 years was lower than expected based on European CVD...
guidelines. In those with known CVD, 68.6% were utilising statins and this figure only increased to 78.6% in those who had experienced more than one type of CVD event. Statin use for primary prevention in those at high risk of CVD was also low, with 57.4% of those with known diabetes and 19.7% of those with a SCORE risk of ≥5% using a statin.

Secondary prevention

Despite strong evidence and clinical guidelines supporting the use of statins for secondary prevention in conjunction with lifestyle interventions, a gap exists between European CVD guidelines and clinical practice in this cohort. Research has demonstrated poor control of risk factors in those with coronary heart disease,19 20 despite improvements in the use of cardioprotective medication. The most recent EUROASPIRE IV study conducted across 24 European countries found that statins were used by 85.7% of patients, 6 months after an initial coronary artery bypass graft, percutaneous coronary intervention or acute coronary syndrome.20 Robust incentives such as the Quality Outcomes Framework (QOF) which rewards general practice for quality care have resulted in an increase in statin prescription across the UK.21 Participation in the QOF is voluntary and almost all practices take part in it. In England, the use of lipid-lowering medication in a community cohort of adults aged 35 years and older who self-reported ischaemic heart disease or stroke was 79% in men and 72% in women in 2011.22 Recent evidence from the Action on Secondary Prevention through Intervention to Reduce Events (ASPIRE-2-PREVENT) survey conducted in a stratified random sample of hospitals and general practices in the UK revealed that over 90% of those with coronary heart disease were on statins.23

Previous Irish research has also demonstrated improved statin usage in patients with established coronary heart disease enrolled on Heartwatch, a programme of secondary prevention in primary care.24 One-fifth of general practices participated in Heartwatch, inviting their patients to attend on a quarterly basis for secondary prevention in addition to usual care. Statin usage increased from 78.5% at baseline in 2003 to 89.9% in 2005 among those enrolled on the programme.25 The current research, conducted 4 years later, shows evidence of lower levels of statin utilisation and failure to achieve guideline targets in a representative sample of adults with known CVD living in the community. The findings reveal that statin use among those with known CVD was lowest in participants who had experienced a stroke or TIA. This finding is of concern given the strong evidence provided by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study to support the use of high-dose statin therapy to reduce adverse outcomes.26 The policy implications of these findings are that secondary prevention should be strengthened at primary care level to reduce the risk of future CVD events in this population.
Primary prevention

In this study, the use of statins for the primary prevention of CVD was examined only in those classified as high or very high risk (≥5%) based on SCORE. There is ongoing debate on the benefits and risks of using statins for the primary prevention of CVD in those at low absolute risk of CVD, and this issue is not addressed in this paper.

In patients without established CVD but with CVD risk factors including diabetes, statins are associated with reductions in all-cause mortality and incidence of major coronary and cerebrovascular events. Primary prevention of CVD in the clinical setting requires a focus on lifestyle modification and individualised risk assessment. This may take the form of a routine assessment of a defined population group similar to the Health Check provided in the UK for all adults aged 40–74 years, or risk assessment on an opportunistic basis as is the current practice in Ireland. A Cochrane review found that general health checks did not reduce morbidity or mortality for cardiovascular causes and insufficient evidence was found to support routine screening of the population. Results from the recent Inter99 study on the use of statins in the groups at high risk of CVD compared to European guideline recommendations 2012 and the estimated number of adults suboptimally treated with statins in Ireland (50–64 years, TILDA wave 1).

Table 3

| Model | RR 95% CI | Adj RR 95% CI |
|-------|----------|---------------|
| Known CVD | 0.97 (0.78 to 1.19) | 0.72 (0.81 to 1.15) |
| Known diabetes | 1.28 (0.97 to 1.68) | 0.91 (0.99 to 1.15) |
| SCORE ≥5% | 2.02 (1.49 to 3.69) | 2.2 (1.1 to 4.3) |

Model 1: unadjusted.
Model 2: adjusted for age, sex, education and frequency of GP visits in the previous 12 months.
*p < 0.05.
Adj RR, adjusted risk ratio; CVD, cardiovascular disease; GP, general practitioner; SCORE, Systematic COronary Risk Evaluation; TILDA, The Irish Longitudinal Study on Ageing.

Table 4

High-risk groups

| Proportion recommended statin in 2012 guidelines, % | Weighted proportion of the population, % (95% CI) | Weighted proportion of those with SCORE ≥5% in the study sample, % | Weighted proportion at risk and on a statin, % (95% CI) | Weighted proportion at risk not on a statin, % (95% CI) | Number sub-optimally treated, N (95% CI) |
|-----------------------------------------------------|-------------------------------------------------|------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------------|
| Known CVD                                           | 5.3 (4.0 to 6.6)                                  | 3.7 (2.9 to 4.6)                                | 3.5 (2.9 to 4.2)                                  | 3.6 (2.8 to 4.4)                                  | 51 (95% CI)                            |
| Known diabetes                                      | 5.3 (4.0 to 6.6)                                  | 4.3 (3.5 to 5.0)                                | 3.5 (2.5 to 4.5)                                  | 1.8 (1.3 to 2.3)                                  | 13 389 (9767 to 17 030)                |
| SCORE ≥5%                                           | 4.3 (3.5 to 5.0)                                  | 3.6 (2.8 to 4.4)                                | 1.9 (1.3 to 2.7)                                  | 0.7 (0.4 to 1.1)                                  | 26 772 (20 889 to 32 665)              |

Total

| Proportion recommended statin in 2012 guidelines, % | Weighted proportion of the population, % (95% CI) | Weighted proportion of those with SCORE ≥5% in the study sample, % | Weighted proportion at risk and on a statin, % (95% CI) | Weighted proportion at risk not on a statin, % (95% CI) | Number sub-optimally treated, N (95% CI) |
|-----------------------------------------------------|-------------------------------------------------|------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------------|
| Known CVD                                           | 5.3 (4.0 to 6.6)                                  | 3.7 (2.9 to 4.6)                                | 3.5 (2.9 to 4.2)                                  | 3.6 (2.8 to 4.4)                                  | 51 (95% CI)                            |
| Known diabetes                                      | 5.3 (4.0 to 6.6)                                  | 4.3 (3.5 to 5.0)                                | 3.5 (2.5 to 4.5)                                  | 1.8 (1.3 to 2.3)                                  | 13 389 (9767 to 17 030)                |
| SCORE ≥5%                                           | 4.3 (3.5 to 5.0)                                  | 3.6 (2.8 to 4.4)                                | 1.9 (1.3 to 2.7)                                  | 0.7 (0.4 to 1.1)                                  | 26 772 (20 889 to 32 665)              |

*Cohort population is based on LDL-C bands in 2012 guidelines, 87% of those with SCORE ≥5% in the study sample fulfilled the criteria for statin therapy according to the guidelines. CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic COronary Risk Evaluation; TILDA, The Irish Longitudinal Study on Ageing.
concur, finding that an individually tailored intervention programme with screening for risk and an individually tailored lifestyle intervention had no effect on ischaemic heart disease, stroke or mortality at the population level after 10 years. In the absence of evidence to support risk assessment of the entire population, opportunistic assessment using appropriate risk assessment tools is required to identify those at highest risk of future CVD who may benefit from primary prevention advice. The findings of the risk assessment together with clinical practice guidelines can be used to guide discussions between physicians and patients with regard to the benefits and risks of long-term statin therapy.

**Suboptimal medication**

Non-adherence to prescribed medications may explain some of the low level of statin utilisation found in our study and the failure to achieve target levels of LDL-C. Non-adherence to prescribed statins is known to lead to adverse outcomes and higher costs of care. Adherence has been found to fall after the acute phase following a CVD event and is low in those taking statins for chronic coronary artery disease. The global Reduction of Atherothrombosis for Continued Health (REACH) study examined long-term adherence to medication in patients with atherothrombotic disease. The study revealed that almost half of patients were deemed adherent to guideline recommended medications over a 4-year period. Reasons for non-adherence to statins may include statin intolerance and cost. The reported incidence of statin intolerance is variable with observational studies reporting muscular symptoms in 10.5% of patients on high-dose statin therapy. The majority of individuals in this study with a SCORE risk ≥5% were at high risk (≥5% and <10%) as opposed to very high risk (≥10%) of CVD mortality. It is, therefore, possible that patient preference and willingness to accept lifelong medication in the absence of overt disease had a role to play in the low level of statin use in this primary prevention group.

In our study, a quarter of the sample was eligible for a medical card which entitled them to free GP visits and heavily subsidised prescribed medications. The remainder were required to pay, out of pocket, for GP visits (approximate cost €50–70 per visit) and prescribed medication. No evidence was found to suggest that medical card status was associated with statin utilisation in the groups with known CVD or diabetes. However, the positive association found between medical card status and statin utilisation in those at high SCORE risk suggests that financial barriers act as a deterrent to primary prevention in this high-risk group. Previous research on eligibility for free GP care in Ireland has demonstrated that those with a medical card are more likely to visit their GP and to visit more frequently than private patients. In the primary prevention context, this provides more opportunity for those with a medical card to avail of opportunistic risk assessment. Previous research in this cohort has similarly demonstrated that cardiovascular medication is utilised more frequently by those with a medical card. The cost of statins during the study period was high; only 8.5% of statins used by this cohort were generic, resulting in high cost for individuals prescribed statins and without access to a medical card.

The low level (19.7%) of statin use for primary prevention in those with a SCORE risk ≥5% may have resulted from a combination of insufficient risk assessment or failure to adhere to clinical guidelines. Evidence that guidelines are sporadically applied was demonstrated in EUROASPIRE. Although physicians have been found to support the use of guidelines and are aware of the need to consider a combination of CVD risk factors, less than half have been found to use guidelines or risk calculators to determine total risk in European studies.

Barriers to CVD guideline implementation include time constraints, patient compliance, financial limitations, including lack of GP remuneration; government health policy; lack of perceived usefulness, including inadequate knowledge of the risk scoring systems; and fear of over-use of medical therapies.

**Strengths and limitations of the study**

The strengths of this study include the large nationally representative sample of community-living adults which allows us to generalise our findings to the population in Ireland; the structured collection of interview data, including medication data; and the use of standardised protocols for measurements taken during the health assessment. Non-fasting blood was analysed for lipid levels; this may be considered a limitation. Research at the pilot stage of TILDA found that mean total cholesterol and LDL-C did not differ by fasting allocation and recent research recommends re-evaluating the recommendation that patients fast before obtaining a lipid panel as non-fasting LDL-C has been found to have similar prognostic value to fasting LDL-C.

While TILDA aimed to generate a nationally representative sample, the non-response rate to the survey may have introduced some selection bias. It is likely that responders had a better risk factor profile compared to non-responders thus providing a more optimistic view of risk factor management in this population. The availability of a home and centre-based health assessment reduced the selection bias associated with the health assessment component of the survey.

This study is limited as it relies on self-reports of doctors’ diagnosis of CVD and diabetes which may underestimate the true prevalence of these conditions. Previous research on this cohort found a lower prevalence of hypertension and atrial fibrillation on self-report when compared to objective measures. Markers of organ damage are not available in the TILDA data set; some asymptomatic individuals with organ damage may, therefore, have been misclassified to a lower level of risk than should be the case. In this research it is not possible to identify individuals who...
were formally risk stratified or those engaged in lifestyle changes before consideration of pharmacological measures. Neither it is possible to identify those who discontinued a statin due to intolerance nor those who declined statin treatment following risk assessment and consultation with their medical practitioner.

CONCLUSION
This is the first study to examine the use of statins in those at high risk of CVD in a nationally representative sample of adults aged 50–64 years in Ireland. Despite strong evidence and clinical guidelines supporting the use of statins for secondary prevention of CVD, this study reveals a gap between guidelines and clinical practice in this group. An immediate policy response is required to strengthen secondary prevention for those with existing CVD. For the remainder of the population without evidence of CVD, population strategies for primary prevention are required as well as opportunistic risk assessment to identify those at high risk of future CVD in order to establish best practice in primary prevention.

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Contributors
CM was the lead researcher and was involved in the design, implementation, analysis and reporting of the study. ES, TF, KB, IG and RAK provided substantial contributions to the conception and design of the work, and all have read and approved the final manuscript.

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