The impact of statin discontinuation and restarting rates on the optimal time to initiate statins and on the number of cardiovascular events prevented

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Abstract

Introduction: A patient is eligible for statins in England if they have a 10-year risk of cardiovascular disease >10%. We hypothesize that if statin discontinuation rates are high it may be better to delay statin initiation until patients are at a higher risk, to maximize the benefit of the drug.

Methods: A four-state health state transition model was used to assess the optimal time to initiate statins after a risk assessment, in order to prevent the highest number of cardiovascular events, for a given risk profile (age, gender, risk) and adherence rate. A Clinical Practice Research Datalink dataset linked to Hospital Episodes Statistics and Office for National Statistics was used to inform the transition probabilities in this model, taking into account observed statin discontinuation and re-continuation patterns.

Results: Our results suggest, if statins are initiated in a cohort of 50-year old men with a 10% 10-year risk, we prevent 4.78 events per 100 individuals. If we wait 10 years to prescribe, at which point 10-year risk scores are at 20%, we prevent 5.45 events per 100 individuals. If the observed discontinuation rate was reduced by a sixth, third or half in the same cohort, we would prevent 7.29, 9.01 or 10.22 events per 100 individuals.

Conclusions: In certain scenarios, extra cardiovascular disease events could be prevented by delaying statin initiation beyond a risk of 10% until reaching a age (59 for men, 63 for women), based on statin discontinuation rates in England. The optimal time to initiate statins was driven by age, not by cardiovascular risk.

1 INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death globally accounting for 31% of all deaths in 2017, and contributes more than any other disease to the total disease burden around the globe. Treatment for primary prevention of CVD is centered around lifestyle modifications such as changes to diet and exercise, and cholesterol-lowering medication such as hydroxymethylglutaryl-coenzyme reductase inhibitors (statins). There has recently been a lot of debate in the literature over the optimal risk to initiate statins for the primary prevention of CVD. Both England (National Institute for Health and Care Excellence guidelines) and the United States (American College of Cardiology/American Heart Association guidelines) have recently dropped their thresholds to a 10-year risk of 10% and 7.5%. However, the European Society of Cardiology still recommend a 10-year risk of a fatal CVD event of 5%, which equates to about a 15% risk of any CVD...
event, while in Scotland the recommended threshold is 20% for asymptomatic individuals. In support of higher thresholds, a recent study found that statins only provide a net benefit over possible harms at higher 10-year risks than the thresholds in current guidelines, and the benefits vary considerably by age and sex.

One factor that will affect the real-world impact of these guidelines is the widely reported suboptimal long-term adherence to and discontinuation from statins. Studies examining factors affecting adherence to statins report consistent relationships between nonadherence and female gender, ethnic minority status, reduced income, lower number of concurrent CVD medications, new statin users, use of statins for primary prevention, smoking, depression, reduced follow-up and increased copayments, while a recent high profile meta-analysis concluded that exaggerated claims about side-effect rates with statin therapy may be responsible for its under-use among individuals at increased risk of CVD. The analyses underpinning the treatment thresholds do not incorporate the effects of non-adherence or discontinuation directly. We suggest that policy decisions around lowering of treatment thresholds may need to take account of real-world statin discontinuation rates in primary prevention. The reason could be that patients are initiating statins at a low risk and then discontinuing the drug when at a higher risk (risk increases with age), not maximizing the benefit of the drug.

The overall aim of this study was to assess the optimal time to initiate statins after a risk assessment in order to prevent the highest number of CVD events, given a patient’s risk profile, and long-term adherence levels derived from real life data. We refer to adherence throughout this study specifically in relation to the combination of discontinuation and restarting rates. We also developed a range of scenarios where discontinuation rates were artificially decreased, allowing us to evaluate the effect that improving adherence would have on the number of CVD events prevented.

**KEY POINTS**

- Current research evaluates when it becomes cost-effective to initiate statins for primary prevention of cardiovascular disease, but does not consider when is the best time in a patient’s life to initiate treatment to prevent the most cardiovascular events.
- We hypothesised if discontinuation rates are high, it may be better to initiate statins at higher cardiovascular risks than 10% to ensure patients get the most benefit from the drug.
- Our results showed in some scenarios that there would be a benefit to delaying statin initiation past the 10% threshold, although the optimal time to initiate was based on age rather than cardiovascular risk.
- Such an approach has ethical concerns as you must base this decision on population level discontinuation rates, rather than the discontinuation time of the individual patient.
- Improving adherence in a meaningful way would lead to more cardiovascular events prevented than adjusting the threshold, but may be difficult to achieve.

2 | METHODS

2.1 | Overview of simulation model design

A four-state health state transition model with cycle length of 1 year was created (Figure 1) to answer our primary aim. Each scenario (age, gender, 10-year CVD risk score and assumed adherence rate) represented a patient having their 10-year risk assessment, which is
when a clinician would decide whether to initiate statin treatment. We varied the year of follow-up in which statins were initiated, and calculated the total number of CVD events expected. For the main analysis the discontinuation and restarting rates were derived directly from the Clinical Practice Research Datalink (CPRD) cohort, then for subsequent analyses the discontinuation rate were artificially decreased. The cost effectiveness of statins at various risk thresholds has already been extensively covered.\textsuperscript{16} Instead, this model was set up to calculate the number of incident CVD events prevented by initiating statins at different times, assuming real life risk profiles and adherence rates, and is what makes this study unique.

2.2 Data source

This project used data from the CPRD linked with Hospital Episodes Statistics (HES) and Office for National Statistics (ONS). CPRD is a primary care database representative of the United Kingdom in terms of age, sex and ethnicity,\textsuperscript{17} although linkage to HES restricts this dataset to England only. The data were used to create two cohorts, a cohort of statin users (statin cohort) and a cohort of patients at risk of CVD (primary prevention cohort).

The primary prevention cohort was defined in the same way as the QRISK3 development cohort.\textsuperscript{18} To be eligible for the cohort, a patient must have had 1 day of follow up in CPRD that met the following inclusion criteria: (a) Aged 25-84, (b) Within study period of 1st Jan 1998 to 31st Dec 2015, (c) At least 1 year prior follow up. The cohort entry date for a patient was defined as the first date that met all these criteria. Patients were then excluded if they met the following exclusion criteria: (a) CVD event (identified through CPRD, HES or ONS) or statin prescription prior to cohort entry date (code lists in Appendix S1). Patients were censored at the earliest date of transferred out of practice, last data collection for practice, death, or 31st Dec 2015.

Inclusion criteria for the statin cohort were: (a) First statin prescription between 1st Jan 1998 and 31st Dec 2015 (code list for statins in Appendix S1), (b) Aged 25 or over on date of first statin prescription. Exclusion criteria were: (a) CVD event prior to first statin, (b) Less than 1 year follow up prior to first statin prescription. Exclusion criteria 2 was to ensure that all patients were first time users of statins, rather than current users who have transferred from another practice. A patient entered the cohort on the date of their first statin prescription and exited the cohort at the end of that statin treatment period (detailed definition in Appendix S2). A patient could leave and re-join the cohort (at the start of their next treatment period) multiple times before their censoring date. A patient was censored if transferred out of practice, at the end of data collection, death or occurrence of a CVD event.

2.3 Estimation of transition probabilities

CVD event probabilities were calculated from the primary prevention cohort. A lifetime risk model was fitted using standard techniques for developing lifetime risk models.\textsuperscript{19-21} This involved fitting a Cox model with age as the time scale, the outcome was time until first CVD event, and the same predictor variables as QRISK3 [atrial fibrillation, atypical antipsychotic use, body mass index, cholesterol/high-density lipoprotein ratio, chronic kidney disease (stage 3/4/5), corticosteroid use, erectile dysfunction (male model only), ethnicity, family history of CVD, HIV/AIDS, hypertension (treated), migraine, rheumatoid arthritis, severe mental illness, systolic blood pressure (SBP), SBP variability, smoking status, systemic lupus erythematosus, type 1 diabetes, type 2 diabetes and Townsend deprivation score; code lists and information about variable derivation provided in Appendix S1]. Using the baseline hazard from this model, for a given age the hazard ratio could be adjusted to obtain a specific 10-year risk (for each scenario), and from this the corresponding lifetime risk could be derived. After deriving this, the conditional probability of having a CVD event in each year of follow up was calculated (conditional on not having had an event prior to that year), giving the transition probabilities $p_c$. Full details on derivation provided in Appendix S2. The transition probabilities of a CVD event while on statin treatment were calculated as $p_c \cdot adj = 0.7 \cdot p_c$. This estimate of statin effectiveness (relative rate: 0.7) was taken from the NICE economic model for cost effectiveness of statins,\textsuperscript{3,16} based on using high intensity statin regimens. Given the varying incidence of each component of the outcome across different age categories and sexes, any single estimate of the relative rate on the composite outcome would be somewhat arbitrary. We therefore chose 0.7 as a conservative estimate for the effect of statins.

The probabilities of discontinuing and restarting statins were calculated using the statin cohort. The data were split into different groups: first treatment period, off treatment for first time, second treatment period, off treatment for second time, etc. Kaplan Meier curves were then fit to each group and the probability of a patient discontinuing/restarting during each day of follow up was calculated. As the duration of follow-up in the simulation was longer than in our data, the discontinuation/restarting rates were extrapolated. If a patient discontinued for a third time we made the assumption they did not restart treatment because the discontinuation rate in the fourth treatment period was high (76%/90% after 1/2 years), and only 314 patients remained in this cohort after 5 years (see Section 3). For the first treatment period discontinuation rates were stratified by age (this was not possible for subsequent periods as sample size was deemed too small for some subgroups). A Cox proportional hazards model was fit to the discontinuation data from the first treatment period with age as a predictor variable, considering fractional polynomials of age using the mfp package.\textsuperscript{22} This allowed the discontinuation rate to be a function of age. Full details of the stratification and extrapolation of the discontinuation rates is provided in Appendix S2.

The transition probabilities of non-CVD related death were calculated using the primary prevention cohort. The date of death was based on the data as recorded in primary care, shown to have 92% concordance with ONS within 2 weeks.\textsuperscript{23} These data were
combined with ONS, for which we had linkage to CVD related deaths. Deaths identified in primary care that were CVD related were then excluded. Incidence rates of death across each age category were then calculated.

2.4 | Implementation of the simulation

Different scenarios were simulated based on a patient having a risk assessment (start of the simulation), and the decision of whether to initiate statins straight away, or delay. Variables that made up the different scenarios were: age, gender and 10-year CVD risk at the start of the simulation, the statin initiation date, and an assumed adherence rate. The ages considered were 40, 50 and 60. For each age, we considered all 10-year risks within the 1 to 99th percentile range of risk scores calculated for patients in that age group from our primary prevention cohort. The statin initiation date was varied in yearly intervals from the start of simulation. Given the discontinuation rate for the first treatment period was stratified by age, this meant the age at statin initiation time impacted the discontinuation rate used in each scenario. Duration of follow up was from the age at start of the simulation (risk assessment), until 90 years of age. Cycle lengths were 1 year. For each scenario we simulated 10,000 patients and calculated the number of CVD events over the course of the entire duration of follow up, which was compared with the number of events if no statins were given, providing the number of events prevented per 100 people.

This process was repeated using four different adherence rates. The discontinuation rate from the first, second and third treatment periods were altered so that the probability of discontinuation was 5/6th, 2/3rd, ½ or 0th (100% adherence) of the rate derived from CPRD.

2.5 | Sensitivity analyses

The simulation was conducted assuming a treatment effect of 0.65 and 0.6, given the uncertain nature of the estimate used in the primary simulation. Also, simulations were conducted using discontinuation and restarting rates from a cohort of statin users where any

### TABLE 1  Baseline table for statin cohort and cardiovascular disease (CVD) primary prevention cohort

|                | Statin users cohort: female | Statin users cohort: male | Primary prevention cohort: female | Primary prevention cohort: male |
|----------------|----------------------------|---------------------------|-----------------------------------|---------------------------------|
| N              | 161,995                    | 181,090                   | 1,965,078                         | 1,890,582                       |
| Demographics   |                            |                           |                                   |                                 |
| Age [mean, (SD)] | 63.49 (11.05)              | 60.07 (11.09)             | 43.07 (15.94)                     | 41.84 (14.57)                   |
| Townsend: 1    | 22.84%                     | 24.91%                    | 21.96%                            | 21.65%                          |
| Townsend: 2    | 23.13%                     | 23.77%                    | 21.98%                            | 21.50%                          |
| Townsend: 3    | 20.66%                     | 20.40%                    | 21.18%                            | 20.78%                          |
| Townsend: 4    | 20.06%                     | 18.80%                    | 20.46%                            | 20.78%                          |
| Townsend: 5    | 13.30%                     | 12.12%                    | 14.42%                            | 15.29%                          |
| Test data      |                            |                           |                                   |                                 |
| Body mass index [mean, (SD)] | 29.26 (6.33)              | 28.95 (5.04)             | 25.60 (5.60)                     | 26.12 (4.54)                    |
| Cholesterol/ high density lipoprotein ratio [mean, (SD)] | 4.36 (1.48)              | 4.88 (1.61)             | 3.72 (1.20)                     | 4.48 (1.40)                    |
| Systolic blood pressure [mean, (SD)] | 140.52 (18.39)           | 140.78 (17.25)           | 123.91 (18.28)                  | 130.03 (16.48)                  |
| Systolic blood pressure variability [mean, (SD)] | 13.10 (5.80)             | 12.15 (5.89)             | 9.47 (5.98)                     | 10.13 (6.80)                    |
| Smoking status | Never = 46.79%             | Never = 32.35%            | Never = 56.04%                   | Never = 46.63%                  |
|                | Ex = 30.33%                | Ex = 40.42%               | Ex = 16.97%                      | Ex = 17.48%                     |
|                | Current = 22.87%           | Current = 27.23%          | Current = 26.99%                 | Current = 35.99%                |
| Medical history |                            |                           |                                   |                                 |
| Atrial Fibrillation | 2.85%                     | 3.61%                     | 0.44%                            | 0.57%                           |
| Chronic Kidney Disease stage 3/4/5 | 7.13%                     | 4.00%                     | 0.45%                            | 0.32%                           |
| Family history of CVD | 29.17%                    | 23.02%                    | 15.08%                           | 11.02%                          |
| Rheumatoid arthritis | 2.08%                     | 0.87%                     | 0.69%                            | 0.26%                           |
| Treated hypertension | 49.03%                    | 43.84%                    | 6.18%                            | 4.50%                           |
| Type 1 diabetes | 1.33%                     | 1.72%                     | 0.21%                            | 0.28%                           |
| Type 2 diabetes | 21.28%                    | 22.33%                    | 1.16%                            | 1.42%                           |
single prescription statin users were removed, a step often taken to identify cohorts of long term statin users.

3 | RESULTS

3.1 | Cohort characteristics

Table 1 contains the baseline characteristics of the two study cohorts, stratified by gender. Patients were older in the statin cohort, (63.49/60.07 vs 43.07/41.84 for females and males respectively), had higher body mass index, cholesterol/high density lipoprotein ratio, systolic blood pressure and fewer never smokers compared with the primary prevention cohort. Comorbidities were also more common.

3.2 | Discontinuation and restarting of statins

Figure 2 presents the discontinuation (2A) and restarting (2B) rates over the first 10 years of each treatment and restarting period. This demonstrates that 30% patients have stopped taking statins by the end of the first year of follow-up during the first treatment period, 38% have stopped after 2 years, and by 10 years 60% have stopped. Of all the patients that discontinue, 50% have restarted a year after the initial discontinuation, 59% after 2 years, and 79% after 10 years. The second discontinuation and restarting rates suggest patients are more likely to discontinue/restart during the subsequent treatment periods. Graphs for the discontinuation rate in the first treatment period stratified by age, extrapolated discontinuation and restarting rates beyond our period of data, and discontinuation and restarting rates for the cohort of long term statin users (no single prescriptions), are all presented in Appendix S2.

3.3 | Effect of delaying initiation on CVD events

Figure 3 shows the number of CVD events prevented compared to no statin treatment when delaying statin initiation by different amounts (for males; results for females are presented in Appendix S3). Each data point in the graphs represents a different scenario. We present separate graphs defined by the age at the start of the simulation. Within each graph, we have a separate trajectory for each risk group (10-year CVD risk at risk assessment). Within each trajectory the cohort of individuals is the same for each data point, the only difference is the year of follow
up in which we initiated statin treatment (and therefore the risk level of the individuals at statin initiation also). We were interested of the maxima of each trajectory, which represents the optimal time to initiate statins for this group. For males aged 40, a delay of 20 years in starting statins resulted in a higher number of CVD events prevented. In contrast, for males aged 60, a delay in starting statins resulted in fewer CVD events prevented. Results were similar for the female cohort, although the trajectories were shifted by around 5 years, with it being optimal to prescribe slightly later (Appendix S3).

Illustrative example: Consider prescribing statins to a cohort of 50-year old men with a 10% 10-year risk of CVD, we prevent 4.78 events per 100 individuals over the 40-year follow up. If we took this same cohort of men, but instead waited 10 years before initiating statins, at which point their 10-year risk of CVD would be approximately 20%, then we prevent 5.45 events per 100 individuals over the 40 years follow up.

3.4 Effect of increasing statin adherence on CVD events

Figure 4 shows the effect of reducing the discontinuation rate to 5/6, 2/3, 1/2 of the rate we found in practice, and no discontinuation. For each age group, a single 10-year CVD risk (close to the median of that age group) was selected to showcase the effects, so all trajectories within a plot consider the same group of patients. It shows the more adherent to statins people are, the more benefit they receive, and this benefit is increased the earlier prescribing is initiated (for males; results for females are presented in Appendix S3).

Illustrative example: Consider prescribing statins to a cohort of 50-year old men with a 7% 10-year risk of CVD. Per 100 individuals, 4.25 events are prevented if discontinuation rates remain as normal, 6.52 if discontinuation is reduced to 5/6, 8.06 events if discontinuation is reduced to 2/3, 9.15 events if discontinuation reduced to 1/2, and 10.51 events if there is no discontinuation. The equivalent number of events prevented for a cohort with 10% 10-year CVD risk are 4.76, 7.29, 9.01, 10.22 and 11.77.

Results from all sensitivity analyses outlined in the methods are provided in Appendix S3. A small discussion is also provided, the results echoing those from the primary analysis.

4 DISCUSSION

There are three key findings from this study. The first is that between the ages of 40 to 70, the statin initiation time had a meaningful effect on the number of events prevented. Furthermore, the risk score of a patient had a negligible effect on the optimal time to initiate statins,
which was driven by age. The second is that discontinuation and restarting rates get higher with consecutive treatment periods, underlining a complex pattern of statin usage over time. The third is that large gains could be made by improving adherence.

We observed fairly large differences in the number of events prevented when statins were initiated between the ages of 40 to 70 with a peak around ages 59 (male) and 63 (female), regardless of the CVD risk scores of the patients. Initiating statins below the age of 50 was associated with far fewer events prevented, however it is unlikely for patients this young to have a CVD risk of 10% (the threshold for cost effectiveness), and so this is unlikely to happen in practice. However it is not uncommon for a 50-year old to have a CVD risk of 10%. Our data indicates that delaying statin initiation by 10 years could prevent an extra 0.67 events per 100 men treated, and 0.96 events per 100 women treated. These gains are small but not insignificant, and are likely to be driven by the observation that adherence improves with age (until around age 70, Appendix S2: Supplementary Figure 2.3), and that patients who restart statins for the second time or more are less likely to continue with treatment (Figure 2). There is therefore a middle ground to be found which ensures patients are offered the drug when they are most adherent, at a high enough risk to gain benefit, but also that the risk of death or having a CVD event prior to receiving treatment is small enough.

Interestingly, for a given adherence level, the optimal time to prescribe was driven primarily by age rather than the 10-year CVD risk. In Figure 3 the maxima of each trajectory are at the same age despite differing risk levels. This suggests that given the suboptimal adherence levels in practice, in order to prevent the most events in the population, the optimal time to initiate statins for men is around 59 (women 63), irrespective of the CVD risk score of the patient. While the CVD risk score may drive the cost-effectiveness of statin treatment, it does not drive the optimal time in a patient’s life to start taking statins to prevent the most CVD events, which our work suggests is driven by age. The distinction can be highlighted by if a patient has perfect adherence (Figure 4), the optimal time to initiate statins is as early as possible, but the treatment may not be cost effective at this point.

The potential to prevent more CVD events in the population using such an approach brings up some important ethical concerns. Gains would be made from ensuring that all patients will receive the drug when it will have most benefit (not too early, not too late). However, alongside any gains made by delaying statin initiation to a certain age, there will be a cost to adherent patients who would have continued treatment if starting at a younger age. Arguably it is unethical to improve the health of the population in this manner. In an ideal world we would know the adherence of a patient before initiating them on treatment, and could then initiate at the most appropriate time for that patient. Unfortunately this is not possible, and we would be forced to use population level discontinuation rates, which has these concerns.

We found inconsistent use of statins by patients in primary prevention. We also found higher discontinuation and restarting rates during the later treatment periods. This provides extra information beyond the current literature, which reports the initial discontinuation and restarting rates. The present study found that improving adherence could have a larger impact than adjusting statin initiation thresholds. This is not unsurprising, given this results in more time on treatment, however could be difficult to achieve. The most recent Cochrane review of 35 studies of statin adherence improving interventions suggested that only intensified patient care interventions (electronic reminders, pharmacist-led interventions) improved

![FIGURE 4 Number of cardiovascular disease (CVD) events prevented over the duration of follow up with different time delays in starting statins, stratified by baseline age and discontinuation rate (male) [Colour figure can be viewed at wileyonlinelibrary.com]](image)
adherence when compared with usual care. Like other studies, this study suggests that people are likely to discontinue their statin when it is newly prescribed. Targeting a patient-centered, theory-based low-cost intervention which focuses on patients’ concerns during this key initial period has been shown to improve adherence by 11% in a range of chronic illnesses, and forms the basis of a National Health Service commissioned service in England (New Medicines Service). This service is not currently provided to people starting statins, however, a randomised controlled trial of delivery of the same intervention in long term statins users demonstrated improved adherence. This suggests that extension of the New Medicines Service into statin users could demonstrate effectiveness.

There were three key limitations we identified in this study. (a) We used prescription data as a proxy for patients taking statins. This is a limitation as we only know a patient was given a prescription by their GP, we do not know if they picked the drug up, or took the drug. Therefore there is a possibility discontinuation rates are higher in practice, which would push the optimal time to prescribe further back. However there is currently no better way to measure adherence in the United Kingdom on a large scale, until prescribing and dispensing data are linked. Secondly, we only consider patients on treatment if they continually pick up their prescriptions (ie, our algorithm). We think it is unlikely patients will have discontinued treatment but continue to pick it up. (b) We extrapolated the statin discontinuation and restarting rates for the length of the simulation. Data on statin usage over an individual patient’s lifetime would be highly valuable to inform work such as this, but is not available. (c) We did not stratify the second and third discontinuation rates or first and second restarting rates based on age, despite age being a predictor of statin adherence. Our reasoning is that this would have significantly reduced the cohort size available to calculate discontinuation rates, a particular issue for the second and third treatment periods at 10 years follow up. Given we were extrapolating data from this point, this was undesirable. Given the impact of discontinuation rates on the optimal time to initiate therapy, further work could be done to explore the impact of changes in statin intensity and dose on discontinuation rates, and subsequently the best time to implement these changes.

4.1 Conclusion

In certain scenarios, extra CVD events could be prevented by delaying statin initiation beyond a risk of 10% until reaching a certain age (59 for men, 63 for women). These findings are based on the discontinuation and restarting rates in England. Currently all thresholds are based around a patient's risk score, which drives cost effectiveness. However a combination of age and adherence levels are the most important factors in determining the optimal point in a patient’s life to initiate statins. However, the clinical benefit must be weighed up against ethical concerns of such a strategy. We cannot know when a given patient will discontinue treatment in advance, and using population level discontinuation rates may disadvantage the most adherent patients. A less controversial strategy which could result in preventing more events would be to focus on improving adherence, although this may be harder to achieve.

ETHICS STATEMENT

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The study was approved by the independent scientific advisory committee for Clinical Practice Research Datalink (protocol no. 17.125RMn2). The data were provided by patients and collected by the as part of their care and support. The Office for National Statistics (ONS) is the provider of the ONS data contained within the CPRD data. Hospital Episode Data and the ONS data (Copyright © 2014) were re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

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AUTHOR CONTRIBUTIONS

All authors meet the ICMJE recommendations for authorship and agree to be accountable for all aspects of the work.

Alexander Pate: Involved in conception and planning of statistical analyses, acquisition and analyses of data and drafting of manuscript.

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REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-e603.

2. Evaluation I for HM and. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016). 2017. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 10, 2019.
3. NICE. CG181 Lipid modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2014. https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-pdf-243786637.

4. Stone NJ, Robinson JG, Lichtenstein AH, et al. Overview of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Future Cardiol. 2014;10:149-152.

5. Catapano AL, Graham I, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37:2999-3058.

6. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 149—Risk estimation and the prevention of cardiovascular disease. 2017. http://www.sign.ac.uk.

7. Yebyo YG, Aschmann HE, Puhan MA. Finding the balance between benefits and harms when using statins for the primary prevention of cardiovascular disease: a modeling study. Ann Intern Med. 2019;170:1-10.

8. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? Curr Atheroscler Rep. 2013;15:1-12.

9. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGRE survey: understanding the use of statins in America and gaps in patient education. J Clin Lipidol. 2013;7:472-483.

10. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. BMJ. 2016;353:i3305.

11. Mauskop A, Borden WB. Predictors of statin adherence. Curr Cardioil Rep. 2011;13:553-558.

12. Simeons S, Sinaeve PR. Patient co-payment and adherence to statins: a review and case studies. Cardiovasc Drugs Ther. 2014;28:99-109.

13. Mann DM, Woodward M, Mintner P, Falcon L, Kronish I. Predictors of non-adherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44:1410-1421.

14. Ofori-Asenso R, Jakuha A, Curtis AJ, et al. A systematic review and meta-analysis of the factors associated with nonadherence and discontinuation of statins among people aged ≥65 years. J Gerontol Ser A Biol Sci Med Sci. 2018;73:798-805.

15. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532-2561.

16. NICE. CG181 Lipid modification Appendices—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2014. https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-appendices-pdf-243786638.

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research Datalink (CPRD). Int J Epidemiol. 2015;44:827-836.

18. 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.

19. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet. 1999;353:89-92.

20. Beiser A, D’Agostino RB, Seshadri S, et al. Epidemiology: computing estimates of incidence, including lifetime risk: Alzheimer’s disease in the Framingham study. The practical incidence estimators (PIE) macro. Tutor Biolstat Stat Methods Clin Stud. 2000;1:1-30.

21. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010;342:93.

22. Bennet A. Multivariable Fractional Polynomials. https://cran.r-project.org/web/packages/mfp/vignettes/mfp_vignette.pdf. Accessed July 24, 2018.

23. Harshfield A, Abel GA, Barclay S, et al. Do GPs accurately record date of death? A UK observational analysis. BMJ Support Palliat Care. 2018;1:1-8.

24. Van Driel ML, Morledge MD, Ulep R, et al. Interventions to improve adherence to lipid-lowering medication. Cochrane Collab. 2016:12;CD004371. https://doi.org/10.1002/14651858.CD004371.pub4.

25. Barber N, Parsons J, Clifford S, et al. Patients’ problems with new medication for chronic conditions. Qual Saf Health Care. 2004;13:172-175.

26. Clifford S, Barber N, Elliott R, Hartley E, Horne R. Patient-centred advice is effective in improving adherence to medicines. Pharm World Sci. 2006;28:165-170.

27. Elliot RA, Boyd MJ, Salema N-E, et al. Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the new medicine service. BMJ Qual Saf. 2016;25:747-758.

28. Department of Health. Pharmacy in England: Building on strengths - delivering the future. https://www.gov.uk/government/publications/pharmacy-in-england-building-on-strengths-delivering-the-future. Accessed February 22, 2019.

29. Lyons I, Barber N, Raynor DK, Wei L. The medicines advice service evaluation (MASE): a randomised controlled trial of a pharmacist-led telephone based intervention designed to improve medication adherence. BMJ Qual Saf. 2016;25:759-769.

30. Hope HF, Binkley GM, Fenton S, et al. Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease. PLoS One. 2019;14:e0201196.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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