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Original Research

Adherence to statin treatment in patients with familial hypercholesterolemia: A dynamic prediction model

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KEYWORDS
Familial hypercholesterolemia;
Statin therapy;
Prediction;
Adherence

Abstract:

Background: Statins are the primary therapy in patient with heterozygous familial hypercholesterolemia (HeFH). Non-adherence to statin therapy is associated with increased cardiovascular risk.

Objective: We constructed a dynamic prediction model to predict statin adherence for an individual HeFH patient for each upcoming statin prescription.

Methods: All patients with HeFH, identified by the Dutch Familial Hypercholesterolemia screening program between 1994 and 2014, were eligible. National pharmacy records dated between 1995 and 2015 were linked. We developed a dynamic prediction model that estimates the probability of statin adherence (defined as proportion of days covered >80%) for an upcoming prescription using a mixed effect logistic regression model. Static and dynamic patient-specific predictors, as well as data on a patient's adherence to past prescriptions were included. The model with the lowest AIC (Akaike Information Criterion) value was selected.

Results: We included 1094 patients for whom 21,171 times a statin was prescribed. Based on the model with the lowest AIC, age at HeFH diagnosis, history of cardiovascular event, time since HeFH diagnosis and duration of the next statin prescription contributed to an increased adherence, while adher-

Abbreviations: FH, Familial hypercholesterolemia; HeFH, Heterozygous familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; CAD, Coronary artery disease; CVD, Cardiovascular disease; PDC, Proportion of days covered; RLS, Record Linkage System; AIC, Akaike information criterion; AUC, Area under the curve; ROC, Receiver operator characteristic; OR, Odds ratio.

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ence decreased with higher untreated LDL-C levels and higher intensity of statin therapy. The dynamic prediction model showed an area under the curve of 0.63 at HeFH diagnosis, which increased to 0.85 after six years of treatment.

Conclusion: This dynamic prediction model enables clinicians to identify HeFH patients at risk for non-adherence during statin treatment. These patients can be offered timely interventions to improve adherence and further reduce cardiovascular risk.

Introduction

Heterozygous familial hypercholesterolemia (HeFH) is a prevalent, monogenetic disorder characterized by a lifelong two- to threefold elevation of plasma low-density lipoprotein cholesterol (LDL-C) and high risk of premature coronary artery disease (CAD) .[1] Since patients with HeFH exhibit signs of atherosclerosis at young age,[2,3] early and aggressive LDL-C lowering interventions are recommended by current clinical guidelines.[4] Statins are the preferred primary pharmacological therapy.[4]

Non-adherence to statin therapy is one of the main challenges that physicians are faced with,[4] as it is associated with an increased risk of CAD in both primary and secondary prevention settings.[5,6] Studies investigating statin adherence show a wide range of adherence rates. For example, in a meta-analysis of 12 studies (comprising data from almost 800,000 adults) on the association between statin adherence and mortality, adherence rates between 20% and 89% were reported.[7] A 10-year follow-up study in young adult HeFH patients showed that 79% were adherent,[8] and another study with HeFH patients up to 40 years reported a mean adherence of 69% in the first year of treatment.[9]

Although prevalence and predictors of statin adherence have been extensively documented in general primary prevention patients,[10] information on predictors of adherence for patients with HeFH is scarce. FH patients are generally younger, asymptomatic and without co-morbidities compared to the general primary prevention patient. Predicting adherence in these patients is of particular importance given the often early start, lifelong necessity and clear benefits of statin therapy in HeFH patients.[11,12] Since FH patients might visit the clinic very infrequently after optimal titration of statin therapy, structural and repetitive monitoring of patients at risk for non-adherence is an important aspect in the prevention of CAD. Better prediction of statin adherence could aid in planning timely interventions in patients at risk for non-adherence.

Therefore, the aim of this study was to develop a dynamic prediction model to estimate the probability of statin adherence for individual HeFH patients for each upcoming prescription.

Methods

We developed a dynamic prediction model that estimates the probability of statin adherence for an upcoming prescription using static and dynamic patient-specific predictors, and by including data on a patient's adherence to past prescriptions. We followed the 'Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)' statement,[13] to ensure that all key elements of our clinical prediction model are transparently reported.

Study design, data sources and study population

For this retrospective cohort study, we linked the database of the national FH cascade screening program in the Netherlands to the Pharmo Record Linkage System (RLS) (Pharmo Institute, Utrecht, The Netherlands). The database of the FH cascade screening program includes both data from patients diagnosed with an FH mutation and unaffected individuals, and contains the following information, which was collected at the time of screening for FH: demographics, medical history, family history, current medication use, and total cholesterol, HDL-C and triglyceride levels. Data were collected by a genetic field worker by means of a standardized questionnaire and a blood sample. The Pharmo RLS is a patient-centric data network of multiple health care databases covering a geographical part of the Dutch health care system, including data from in- and outpatient pharmacies. Combining the information from these databases resulted in longitudinal follow-up data for a large (random) subset of the participants of the FH screening program from January 1995 until April 2015.

We selected all individuals aged 18 years and above, in whom a genetic variant for FH was identified upon sequencing in the screening program between January 1994 and January 2014, and for whom data was available on at least two statin prescriptions after diagnosis with FH. Homozygous, compound heterozygous and double heterozygous FH patients as well as carriers of a non-deleterious mutation were excluded.

All participants gave informed consent and the study was approved by the Medical Ethical Committee of the AMC in Amsterdam.

Outcome: adherence per prescription

The outcome of interest was adherence (yes or no) to statin treatment for a future prescription. We considered a patient adherent for any specific prescription if the number

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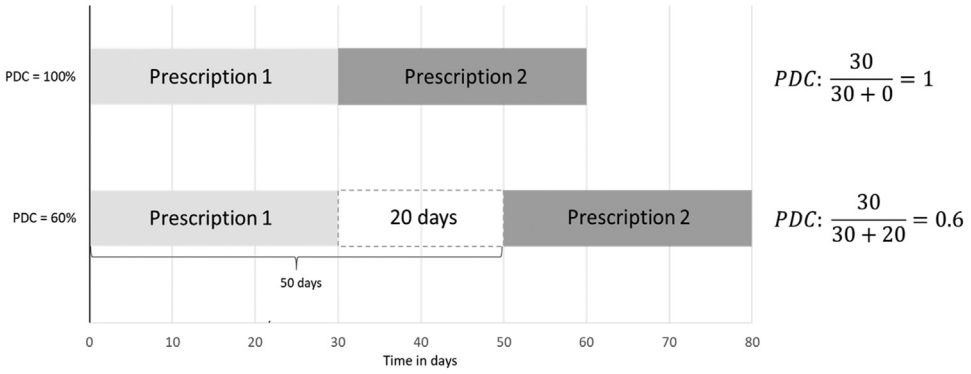


Fig. 1 Calculation of proportion of days covered per prescription. This figure illustrates the proportion of days covered (PDC) in two instances. The PDC is calculated as the number of days for which a prescription was obtained, divided by the total number of days before a patient collects his new prescription.

of days for which a prescription was obtained, divided by the number of days before a patient collects a new prescription x 100 (i.e., proportion of days covered [PDC]), was 80% or higher.[14,15] For example, a patient will be considered adherent to the statin therapy when he/she has a prescription for 30 days and collects his/her next prescription after 30 days (PDC = 30/30 × 100 = 100%), and non-adherent with a prescription for 30 days and a next prescription after 50 days (PDC = 30/50 × 100 = 60%) (Fig. 1). We accounted for oversupply of prescriptions that were collected a few days prior to the ending of the previous prescription. We stop predicting adherence once a patient has no more filled prescriptions in the data available in the database.

Candidate predictors

The list of candidate predictors for our prediction model was based on the literature and the availability in the dataset and was, for reasons of applicability in a clinical setting limited to those that can be easily obtained in daily clinical practice.

We considered the following patient characteristics, measured at the time of FH diagnosis, as candidate predictors: age, sex, untreated LDL-C (calculated using the Friedewald formula), a history of diabetes, hypertension, and previous cardiovascular events (myocardial infarction, coronary artery bypass graft, percutaneous transluminal angioplasty, or ischemic cerebrovascular accident). In addition, we gathered the following information that was obtained at each statin prescription: the intensity of the statin therapy that will be prescribed, time since FH diagnosis, number of prescriptions received after FH diagnosis and length of the future prescription. The intensity of statin therapy was classified as defined by the American College of Cardiology/American Heart Association guidelines.[16]

Model specification

Model fitting and dynamic prediction

A mixed effect logistic regression model was fitted to the data using the R statistical package, version 3.5.2 (R foundation for Statistical Computing; Vienna, Austria). A detailed description of the dynamic prediction model, including the estimation of the random effect using Bayes' rule[17] is enclosed in the supplemental methods.

Predictor selection

To determine the most optimal set of variables for the prediction model, we added or removed one or more of the available variables (see candidate predictors) to the model based on the Akaike Information Criterion (AIC). The AIC deals with the trade-off between the goodness of fit of the model and the simplicity of the model. In case all candidate predictors in a patient were missing, this patient was excluded for the development of the model. We considered the model with the lowest AIC value to indicate the best-supported model given the data.

Prediction model evaluation

To assess the predictive performance of the model, we used a single 50-fold cross validation to internally validate our model. The patient population was split into 50 sets. One by one a set was selected as test set, while the 49 remaining sets formed the training set. The performance of our dynamic prediction model for each time point was assessed using an area under the curve (AUC) for the receiver operating characteristic (ROC).

Results

Study population

From January 1994 until April 2013, 33,357 participants of the FH screening program (including both patients with FH and unaffected individuals) provided informed consent to collect health care data after their initial visit. Of these participants, a subset of 7339 (22.5%) could be identified in the Pharmo RLS database. Of this subset of participants, 1094 (16%) had an HeFH diagnosis, were 18 years or older, and had at least 2 statin prescriptions listed within this database.

Table 1 Demographic and clinical characteristics of patients with familial hypercholesterolemia at diagnosis who were prescribed statin treatment.

	Patients with FH $n = 1094$
Age (years), mean (SD)	49.4 (16)
Male sex, *n* (%)	545 (50)
Weight (kg), mean (SD)	78.7 (15)
Height (cm), mean (SD)	174 (9.7)
BMI (kg/m^2), mean (SD)	26 (4.5)
Lipid profile (mmol/L)	
Total cholesterol, mean (SD)	5.88 (1.53)
LDL-C, mean (SD)	4.08 (1.43)
Untreated LDL-C (mmol/L), mean (SD)	5.85 (1.95)
HDL-C, mean (SD)	1.16 (0.36)
Triglycerides, median (IQR)	1.20 (0.81 - 1.80)
Hypertension, *n* (%)	213 (19.5)
Diabetes, *n* (%)	54 (4.9)
Alcohol use, *n* (%)	603 (55.7)
Smoking, *n* (%)	158 (18.9)
History of cardiovascular disease*, *n* (%)	166 (15.2)

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; n: number; SD, standard deviation.

*Cardiovascular disease is defined as: myocardial infarction, coronary artery bypass graft procedure, percutaneous transluminal coronary angioplasty, cerebrovascular accident or onset of angina pectoris.

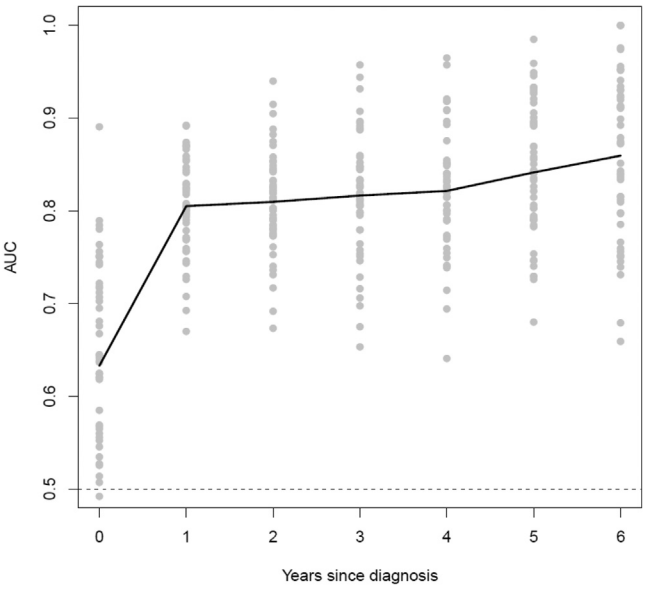


Fig. 2 AUC assessment over time. This figure shows the progression of the AUC over time. The AUC increases due to a better estimation of the random effect, by including all available data before a certain time-point to estimate the adherence probability for the upcoming prescription.

Demographic and clinical characteristics of these patients at genetic diagnosis of FH are summarized in Table 1. The mean (standard deviation [SD]) age was 49.4 (16) years and 545 (50%) were males. The median (range) duratiosn of follow-up was 5.59 (0.02–9.74) years.

Statin prescription and adherence

Between January 1995 until April 2015, these 1094 patients received a total of 21,171 statin prescriptions. Of these, 7483 (35%) were classified as high intensity statins, 12,723 (60%) as moderate-intensity statins, and 965 (5%) as low intensity statins. The median (min, max) number of prescriptions per patient was 17 (2, 213), and the median (min, max) length of a prescription was 90 (7157) days. Out of the 21,171 statin prescriptions, 17,324 (82%) were defined as prescriptions where the patient was adherent; i.e., the patient filled the next prescription in time. In Supplemental Figure 1 the follow-up duration and adherence status are depicted for all patients. A total of 852 (22%) patients were not adherent for a minimum of one prescription, during their follow-up period.

Predictor selection

Based on the lowest AIC score, the final prediction model included the following information that was obtained at diagnosis: age, untreated LDL-C levels, and history of cardiovascular events. In addition, the following information that was obtained at prescription was included: time since diagnosis, length of future prescription, and intensity of the prescribed statin.

Fitted model and model performance

The model parameters are presented in odds ratios (OR) and their 95% confidence intervals (95% CI) in Table 2. Age (in years) at diagnosis (OR: 1.030, 95% CI: 1.024–1.036), time passed (in years) since diagnosis (OR: 1.036, 95% CI: 1.015–1.057), and the duration of the prescription in intervals of 30 days (OR: 1.431, 95% CI: 1.357–1.509) were positively associated with the odds of being adherent. A history of a cardiovascular event at diagnosis showed a trend to increased adherence (OR: 1.256, 95% CI: 0.969–1.629), as well as low-intensity and moderate-intensity statin therapy compared to high-intensity statin treatment (OR: 1.346, 95% CI: 0.990–1.839 and OR: 1.063 95% CI: 0.939–1.205, respectively). Higher untreated LDL-C was found to decrease the odds of adherence (OR: 0.901, 95% CI: 0.862–0.942). The past adherence was included in the model by estimating the random effect.

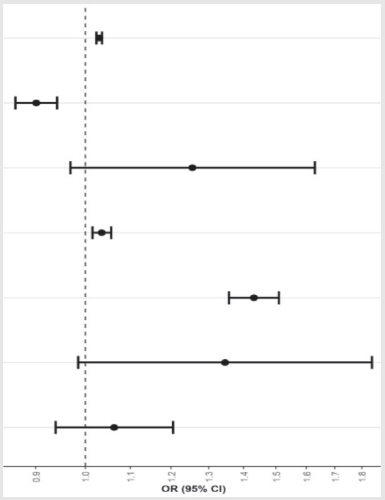
The AUC for our dynamic prediction model is shown in Fig. 2. At diagnosis, the AUC is 0.63. The model's performance increases over time to an AUC of 0.85 after 6 years. An example of the effect of past adherence is given in more detail under the heading Clinical applicability' and in Table 3.

Clinical applicability

To demonstrate the clinical applicability of the model, we stepwise calculated the probability of adherence for five

Table 2 Odds ratios with 95% confidence intervals of the fixed parameters of the prediction model.

Variable		OR	95% CI
Age at diagnosis (years)		1.030	1.024 – 1.036
Untreated LDL-C at diagnosis (mmol/L)		0.901	0.862 – 0.942
History of CV event at diagnosis		1.256	0.969 – 1.629
Time since diagnosis (years)		1.036	1.015 – 1.057
Duration of future prescription		1.431	1.357 – 1.509
Intensity of statin therapy	Low vs. High	1.346	0.985 – 1.839
	Moderate vs. High	1.063	0.939 – 1.205



LDL-C, high-density lipoprotein cholesterol; CV cardiovascular; OR, odds ratio; 95% CI, 95% confidence interval.

Table 3 Example of the estimated probability of adherence for a patient who is prescribed statins.

Prescription number	Age at diagnosis (years)	Untreated LDL-C (mm/L)	CVD event in history	Statin intensity	Time since diagnosis (days)	Prescription duration (days)	Was adherent for previous prescription	Probability of adherence (%)					
								No prescription	including all prescription data until and including prescription number:				
									1	2	3	4	5
1	35	5.8	No	Moderate	16	90	–	**75.8**					
2	35	5.8	No	Moderate	102	90	Yes	76.0	**80.3**				
3	35	5.8	No	Moderate	209	90	Yes	76.2	80.5	**83.2**			
4	35	5.8	No	Moderate	303	**30**	Yes	61.2	67.0	70.9	**73.7**		
5	35	5.8	No	Moderate	341	30	**No**	61.3	67.1	71.0	73.8	**62.9**	
6	35	5.8	No	Moderate	369	**90**	Yes	76.5	80.7	83.4	85.3	77.7	**81.2**

LDL-C, high-density lipoprotein cholesterol; CVD cardiovascular event.

subsequent prescriptions for a fictive patient diagnosed with genetically proven HeFH at the age of 35 (Table 3). For each subscription, we calculated the adherence probability including adherence to previous prescriptions in a stepwise manner (e.g., including adherence for 0 to the maximum prescriptions available for that timepoint). This patient has an untreated LDL-C of 5.8 mmol/L, and no cardiovascular event in his/her medical history. Sixteen days after HeFH diagnosis, the patient returns to the clinic and is prescribed a moderate-intensity of statin therapy for 90 days. Since this is the first time a statin is prescribed, no patient history of statin adherence was available and we determine the estimated probability of adherence on the patient characteristics (i.e., the fixed effects) only. We obtain an estimated probability of adherence for the upcoming prescription of 75.8% (Table 3). At the time of the second prescription (102 days after diagnosis, 86 days after the previous prescription), we observe that the patient was adherent to statin treatment after the first prescription (90 days/86 days ≥80%). Based on the patient characteristics (fixed effects) and the statin prescription history (random intercept), we determine that the patient has an 80.3% probability to be adherent for the second prescription. For the third prescription, no changes are made and the patient collected his third prescription in time (thus adherent), resulting in an 83.2% probability of adherence. The patient was adherent for his third prescription, but when collecting his fourth prescription, the prescription duration was changed from 90 days to 30 days, and therefore the adherence probability for this prescription dropped to 73.7%. The adherence probability for the fifth prescription

was further decreased to 62.9 since the patient was not adherent for the fourth prescription. Based on the facts that the patient was then adherent to the fifth prescription and that the prescription duration was changed to 90 days led to an increase of the probability of adherence to 81.2% for the sixth prescription.

Discussion

We developed a dynamic prediction model to estimate the real time probability that a HeFH patient will be adherent for a next statin prescription. The final model was based on the following variables: age at diagnosis, untreated LDL-C at diagnosis, a history of CV events at diagnosis, time since diagnosis, duration of the future statin prescription and intensity of the future statin therapy prescription. Additionally, by utilizing statin-adherence history including all past prescriptions until the upcoming prescription, we improved the precision of our adherence prediction for each subsequent prescription. Our dynamic prediction model shows a modest initial predictive ability at diagnosis with an AUC of 0.63, whereas the predictive ability increased over time, towards an AUC of 0.85 at six years after diagnosis.

Our findings that a higher age at diagnosis and time since diagnosis were positively associated with adherence, are supported by the results of a recent systematic review on predictors of statin adherence in primary prevention of cardiovascular disease (CVD), showing that older age was associated with increased statin adherence.[10] However, results of a study in 274 young HeFH patients did not show a significant association between age and adherence.[8] The initiation of statin therapy at very young age may be an exception to the notion that older patients are more adherent, as early customization to the use of medication favors long-term adherence despite the young age range.[8] We also found that a longer duration of the statin prescription is associated with an increased probability of adherence, which is in line with a study in primary prevention patients, showing that a 60-day prescription improves adherence compared to a 30-day prescription.[18] Data from this and our study contribute to the suggestion that longer prescription duration increases adherence through the facilitation of a more regular treatment scheme.

Our observation that, although not statistically significant, a history of CVD had a positive influence on adherence, is supported by the results of previous studies including HeFH and non-HeFH populations.[9,19–21] Further evidence comes from a qualitative study on health beliefs in FH patients, showing that patients without a history of CVD perceive their risk to be lower and are less likely to be adherent [22], and by a study observing that patients who received results of higher coronary artery calcium on their scans were significantly more adherent to statin therapy after one year.[22]

We observed an inverse influence of intensity of statin therapy on adherence. The association of statin intensity with adherence is inconsistent in the literature, with a study in FH patients showing that high-intensity statins were associated with higher adherence,[9] and other studies including clinical trials observing inverse associations between intensity of statin therapy and adherence in both primary and secondary prevention setting.[23–26] This may relate to the increased prevalence of side effects experienced during high-intensity regimens, which is a major reason for statin discontinuation.[23,27]

To our knowledge, only one other adherence prediction model has ever been developed for HeFH-patients.[28] This questionnaire-based study in 321 HeFH-patients investigated an adherence score based on three independent variables: untreated total cholesterol, treated total cholesterol and age. Our study differs through the use of PDC as measurement of adherence, and the number and nature of variables in our model. A questionnaire-based assessment is acknowledged to overestimate adherence and may suffer from recall bias, while PDC is generally recommended as the 'gold' standard in assessing long-time adherence.[29] Moreover, our model includes statin adherence for past prescriptions, leading to a more accurate estimation of forthcoming adherence to statins in an individual patient. The latter is supported by a study showing that including previous adherence to other chronic preventive medication in their established prediction model improved the c-statistic from 0.665 (95% CI 0.659–0.670) to 0.695 (95% CI 0.690–0.700) .[30] However, the model does not follow-up on *previous* statin adherence for future prescriptions and thus can be regarded more 'static' than our model. Another study showed that statin non-adherence (as measured by PDC <0.8) in the first 90 days after initiation of a statin was strongly associated with non-adherence in the period of 91–365 days after initiation.[31]

Cumulating evidence supports the superior efficacy of early and sustained intervention in FH in preventing increased cumulative LDL-C burden and CVD risk.[11] Implementing this model in the emerging patient information databases could aid clinicians and/or pharmacists by listing adherence probabilities for every collected repeat prescription and signaling when the probability of adherence reaches a predefined threshold. With patients increasingly being connected to their electronic health dossier through apps, intervention could even start by sending automatic messages to these apps. The feasibility for this is supported by a study showing that, reinforcement, education and reminders increase adherence by 13 to 24%.[32] Although this particular (dynamic) model has been developed for FH patients, future research could evaluate a similar dynamic prediction model in all patients at risk for CVD.

The present study has some limitations that warrant further discussion. Firstly, although we internally validated our prediction model by 50-fold cross validation to provide a more accurate estimate of model performance, our model was not externally validated. Therefore, it is unknown whether our model's performance will be comparable in different settings and/or other HeFH patient populations. Furthermore, we limited the number of potential variables for selection in our model, based on measurability and availability in our dataset and general practice. By using the AIC,

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we provided a standardized framework for variable selection and the variables in the model are thus practically always measured and recorded in medical charts by physicians in charge of cardiovascular risk management, and this will improve the feasibility of implementation of our model into standard care. Our model does not explicitly incorporate possible important predictors that could emerge over time (e.g., incidence of novel cardiovascular events). However, if these predictors are linked to adherence, they will be intertwined with adherence of past prescriptions, and are as such included in the random effect estimation of our model. For example, if a patient develops side-effects and starts to adhere less to their therapy, the change in adherence will be picked up automatically by the dynamic part of the prediction model. Still, this also means that we did not investigate some predictors that have been found to be associated with adherence in a number of other studies, including primary prevention studies. Finally, we assumed linear effects of all continuous variables on the log-odds of adherence. Since these variables could have a non-linear effect on the log-odds of adherence, we explored non-linearity by adding spline functions to the model. The results showed that the AUC obtained with the latter model were comparable to those obtained with the original model (data not shown).

In conclusion, we developed a dynamic prediction model to calculate the probability of statin adherence for individual HeFH patients who were prescribed statins, for each subsequent repeat prescription. Our model uses data on individual patient adherence for past statin prescriptions to predict adherence for upcoming prescriptions, which improves the accuracy of the prediction in the individual patients over time. This dynamic prediction model could enable clinicians to identify HeFH patients at risk for non-adherence during statin treatment, when integrated with patient information databases.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author and after permission of the relevant medical ethical committees.

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Author's contribution

A.J.C., M.H.H., L.Md.B., B.A.H. contributed to the conception, design, analyses and interpretation of the data, and drafted the manuscript. R.H., E.S.G.S., J.J.P.K., G.K.H. contributed to the interpretation of the data and critically revised the manuscript.

Declaration of conflicting interest

A.J.C., M.H.H., L.Md.B., R.H. report no conflict of interests. E.S.G.S. has received fees paid to his institution from Amgen, Akcea, Athera, Sanofi-Regeneron, Esperion, Novo Nordisk, Lily, and Novartis. J.J.P.K. is the CSO of NewAmsterdam Pharma, the CMO of Staten Biotechnology is on the Board of North Sea Therapeutics and Oxitope, has received consulting fees from Akcea Therapeutics, AstraZeneca, CiVi Biopharma, Corvidia Therapeutics, CSL Behring, Daiichi Sankyo, Draupnir Bio, Esperion, Gemphire Therapeutics, Madrigal Pharmaceuticals, Matinas BioPharma, NorthSea Therapeutics, Novo Nordisk, Novartis, Regeneron Pharamaceuticals, REGENXBIO, Staten Biotechnology, and 89bio. GKH reports institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron (fees paid to the academic institution); and part-time employment at Novo Nordisk. BAH has received a research grant from Silence Therapeutics.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.12.004.

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