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Using CART to identify prescribing thresholds for cardiovascular disease.

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Using CART to identify prescribing patterns for cardiovascular disease.

Abstract

Background and objective

Many guidelines for clinical decisions are hierarchical and non-linear. Evaluating if these guidelines are used in practice requires methods that can identify such structures and thresholds. We use classification and regression trees (CART) to analyse prescribing patterns of Australian general practitioners (GPs) for the primary prevention of cardiovascular disease. Our aim is to identify if GPs use absolute risk (AR) guidelines in favour of individual risk factors to inform their prescribing decisions of lipid-lowering medications.

Methods

We employ administrative prescribing information that is linked to patient level data from a clinical assessment and patient survey (the AusHeart Study). We assess prescribing of lipid-lowering medications over a twelve month period for patients (n=1903) who were not using such medications prior to recruitment. CART models are developed to explain prescribing practice. Out-of-sample performance is evaluated using receiver operating characteristic (ROC) curves and optimized via pruning.

Results

We find that individual risk factors (*low-density lipoprotein, diabetes, triglycerides and cardiovascular disease (CVD) history*), GP-estimated rather than Framingham absolute risk, and socio-demographic factors (*household income, education*) are the predominant drivers of GP prescribing. However, socio-demographic factors and some individual risk factors (*triglycerides* and *CVD history*) only become relevant for patients with a particular profile of other risk factors. The ROC area-under-the-curve is 0.63 (95% confidence interval (CI) 0.60, 0.64).

Conclusion

There is little evidence that AR guidelines recommended by the National Heart Foundation and National Vascular Disease Prevention Alliance, or conditional individual risk eligibility guidelines from the Pharmaceutical Benefits Scheme, are adopted in prescribing practice. The hierarchy of conditional relationships between risk factors and socio-economic factors

identified by CART provides new insights into prescribing decisions. Overall, CART is a useful addition to the analyst's toolkit when investigating health care decisions.

Key Points for Decision Makers

- CART provides a methodology to highlight how and why variation between practice and guidelines occurs, not just that an evidence-practice gap exists
- Prescribing practices for lipid-lowering medications do not follow absolute risk guidelines or eligibility criteria for subsidization by the Pharmaceutical Benefits Scheme. There are potentially significant gains from clarifying best practice prescribing, to promote either greater adherence to guidelines, or increased clinical freedom
- Big data techniques such as CART are applicable to a wide range of healthcare applications, including those where big data are absent

1. Introduction

Physicians employ a range of risk assessment strategies when making prescribing decisions for primary prevention of cardiovascular disease, including assessment against thresholds on individual cardiovascular disease (CVD) risk factors, and assessment of total or absolute risk (AR) of cardiovascular (CV) events [1, 2].

Internationally, many clinical practice guidelines recommend calculation of AR of CV events, with lipid-lowering medication (typically statins or statins in combination with another drug) recommended for patients evaluated as high risk[1]. In Australia, an AR approach is recommended by the National Vascular Disease Prevention Alliance (NVDPA) [5] and the National Heart Foundation (NHF) [6]. However the Australian Government's universal drug insurance scheme, the Pharmaceutical Benefits Scheme (PBS), limits the subsidising of these medicines using eligibility criteria based on individual risk factors such as diabetes and cholesterol.

In practice, several studies suggest that clinicians deviate from guidelines and/or eligibility criteria [7, 8], perhaps in response to care seeking behaviour from patients or other aspects of patient preference [1, 2]. However Bonner et al [1] noted that while CVD risk management is not consistently based on AR, "little is known about… …the alternative strategies employed when AR is not the focus of assessment". Similarly, few studies have formally tested whether different prescribing thresholds are being applied in different patient groups and many have struggled to characterise the complexity of prescribing practice [1, 9].

The purpose of this paper is to employ classification and regression trees (CART) to analyse the prescribing patterns of Australian general practitioners (GPs) of lipid-lowering medication for the primary prevention of CVD. CART is a machine-learning 'big data' technique that has been shown to be particularly valuable when analysing non-linear relationships and interactions, where it can outperform standard regression models for classification [10]. We aim to use CART to improve our understanding of clinical practice; potentially identifying prescribing thresholds and patient sub-groups missed by traditional analyses, and to demonstrate how CART can be useful for understanding complex treatment decisions in health care.

[1] For example, the American Heart Association (AHA) recommends using a modified Framingham equation [3]. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) recommends an absolute CVD risk algorithm known as QRISK2 [4].

2. Methods

2.1 Data

We use linked survey and administrative data from the AusHeart Study, a cluster-stratified, cross-sectional survey of CVD risk management in primary care fully documented elsewhere [7, 11, 12]. The study enrolled GPs from across Australia, who recruited 15-20 consecutively-presenting adults aged 55 years or older. It gathered information on patient socio-economic factors, CVD risk factors, prescribed medications, and the GP's own estimation of the patient's AR of a CV event within the next 5 years [7].

These data were linked for consenting patients to Medicare administrative data containing records of all pharmaceuticals purchased under the PBS from 1 March 2008 to 1 January 2010 [12]. To avoid complications associated with prior exposure to medication, we reduce the dataset to 1,903 patients who had not been prescribed lipid-lowering medication prior to GP recruitment[2]. We develop models to classify these patients according to prescription or not of any lipid-lowering medication (Anatomical Therapeutic Chemical code C10) during a one year period.

2.2 CART methodology

CART sorts observations into increasingly homogeneous sub-groups [13]. At each step, CART splits observations using a simple decision-rule (e.g. if total cholesterol exceeds *7.0 mmol/L* then prescribe medication) chosen to minimise diversity (with respect to the binary outcome or classification) in right and left 'child nodes'. Branches and nodes are added until a stopping criteria is met and the tree terminates in 'leaves' or 'bins' containing proportions of correctly and incorrectly classified observations [10][3].

There are three distinct strengths of CART that make it particularly applicable to analysing complex decision-making processes such as those employed in clinical practice. First, the hierarchical structure of CART models is often more intuitive than traditional regression models, because it mimics the heuristics of decision making [14, 15]. Second, CART can outperform standard regression models when predicting outcomes in the presence of non-linear relationships and interactions [10]. In clinical practice, treatment decisions may depend on non-linear thresholds with respect to one or more risk factors, and thresholds may vary with other risk factors. For example, PBS guidelines allow prescribing of statins for patients

[2] Prior exposure to medication is not preferred as we would observe risk factors *after* response to treatment.
[3] See Schilling et al (forthcoming) for a step-by-step guide to CART modelling.

with hypercholesterolemia (>9 mmol/L) [16]. This drops to >5.5mmol/L if the patient has diabetes [16][4]. Third, CART affords the data greater freedom to speak for themselves [20]. Whereas regression models are refined by comparing across a limited number of possible specifications, CART performs an exhaustive search over all possible cut-points and predictors [10]. As a result, the precise form of the relationship between a predictor and outcome is not delimited by the inclusion/exclusion of higher order terms. It is this strength that has seen CART used in a variety of prognostic analyses to identify risk thresholds for in-hospital mortality [21], vertebral fractures [22] and cirrhosis [23].

CART is however subject to a number of limitations. CART "…tends not to work very well if the underlying relationship is linear" [10]. A second limitation in CART is the risk of overfitting [24, 25]. Finally, CART can be prone to instability. Small differences in the training data can lead to very different trees [26]. We manage these limitations in the methodology below.

2.3 Using CART to understand prescribing in CVD

We use a 3-stage approach to construct the CART. In CART-1, we limit predictors to patient socio-demographics (age, gender, Aboriginal/Torres Strait Islander, household income and education level) and GP-estimated 5-year AR of a CV event. This provides a benchmark for which to compare performance. In CART-2, we add individual risk factors (smoking, body mass index, systolic and diastolic blood pressure, low and high density lipoprotein cholesterol, total cholesterol, triglycerides, kidney disease, diabetes, CVD history, weekly exercise and self-reported health) "…to determine whether cardiovascular risk factors might have an additional influence on prescribing beyond their contribution to [GP-estimated] cardiovascular risk" [27]. Finally in CART-3 we add AR estimated using the 1991 Framingham risk equations. Framingham AR forms the basis of the NHF 2004 and NVDPA 2008 guidelines. If GPs adopt NHF or NVDPA guidelines, we would expect the addition of Framingham AR to improve the predictive validity of the CART, and to see cut-off thresholds and a hierarchy similar to the guidelines (described in Appendix 1).

We implement CART using the Matlab *fitctree* function [28]. We use Gini's diversity index as the default splitting criterion as suggested by Breiman et al [24], and compare model

[4] Similar complications exist in clinical decision-making in general [17], and in observed (as well as recommended) prescribing patterns for statins [1, 18, 19].

performance under entropy splitting to check model robustness. In our default models, variables with missing data still enter the model, but training uses only valid values. In prediction, an observation with a missing value is assigned to the largest split group. An alternative method for dealing with missing data in CART is to find 'surrogate' variables, by applying CART with the missing data as the dependent variable [28]. We check model performance under these two methods to test robustness. We use ten-fold cross validation to indirectly evaluate out-of-sample performance[5]. We bootstrap the cross-validation one hundred times to describe the distribution of mean out-of-sample error and receiver operating characteristic (ROC) area-under-curve metric. We prune the CART to reduce overfitting and optimise out-of-sample performance. This helps to eliminate illogical branches that can grow from the sample data but that would not perform well out-of-sample (e.g. where a node suggests that patients with a household income between $52,000 and $72,799 are less likely to be prescribed than those with a household income below $52,000 or above $72,799). Where there is no difference in out-of-sample performance, we follow Breiman et al [24] in preferring smaller trees over larger ones.

Once optimised, we evaluate the structure of the CART to identify patient sub-groups and prescribing thresholds. We calculate a predictor-importance metric for the preferred model using the *predictor-importance* Matlab algorithm[6]. Next, we compare patient sub-groups and prescribing thresholds identified by the CART against NHF 2004, NVDPA 2008 and PBS guidelines to identify similarities and differences.

Finally, we evaluate the stability of our results. The robustness of predictor-importance and specific hierarchies is difficult to assess, because of the conditional nature of the CART [30]. As a simple guide, we train one hundred 'bagged' trees[7] on bootstrapped samples of the data, and count the number of times each predictor appears [32, 33]. Following Dannegger [32], we calculate confidence intervals and density functions of the cut-off thresholds used at key decision nodes to highlight stability.

3. Results

3.1 Prescribing and risk factor statistics

[5] This has been shown to be an optimal method for model selection [29].
[6] This identifies all the nodes where the predictor is selected, sums the improvement in classification from each of these and divides by the number of tree branches [28].
[7] Bagging or 'bootstrapped aggregating' is a method for generating multiple versions of a tree to allow evaluation of predictor stability [31].

Table 1 provides the sample mean and standard deviation or frequency count and percentage for demographic and clinical characteristics. Of the 1,903 patients 296 (16%) were prescribed lipid-lowering medication.

INSERT TABLE 1 HERE

3.2 Model performance

CART-1 considers only patient demographics and the GP-estimated 5-year AR of a CV event. It provides a performance benchmark but is not expected to perform well given the absence of individual risk factors or Framingham AR. The unpruned CART-1 correctly identifies 1,560 (97%) of patients who were not prescribed lipid-lowering medication, but only 115 (39%) of those who were, for an overall within-sample error rate of 12%. As expected, the performance of CART-1 drops when moving out-of-sample; error increases to 20% (95% CI: 20%-21%) but with pruning this is reduced to 18% (17%-18%). The out-of-sample ROC metric is 0.53 (0.51-0.55), indicating the model is barely better than a random guess at predicting prescribing patterns (Table 2).

CART-2 adds thirteen individual risk factors to CART-1. This improves both within and out-of-sample performance. Within sample, the model correctly identifies 1,585 (99%) of patients who were not prescribed lipid-lowering medication, and 157 (53%) of those who were, for an overall error rate of 8%. After pruning, the out-of-sample error is 17% (16%-17%) and the ROC metric is 0.63 (0.60-0.64).

CART-3 adds Framingham AR to CART-2, which should identify NHF and/or NVDPA guidelines if they are followed. Within sample, the model correctly identifies 1,579 (98%) of patients who were not prescribed, and 172 (58%) of those who were, for an overall error rate of 8%. After pruning, the out-of-sample error is 17% (16%-18%) and the ROC metric is 0.62 (0.60-0.63), which is not significantly different from CART-2. Framingham AR does not appear in the pruned version of CART-3.

INSERT TABLE 2 HERE

3.3 Predictors of prescribing

Household income, *GP-estimated AR* and individual risk factors *LDL*, *diabetes*, *total cholesterol*, *CVD history* and *triglycerides* all influence GP prescribing under the pruned

CART-2 model. The predictor-importance results suggest that *LDL, GP-estimated AR* and *diabetes* make the most improvement to classification, followed by *triglycerides, income, total cholesterol* and *CVD history* (Table 3).

Figure 1 shows interactions between the AR assessments, individual risk factors, and socio-demographic factors, and highlights the paths that lead to prescribing. On the right hand side of the tree, prescribing is most likely for patients with high *LDL* (>4.09 mmol/L), high *total cholesterol* (>6.95 mmol/L), high *GP-estimated AR* (>17.5%) and relatively low *household income* (<$52,000). On the left-hand side of the tree, patients without high *LDL* (<4.09 mmol/L) are more likely to be prescribed if they have high *triglyceride*s (≥4.25 mmol/L for patients with diabetes; ≥4.35 mmol/L for patients without diabetics and with *GP-estimated AR* ≥ 2.5%), or if they have previously had a coronary artery event.

CART also highlights interactions where prescribing is unlikely. Patients with high *LDL, total cholesterol* and *GP-estimated AR* are less likely to be prescribed lipid-lowering medication if they have relatively high *household income* (≥$52,000). Patients with high *LDL* and high *total cholesterol* but without high *GP-estimated AR* are also less likely to be prescribed. Finally, prescribing is less likely for patients with high *LDL* but without high *total cholesterol*.

INSERT FIGURE 1 HERE

3.4 Robustness of results

Comparison of CART-2 performance under different splitting criteria and approaches to missing data show no significant differences in ROC out-of-sample performance (Table 2). Comparison of the 100 bagged trees highlights robustness of the specific hierarchies and decision nodes within CART-2. *LDL* and *diabetes* appear in all 100 trees, at the root and second node positions, and have the highest average predictor-importance (Table 3). The *LDL* decision threshold is bimodal, with a mode at 4.6 mmol/L in addition to the 4.1 mmol/L suggested in CART-2 (Figure 2), however the difference between modes is less than one standard deviation in *LDL* in the sample (0.8 mmol/L). By contrast, *total cholesterol,* appears at the third node in only 6 of the 100 bagged trees. *Education* (those with University education are less likely to be prescribed) appears 44 times at node 3. *Triglycerides* and *GP-estimated AR*, which appear twice in CART-2, appear 171 and 116 times respectively within the first 10 nodes. The *triglyceride* decision threshold shows the cut-off at 4.3 mmol/L as seen in CART-2, but also identifies another mode at 2.0 mmol/L. *Household income* appears 76 times in the first 10 nodes with the median cut-off at $52,000 as per CART-2. *Exercise, Framingham AR* and *self-rated health status* are not present in the pruned CART-2 model, but appear in 38, 10 and four of the 100 bagged trees' first 10 nodes.

INSERT TABLE 3 HERE

INSERT FIGURE 2 HERE

4 Discussion

4.1 Key findings

Prescribing varies across GPs and does not appear to follow AR guidelines or PBS regulations

We find that prescribing practices do not appear to be congruent with NHF, NVDPA or PBS eligibility guidelines. NHF and NVDPA use Framingham AR assessment as the basis of their guidelines, yet thresholds on Framingham AR rarely appear in the CART. The guidelines also recommend prescribing on the basis of individual risk factors (e.g. for patients with kidney disease or diabetes). Kidney disease does not appear in CART-2. Diabetes does appear, but is neither necessary nor sufficient for prescription.

Similarly, the PBS has conditional criteria based on individual risk that govern eligibility, such as total cholesterol >5.5 mmol/L for patients with diabetes, and >6.5 mmol/L for patients with HDL <1 mmol/L. These decision branches do not appear in CART-2. However the model suggests that prescribing is more likely for low LDL patients with triglycerides >4.25 mmol/L (for patients with diabetes) and >4.35 mmol/L (for patients with high GP-estimated AR). This is somewhat consistent with the PBS, which allows prescribing for a subset of patients with triglycerides >4 mmol/L.

Our findings contribute to a growing body of evidence [2, 7, 18, 27] suggesting there is considerable room for improvement in the prescribing practices for CVD. If guidelines provide an accurate description of optimal treatment, divergence from guidelines is likely to be costly, both in terms of health expenditure and patient outcomes. For example, the prescription of drugs to patients that fall outside the specified indications, often referred to as leakage [34], is likely to diminish the real-world cost-effectiveness of pharmaceuticals if it results in patients gaining a lower average benefit than was assumed at the time of the approval for use. There may then be dividends from interventions to improve adherence to guidelines, such as IMPLEMENT, ALIGN and IRIS [35-37]. CART would be an appropriate method to assess such adherence. Conversely, if thresholds for reimbursement constrain best practice prescribing (e.g. based on total or AR of CV events or a more thorough understanding of the patient), there may be a case for removing thresholds for reimbursement and allowing increased clinical freedom in prescribing. Either way, there are potentially significant opportunity costs to this uncertainty.

While we find discordance between practice and guidelines, we do not identify one standard decision-tree that consistently explains prescribing behaviour across our representative dataset. Instead we find that prescribing practices vary across the GP population. This is perhaps unsurprising given the volume of guidance available [38] and the potential for between-GP variation in uptake and acceptance of decision-support tools and guideline recommendations [39]. We posit that the low ROC performance of the CART models is a result of this variation. In an environment of clearer and more widely adopted guidelines, we would expect the ROC performance to improve.

CART suggests how and why GP prescribing deviates from guidelines

The CART analysis provides additional insights regarding the roles of individual risk factors and the hierarchy of GP decision-making. *LDL* is the root node in all bagged trees, suggesting it is the first risk factor used in the decision-making process. Similarly, *diabetes* is consistently the second node in the decision-tree, suggesting it is an important risk factor that GPs consider in decision-making. It is well established that lowering CV risk is associated with the degree to which statins reduce LDL cholesterol [40]. Similarly statins have been widely prescribed in people with diabetes given their higher CV risk [41]. It appears that evidence regarding these risk factors takes precedence over AR and the eligibility criteria.

We also show that prescribing to high-risk patients varies based on the patient's household income and/or educational attainment, with those with household income above $52,000 or with a university degree unlikely to be prescribed. There has been some evidence of this internationally [42, 43] however the CART method uncovers the hierarchy of these factors. Specifically, we show that income/educational attainment are deciding factors at the bottom of the prescribing decision-tree, after clinical establishment of high risk. However there is likely to be confounding between these factors and patient health and lifestyle. *Self-rated health* and *exercise* are significantly collinear with *household income* (Pearson χ^2 *p*-values of 0.016 and 0.000), and both entered some trees in the robustness analysis. Nonetheless, the results concord with theories that GPs use clinical judgement and knowledge of the patient to make decisions based on a wide range of factors, not just AR based guidelines involving absolute or individual risk factors [1].

Finally, we show that CVD history is taken into consideration for otherwise low-risk patients, with those patients with CAD more likely to be prescribed. This concurs with previous research that highlighted inconsistent CV risk perceptions across vascular territories [44].

4.2 Limitations

There are limitations to this study. First, the analysis uses filled prescriptions, rather than written prescriptions, as the measure of prescribing. To the extent that patients with unfilled scripts differ in some respect from more compliant patients, the CART may not characterise prescribing practice across all patient groups[8]. Caution should therefore be exercised in generalising our findings to patients prescribed but who do not go on to fill their prescriptions.

Second, the AusHeart sample is a stratified random sample of GPs who had previously expressed an interest in participating in the study. While this approach produced a nationally representative sample with respect to a number of observable GP characteristics [7], it may have selected GPs with a greater than average interest in CVD management and the guidelines associated with it. There are also some limitations from the survey design: for example, we do not know the time interval of prescribing or non-prescribing prior to study.

Finally, the CART method has limitations. Overall model performance is low. This could be because of variance in prescribing practices; each GP might use a different tree for each patient. We discuss GP variability and clustering in Appendix 2. Instability in trees uncovered by CART can be difficult to measure and visualise.

5 Conclusion

[8] For example, there is some evidence to suggest that compliance increases with the number of risk factors [45].

While previous studies showed discordance between evidence and practice, CART extends traditional analyses by highlighting the alternative decision-trees and key factors that GPs use in practice to make prescribing decisions. The advantages of CART are the ability to identify hierarchies and non-linearities, and to provide results that are relatively easy to understand. These strengths are evident in this analysis, which show hierarchical decisions with complex interactions between individual risk factors and socio-demographic factors.

This example has shown that the CART big data technique is applicable to a wide range of healthcare topics, including those where big data are absent. There are an increasing range of applications in healthcare that utilize CART's strength in uncovering non-linear thresholds and hierarchies to develop guidelines for clinical decisions. It follows that evaluating if these guidelines are used in practice requires methods that can identify such structures and thresholds. In these instances, CART provides a useful addition to the analyst's toolkit.

Table 1: Characteristics of the patients in the AusHeart study*

Variable	Total (n = 1,903)	CART model
Prescribing		Dependent variable
C10- lipid-lowering medication	296 (16%)	
Socio-demographic variables		Explanatory variables in all models
Age (years)	66±9	
Female	1,131 (59%)	
Aboriginal/Torres Strait Islander	16 (1%)	
Household income (annual)		
Negative/Nil	28 (1%)	
$1-$18,199	401 (21%)	
$18,200-$33,799	466 (24%)	
$33,800-$51,999	253 (13%)	
$52,000-$72,799	166 (9%)	
$72,800-$103,999	124 (7%)	
$104,000 or more	101 (5%)	
Missing	364 (19%)	
Education		
None/very little	527 (28%)	
School/Diploma	901 (47%)	
University	435 (23%)	
Missing	40 (2%)	
Individual risk factors		Explanatory variables in models 2 and 3
Current smoker	163 (9%)	
Body mass index (kg/m2)	28.2±5.6	
Missing	55 (3%)	
Systolic blood pressure (mmHg)	136±17	
Diastolic blood pressure (mmHg)	77±10	
Low-density lipoprotein cholesterol (mmol/L)	3.22±0.84	
High-density lipoprotein cholesterol (mmol/L)	1.47±0.45	
Total cholesterol (mmol/L)	5.36±0.93	
Missing	26 (1%)	
Triglycerides (mmol/L)	1.49±0.82	
Missing	30 (2%)	
Kidney disease	69 (4%)	
Diabetes	250 (13%)	
Missing	3 (0%)	
CVD history		
None	1,618 (85%)	
Stroke/Transient ischemic attack (TIA) only	170 (9%)	
Coronary artery disease (CAD) only	86 (5%)	

Both Stroke/TIA and CAD	29 (2%)	
Exercise per week (> 30 minutes moderate)		
None	352 (18%)	
1-2 days/week	541 (28%)	
3-4 days/week	523 (27%)	
5-7 days/week	439 (23%)	
Missing	48 (3%)	
Self-rated health		
Excellent	124 (7%)	
Very good	508 (27%)	
Good	841 (44%)	
Fair	353 (19%)	
Poor	47 (2%)	
Missing	30 (2%)	
Absolute risk assessments		
GP-estimated absolute 5 year risk (%)	14±17	Explanatory variable in all models
Missing	182 (10%)	
Framingham absolute 5 year risk (%)	10±7	Explanatory variables in model 3
Missing	87 (5%)	
Patient self-reported absolute 5 year risk (%)	33±23	
* Data are mean ±standard deviation or frequency counts (%). CVD: cardiovascular disease; AR: absolute risk; GP: general practitioner		

Table 2: Model performance (%)

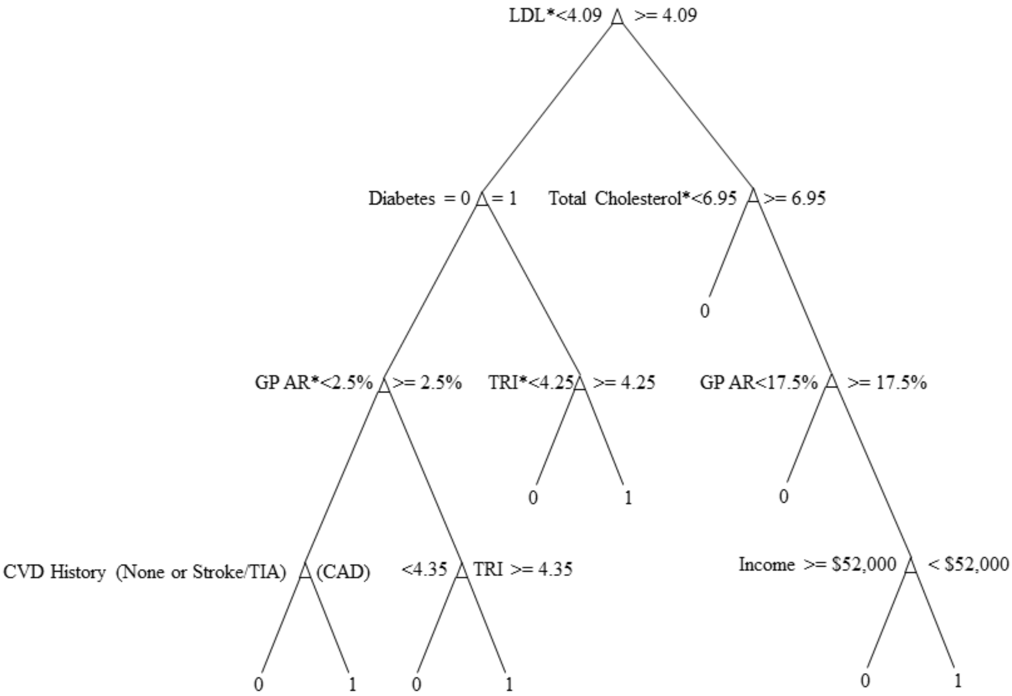
Model	**CART-1**		**CART-2**		**CART-3**		**CART-2 robustness check**	
Demographics Individual risk factors Absolute risk factors	All None GP-estimated		All All GP-estimated		All All GP-estimated, Framingham		All All GP-estimated	
Pruning	None	Pruned	None	None	Pruned	Pruned	Pruned	Pruned
Splitting criterion	GDI	GDI	GDI	GDI	GDI	GDI	Entropy	GDI
Missing data	Default	Default	Default	Default	Default	Default	Default	Surrogates
Within-sample error	0.12	0.15	0.08	0.08	0.15	0.15	0.14	0.14
Sensitivity	0.97	0.99	0.99	0.99	1.00	1.00	0.99	1.00
Specificity	0.39	0.09	0.53	0.53	0.07	0.07	0.10	0.09
Out-of-sample error	0.20	0.18	0.22	0.22	0.17	0.17	0.16	0.17
95% lower bound	0.20	0.17	0.22	0.22	0.16	0.16	0.16	0.16
95% upper bound	0.21	0.18	0.23	0.23	0.17	0.17	0.17	0.17
Out-of-sample ROC area	0.53	0.53	0.57	0.57	0.63	0.63	0.62	0.61
95% lower bound	0.50	0.51	0.55	0.55	0.60	0.60	0.60	0.58
95% upper bound	0.56	0.55	0.59	0.59	0.64	0.64	0.64	0.64
* GP: general practitioner; GDI: Gini's diversity index; ROC: receiver operating characteristic								

Table 3: Predictor results*

Predictor	Predictor-importance		Counts in bagged trees		Threshold*
	Pruned CART-2	Bagged trees	Nodes 1-3	Nodes 4-10	
LDL	1.31	1.59	100	54	4.3 mmol/L (4.1:4.6)
GP-estimated AR	1.05	0.38	0	116	30% (2.5:80.5)
Diabetes	0.94	0.56	100	0	Yes
Triglycerides	0.47	0.33	1	171	2.4 mmol/L (0.4:4.4)
Income	0.31	0.21	3	73	$52,000
Total cholesterol	0.28	0.08	6	31	5.2 mmol/L (3.6:7.0)
CVD history	0.11	0.08	0	63	Both
Education	0	0.21	44	9	University
Framingham AR	0	0.08	0	10	10.6% (1.6:30.6)
Exercise per week	0	0.04	0	38	No exercise
Self-rated health	0	0.09	0	4	Very good

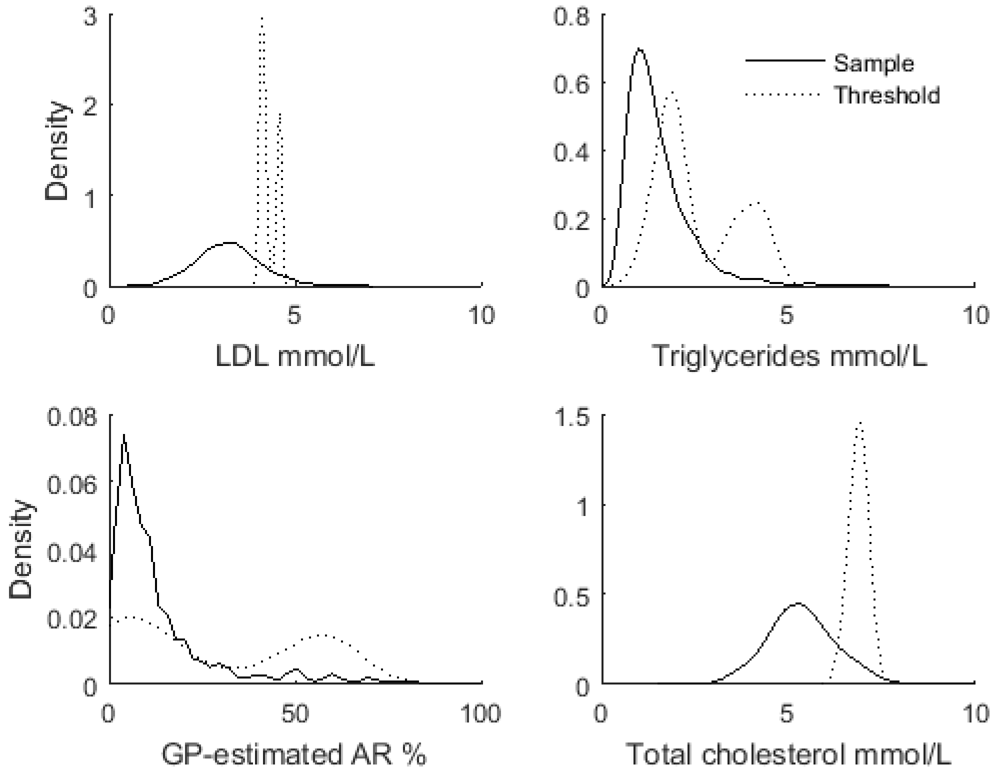
* confidence intervals for continuous variables; median threshold for discrete variables. CVD: cardiovascular disease; AR: absolute risk; GP: general practitioner; LDL: low density lipoprotein

Figure 1 CART-2*



***** 0 = not prescribed medication; 1 = prescribed medication. LDL: low density lipoprotein (mmol/L); total cholesterol (mmol/L); GP AR: general practitioner-estimated absolute risk (5); TRI: triglycerides (mmol/L); CVD: cardiovascular disease; CAD: coronary artery disease; TIA: transient ischaemic attack; Income: Household income ($).

Figure 2 Sample and threshold densities for selected risk factors*



* AR: absolute risk; GP: general practitioner; LDL: low density lipoprotein

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Appendix 1

Table A.1 Summary of Australian guidelines current during the study period to inform the prescribing of lipid-lowering medication

Guideline	Guidance to inform prescribing of lipid-lowering medication	Use of absolute risk?
NHF, 2008*	Use of lifestyle modification first line. Use of drugs for: • those with existing disease (vascular, diabetes, kidney or hypercholesterolemia), Aboriginal Torres Strait Islander people, and those with AR ≥15% in 5 years • those with AR 10-15% and family history of CHD, or with metabolic syndrome	Yes, Framingham 1991 equation
NVDPA, 2009	Adults with any of the following high risk conditions: • diabetes and age > 60 years • diabetes with microalbuminuria (> 20 mcg/min or urinary albumin:creatinine ratio > 2.5 mg/mmol for males, > 3.5 mg/mmol for females) • moderate or severe CKD (persistent proteinuria or eGFR < 45 mL/min/1.73 m2) • a previous diagnosis of familial hypercholesterolaemia* • systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg • serum total cholesterol > 7.5 mmol/L Use of Framingham to assess risk in those not considered 'high risk'	Yes, use of Framingham (for patients not assessed as high risk using other criteria)
PBS, 2014	Dietary therapy should be trialed prior to drug therapy for all patients who are not very high risk. Use of drugs for: • very high risk patients (eg existing CHD, vascular disease or diabetes, or family history CHD) • patients not considered very high risk who have combinations of risk (eg diabetes, Aboriginal, high HDL cholesterol, family history) along with particular lipid levels. For example an Aboriginal patient with total cholesterol >6.5mmol/L. See PBS (2014) for complete details.	No, evidence included the Heart Protection Study (HPS), the United Kingdom Prospective Diabetes Study (UKPDS), Australian data audits and input from experts

*Guideline refers readers to the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand Position Statement on Lipid Management (2005).

Appendix 2

After condensing the data to obtain a single-observation per patient, our CART makes no further adjustment for clustering of observations by GP. GPs see on average eight patients within the dataset (minimum of one patient per GP; maximum of 16). Stability across bagged trees may be overestimated if ‘bags’ of observations are drawn from clustered data. In supplementary analyses, we evaluated stability of the CART in 100 samples drawn using cluster-bootstrap methods [46]. Predictor counts and threshold densities were much the same with the cluster-bootstrap as for the simple bootstrap on clustered data described above.

Similarly, while detailed contextual data on each GP was not available, the data did contain a State location variable that identifies the GP’s geographic region. In supplementary analyses, we included this variable within the predictor set, however it did not enter into the preferred CART model shown in Figure 1.