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Australian general practitioners initiate statin therapy primarily on the basis of lipid levels; New Zealand general practitioners use absolute risk

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ABSTRACT

Objectives: To compare the determinants of initial statin prescribing between New Zealand and Australia. New Zealand has a system-wide absolute risk-based approach to primary care cardiovascular disease (CVD) management, while Australia has multiple guidelines.
Method: Classification and Regression Tree (CART) analysis of two observational studies of primary care CVD management from New Zealand (PREDICT-CVD) and Australia (AusHeart). Over 80% of eligible New Zealanders have been screened for CVD risk. PREDICT-CVD is used by approximately one-third of New Zealand GPs to perform web-based CVD risk assessment in routine practice, with the sample consisting of 126,519 individuals risk assessed between 1 January 2007 and 30 June 2014. AusHeart is a cluster-stratified survey of primary care CVD management that enrolled 534 GPs from across Australia, who in turn recruited 1381 patients between 1 April and 30 June 2008. Eligibility was restricted to 55–74 year old patients without prior CVD.
Results: The CART analyses demonstrated that New Zealand GPs prescribe statins primarily on the basis of absolute risk, while their Australian counterparts are influenced by a variety of individual risk factors, including total cholesterol, LDL cholesterol and diabetes.
Conclusions: Countries seeking to improve their management of CVD should consider adopting a 'whole of system' absolute risk-based approach with clear guidelines that are consistent with drug reimbursement rules; and include computerized decision-support tools that aid decision-making and allow monitoring of outcomes and continual improvement of practice.

1. Introduction

The benefits of statins for the prevention of cardiovascular disease (CVD) have been shown to be proportional to a patient's estimated absolute CVD risk prior to treatment initiation [1]. As a result, many prediction models have been developed to estimate a patient's absolute risk of CVD, with a recent systematic review identifying 363 of such models across North America, Europe, Asia and Oceania [2]. While knowing a patient's absolute risk of CVD should help a general practitioner (GP) determine optimal treatment, in practice this appears to be lost in the translation from model development to GP behaviour to patient outcome. The proliferation of prediction models has not resulted in real benefits to patients [3].

Australia and its close neighbour New Zealand share many cultural, economic and historical similarities, and cooperate closely on a range of socio-economic policies including immigration (a trans-Tasman travel arrangement allows citizens of one country to freely enter, live and work in the other), trade (a comprehensive bilateral free-trade agreement) and defence (ongoing relationships since the ANZACs of 1915 and before). The similarities and cooperation continue in health care delivery. The Australian Medical

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Council collaborates with its equivalent, the Medical Council of New Zealand, in assessment, accreditation and professional development programs. The countries share many organisational and representative bodies, including the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons and the Cardiac Society of Australia and New Zealand. However the two countries have contrasting models of primary care: access to publically funded primary health care in New Zealand requires eligible persons to enrol with a general practitioner and practices have a population health responsibility [4]. This has not been the case in Australia where practice enrolment and payment models designed to support prevention, coordination and integration of primary care are only now receiving serious attention [5]. The two countries have also followed different paths when specifying guidelines for prevention of cardiovascular disease. New Zealand was an early adopter of absolute risk assessment with the inclusion of a Framingham-based risk equation in their 1993 hypertension guidelines. Across the Tasman, the Framingham risk equation did not appear in hypertension guidelines until a decade later. These differences have been amplified by early adoption of one unified national CVD risk management guideline in New Zealand, accompanied by decision support tools to help translate the guideline into clinical practice [6], while Australia has had a range of sometimes conflicting guidelines. For example, the National Vascular Disease Prevention Alliance (NVDPA) guidelines are now based on absolute risk, while the Pharmaceutical Benefits Scheme (PBS) drug subsidy program limits eligibility on the basis of individual risk factors.

We compared the initial prescribing of statins for the primary prevention of CVD between Australia and New Zealand. We hypothesized that the system-wide approach to CVD risk management in New Zealand, including unified absolute risk-based guideline and long-standing use of web-based decision support tools integrated with electronic medical records, would result in GP initial prescribing practices being more consistent with absolute risk-based guidelines in New Zealand than in Australia. To test this hypothesis, we identified and compared the determinants of initial prescribing in each country using a classification tree technique often used in 'big data', and compared the resulting initial prescribing outcomes across the two countries. The determinants of initial statin prescribing in Australia have been previously established in Schilling et al. (2016) [7]; that analysis is revised here to allow comparability with the New Zealand dataset.

2. Background of CVD management in New Zealand and Australia

In New Zealand, paper-based CVD risk assessment charts were originally distributed to GPs in the early 1990s [6,8]. These were subsequently replaced in the early 2000s with web-based tools, of which PREDICT was the first and remains the most frequently used [6]. The PREDICT electronic decision support system provides clinicians with a user-friendly and patient-specific translation of New Zealand's single, unified national CVD risk management guideline. It recommended drug therapy for all patients with an estimated absolute risk above 15 per cent in 5 years when it was first introduced in 2003, and more recently has recommended shared decision-making between the GP and the patient about initiation of drug therapy for those with absolute risk above 10 per cent over 5 years [9]. Computerized decision-support tools integrated with patient management systems are available in most primary care settings to estimate absolute risk. In 2012, CVD risk assessment was made a national priority by the New Zealand Ministry of Health with an aspirational target of 90% coverage supported by modest funding to help primary care organisations reach the target [10].

In Australia, historically there have been a range of guidelines available to inform GPs about managing CVD based on individual risk factors such as hypertension, dyslipidaemia and diabetes [11]. During the 2000s, many Australian guidelines followed the trend away from managing isolated risk factors towards assessment based on absolute CVD risk [12]. The National Heart Foundation's *Hypertension management guide for doctors 2004* and subsequent *Guide to management of hypertension 2008* used Framingham absolute CVD risk calculations with some adjustments [13]. In 2009, Diabetes Australia, Kidney Health Australia, the Heart Foundation and the Stroke Foundation, aligned to release specific CVD risk guidelines based on absolute risk under the banner of the National Vascular Disease Prevention Alliance [14]. However the Australian Government's universal drug insurance scheme, the Pharmaceutical Benefits Scheme (PBS), limited the subsidising of lipid-lowering medicines using eligibility criteria based on individual risk factors such as diabetes and cholesterol [15], perhaps because of the lack of widely adopted decision-support tools that could help translate the guideline(s) into practice [12]. This was the background at the time of data collection for the Australian Hypertension and Absolute Risk (AusHeart) study which reviewed CVD management practices across Australia [11]. As a result, lipid levels were found to be the predominant driver of prescribing practices [7], and there were large variations in prescribing practices across GPs [16]. Today, there is increased consensus around the NVDPA's absolute risk guideline [17]; however there are still no widely adopted decision-support tools and the PBS guidelines still base eligibility on individual risk factors [15]. There are no routinely collected data that allows the evaluation of prescribing patterns or the determinants of prescribing in relation to CVD management.

3. Methods

3.1. Data

We used country-specific but broadly equivalent data from New Zealand and Australia. In New Zealand, we used CVD risk assessment data from the PREDICT-CVD cohort study from 1 January 2007 to 30 June 2014 [18]. Since 2002, PREDICT-CVD has been available for GPs to perform web-based risk assessment in routine practice. National pharmaceutical dispensing records for lipid lowering medications were linked for each individual via an anonymized linkage system. PREDICT-CVD is used by 35–40% of GPs across New Zealand [18] but there are other similar tools being used by GPs to help meet the Ministry of Health's 90% CVD screening target [10].

In Australia, we used linked survey and administrative data from the AusHeart Study, a cluster-stratified survey of primary care CVD management [13]. 534 GPs were enrolled from across Australia, and in turn recruited 15–20 consecutively presenting adults between 1 April to 30 June 2008 aged 55 years or older, and gathered a range of patient information including CVD risk and socioeconomic factors. These data were linked to pharmaceuticals dispensed under the PBS [13]. Unfortunately no later Australian data exists to compare with the New Zealand data, however in supplementary analyses we limited the New Zealand sample to GP visits during 2008, and complete a propensity score matching procedure to better align the two samples.

Data exclusions were designed to deliver similar samples across the two countries: in both countries, we excluded those with prior CVD or exposure to statin treatment to minimize the possibility that prior treatments had influenced observed risk factors; those younger than 55 years of age or over 75 years of age to align the age cohort for which risk assessment is promoted. In the New Zealand dataset, where an individual had more than one risk assessment, the earliest assessment was retained. After exclusions, we had New

Zealand data for 126,519 individuals, and Australian data for 1381 individuals, with the size discrepancy a result of the data being routinely collected in New Zealand, versus specifically recruited in Australia.

The dependent classification variable of interest was initial prescribing of statins or combination therapies including statins over the following 12 month period after the GP visit. The variables that were used to potentially explain the initial prescribing were: gender, age at assessment, ethnicity, diabetes status, smoking status, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and an absolute CVD risk estimate. Categorised household income and education level were available in the Australian sample; a socioeconomic deprivation index was available in the New Zealand sample.

3.2. Analysis

We compared CVD-related and socioeconomic patient attributes between the two countries by estimating standardised mean differences commonly used in observational studies to assess covariate balance [19]. A smaller standardised mean difference indicates a tighter balance, with a thresholds of 0.10–0.25 typically considered acceptable in the literature [19]. We used a Classification and Regression Tree (CART) approach to investigate the initial prescribing behaviour of New Zealand and Australian GPs, as per a previous analysis of initial prescribing behaviour of Australian GPs [7], however using a revised Australian sample as described above, and a different software package for comparability with the New Zealand analysis. CART is a decision tree technique that is well-suited to analysing non-linear and hierarchical problems, and particularly useful for uncovering thresholds in the data [20]. CART has often been used to establish clinical guidelines [21,22]; here we used it to analyse if such a guideline was followed. We constructed a CART model for each country using all of the potential predictors. We tested the CART model with surrogates for missing data (analogous to imputation) and without surrogates (equivalent to complete case analysis) to test for sensitivity to missingness [23]. CART models are prone to overfitting to the sample data [24]; we therefore pruned the tree to optimize out-of-sample classification performance, to generate a final pruned tree that performs well on new datasets. Out-of-sample performance was assessed via ten-fold cross validation, shown to be an optimal method for model selection [25]. The metric adopted was the ROC area-under-curve value where a result of 1 indicates a perfectly predicting model and a result of 0.5 indicates a model no better than random selection. We evaluated the value of each predictor to the decision-making process using the CART predictor-importance metric that sums the improvement in classification as measured by the Gini Diversity Index generated by the predictor across all branches within the tree, and rescaled the metric so that the best score was 100 [26,27]. We then bootstrapped the process 500 times to evaluate robustness and to describe the distribution of the results. As a further robustness check, in supplementary analyses we repeated the evaluation using subsets of the New Zealand sample: first limited to 2008 GP visits; and second, after propensity score matching using a 1:10 nearest neighbour approach to better align with the Australian sample. All analysis was completed in R using the rpart package [28].

Table 1
Cohort data.

Variable	New Zealand	Australia	Standardised mean difference
Total sample n	126,519	1381	
Male	54,564 (43.1%)	520 (37.7%)	0.111
Age	61.8 (5)	63.5 (6)	0.308
Ethnicity			
Asian	3932 (3.1%)		
Chinese	10,108 (8.0%)		
European	90,169 (71.3%)		
Indian	4820 (3.8%)		
Maori	9052 (7.2%)		
Pacific	7034 (5.6%)		
Other	1404 (1.1%)		
Aboriginal/Torres Strait Islander		12 (0.9%)	
Deprivation index/Income quintile			
1	31,399 (24.8%)	280 (20.3%)	0.143
2	26,275 (20.8%)	484 (35.0%)	0.292
3	22,480 (17.8%)	102 (7.4%)	0.343
4	20,336 (16.1%)	273 (19.8%)	0.072
5	17,884 (14.1%)	242 (17.5%)	0.068
missing	8145 (6.4%)	83 (6.0%)	
Diabetes	10,125 (8.0%)	158 (11.4%)	0.116
Current smoker	12,564 (9.9%)	128 (9.4%)	0.021
Systolic blood pressure (mmHg)	131.0 (17.2)	135.7 (16.8)	0.276
Total cholesterol (mmol/L)	5.5 (1.0)	5.4 (0.9)	0.084
HDL (mmol/L)	1.5 (0.5)	1.5 (0.5)	0.042
missing	*5 (0.0%)*	*59 (4.3%)*	
LDL (mmol/L)	3.2 (0.8)	3.3 (0.8)	0.086
missing	*22,932 (18.1%)*	*59 (4.3%)*	
Triglycerides (mmol/L)	1.6 (1.3)	1.5 (0.8)	0.101
missing	*22,932 (18.1%)*	*19 (1.4%)*	
5-year absolute CVD risk	8.1% (5.0%)	8.5% (5.8%)	0.074
Statin prescribing			
>15% 5-year absolute CVD risk	3158 (21.7%)	42 (18.8%)	0.072
10–15% 5-year absolute CVD risk	2440 (11.2%)	34 (14.7%)	0.104
<10% 5-year absolute CVD risk	3709 (4.1%)	98 (10.6%)	0.251

Mean (standard deviation) for continuous variables; count (percentage) for categorical variables

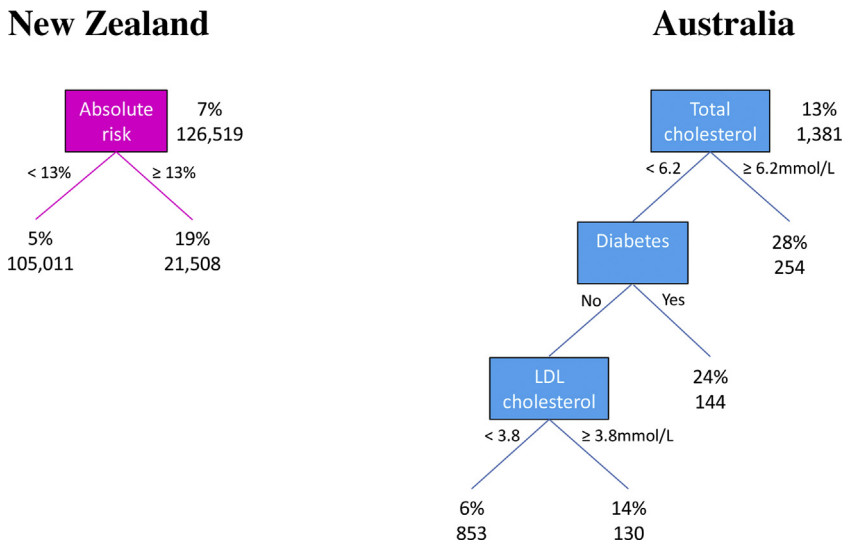

Fig. 1. Revealed classification trees of GP initial statin prescribing.
Fig. 1 legend: Percentage results show proportion prescribed statins; number results show volumes of patients in each group.

4. Results

4.1. Patient attributes and prescribing

The patient attributes are described in Table 1 for both New Zealand and Australia. The majority of attributes including the key CVD-related factors such as absolute risk, total cholesterol and LDL cholesterol are well balanced, highlighting the comparability of the two populations. The propensity score matching supplementary analysis provided a further improved balance, particularly on diabetes, age and gender (Supplementary Table 3). Table 1 also contains descriptive statistics on the prescribing of statins by 5-year absolute CVD risk. This show that New Zealand is better at targeting medication to patients at high risk.

4.2. Models of GP prescribing

We found strong evidence of GP adherence to CVD guidelines in the use of absolute risk in the New Zealand primary care setting. The optimal decision tree to explain initial prescribing in New Zealand was simply an absolute risk node (Fig. 1, left), implying that all the information that a GP used for decision-making is captured within the estimate of the patient's absolute CVD risk. This was in stark contrast to the factors used by Australian GPs to determine initial prescribing of lipid-lowering medications: the optimal decision tree uncovered by the CART analysis included the individual risk factors of total cholesterol, diabetes, and LDL cholesterol (Fig. 1, right). While these individual risk factors are inputs into the absolute risk equation used in New Zealand, the equation also includes other factors (e.g. age, gender, smoking status) and combines these factors in a multiplicative manner.

The out-of-sample performance as evaluated by the ROC area-under-curve values was 0.68 (95% confidence interval: 0.67-0.69) for the New Zealand decision tree versus 0.65 (0.56-0.75) for the Australian decision tree, indicating that there was no statistically significant difference in the classification accuracy between the two trees. There was more uncertainty in the accuracy of the Australian decision tree however, most likely as a result of the smaller sample size but potentially also due to higher variability in the initial

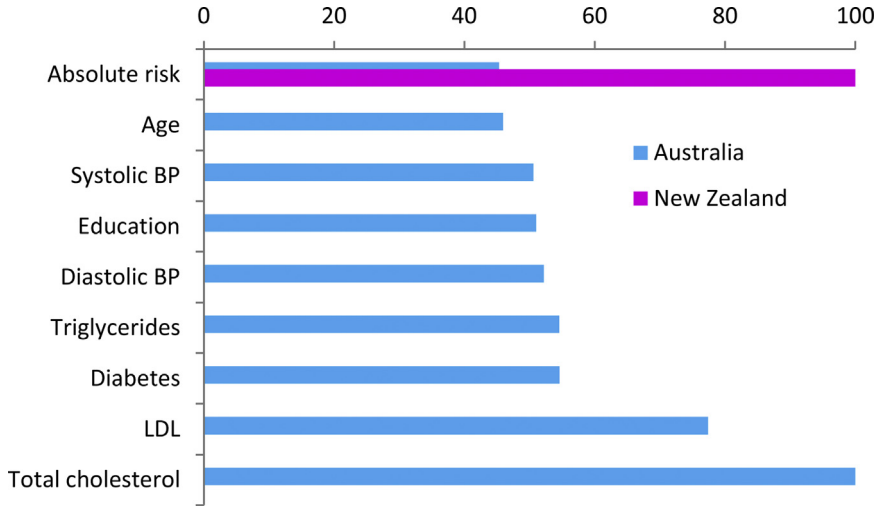

Fig. 2. Relative importance of patient attributes in GP initial statin prescribing.
Fig. 2 legend: Predictor importance results from bootstrapping exercise, scaled relative to highest importance of 100. BP: blood pressure; LDL: low density lipoprotein cholesterol.

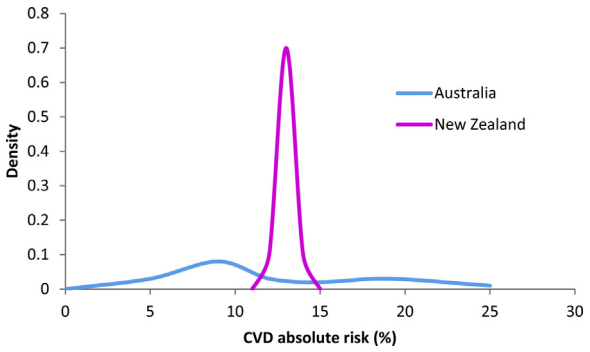

Fig. 3. Density plot of absolute risk threshold used to determine initial statin prescribing.
Fig. 3 legend: Absolute risk thresholds when absolute risk selected within optimal tree in bootstrapping exercise.

prescribing behaviour across Australian GPs or other unobserved characteristics.

4.3. Determinants of GP prescribing

The predictor importance results shown in Fig. 2 highlight the differences in the determinants of initial prescribing between the two countries: New Zealand GPs overwhelmingly used absolute risk, while a range of individual risk factors were important for decision making by Australian GPs, with total cholesterol being the most important. These results represent an average across the GP cohort, and potentially show that in Australia different GPs used different criteria to initiate statin prescribing.

4.4. Absolute risk thresholds for initial prescribing

The absolute CVD risk threshold that GPs used to determine initial prescribing is shown in Fig. 3. In New Zealand, where absolute risk is the only consideration for GP initial prescribing, a clear decision threshold was found at 13 per cent, with those below 13 per cent less likely to be prescribed statin treatment, while those above 13 per cent were more likely to be prescribed. The initial prescribing threshold spans the region of shared-decision making suggested by the guideline. In Australia, absolute risk is not a particularly important attribute used in GP decision-making, as shown in Fig. 2. However when it is used to inform initial prescribing, the most common decision threshold is at 10 per cent as per Australian guidelines, consistent with previously published results [7].

4.5. Supplementary analyses robustness checks

The optimal initial prescribing tree for the 2008 subset of the New Zealand data was an absolute risk node in 99 per cent of the bootstrapped samples, with total cholesterol and LDL cholesterol the key determinants of initial prescribing in the other 1 per cent of bootstrapped samples. The absolute risk threshold for initial statin prescribing was 12.4 per cent, however the threshold had a wider distribution due to the smaller sample size. Using the propensity matched cohort, the optimal New Zealand initial prescribing tree was again an absolute risk node, and the threshold for initial prescribing was 12.6 per cent, consistent with the main analysis (Supplementary Fig. 4). CART models with and without surrogates for missing data showed no significant differences.

5. Discussion

5.1. Principal findings

The clinical significance of achieving appropriate primary care management of CVD is hard to overstate: CVD remains the leading cause of morbidity and mortality worldwide [29], and the clinical evidence shows that the benefits of statins are directly proportional to the patient's absolute CVD risk [1]. This indicates that GPs should be using absolute risk as the key indicator for treatment. We have shown that this occurs in New Zealand, but much less so in neighbouring Australia, a country with a broadly comparable population and healthcare system.

While our CART results show that New Zealand is more efficient at targeting the prescribing of statins, the absolute use of statins amongst high risk individuals appears low in both countries. This suggests there is still room for improvement in New Zealand. By design, our analysis focused on the targeting of statin initiation using a dataset that excluded patients already on statins. Previous descriptive analyses that have focused on absolute statin use have shown greater utilisation in high risk cohorts in New Zealand [30] versus Australia [13].

5.2. Strengths and limitations

The strength of this study is the use of a CART technique combined with detailed patient-level data to uncover the factors used in GP decision-making for the initial prescribing of statins. This allowed us to identify if individual risk factors or absolute-risk estimates were being used by GPs in the initial prescribing of statins in New Zealand and Australia. As expected given the similarity in data and methods, our results that individual risk factors are used in Australia are consistent with the earlier Australian findings on drivers of initial statin prescribing [7]. This paper adds New Zealand findings from an analysis of a large routinely collected dataset that show a stark contrast to the Australian findings. More generally, the New Zealand example shows how large, routinely collected datasets can be used to evaluate how policy is translated into clinical practice. In New Zealand, this evaluation can be regularly performed to ensure policy is delivering on its aims; Australia has no such luxury.

There were limitations to our study. First, as in the comparable Australian research [7], our analysis used dispensed prescriptions rather than written prescriptions, as the measure of initial prescribing. Our results may vary if our data included all (filled and unfilled) prescriptions and if prescribing practices were different for those patients who did not fill their prescriptions. Second, while we used rich observational datasets containing key patient-related factors related to CVD, we did not consider GP characteristics that could influence initial prescribing practices. Third, the Australian dataset was significantly smaller in both sample size and duration of collection when compared to the New Zealand dataset, however it has been shown to be representative of Australian GPs across a number of GP characteristics [13], and the Australian PBS still subsidises statins on the basis of individual risk factors, at odds with the clinical guidelines. That the New Zealand system routinely collects population data on CVD that allows for analysis of hundreds of thousands of observations highlights an advantage of the system-wide approach to CVD management. Finally, there was potential bias in the selection of the New Zealand GPs that used the PREDICT decision support tool. However the decision to use PREDICT was made by GP organisations rather than the GPs themselves. It is used by approximately 35–40% of all New Zealand GPs [16], but due to the Ministry of Health's targeting of CVD risk assessment, over 80% of all eligible patients nationally had completed an absolute CVD risk assessment by the end of the data collection

period [31]. This highlights that risk stratification is common across the country, and not restricted to the PREDICT sample; there are many other absolute-risk decision support tools that are available to GPs including the National Heart Foundation's 'Your Heart Forecast' tool. This provides confidence that the New Zealand results are likely to be representative of the wider population.

5.3. What can other countries learn from the New Zealand experience?

There are several factors that may have contributed to the improved New Zealand performance that other countries could take note of. First, like a number of countries, New Zealand and Australia have adopted an absolute risk-based approach to CVD risk management. However in contrast to Australia, New Zealand has managed to present GPs with one unified CVD risk management guideline, rather than a number of often competing single risk factor guidelines from different sources. Other countries should consider whether the guidelines being presented to GPs are consistent, clear and unified. Second, the use of electronic decision support tools in New Zealand has facilitated the translation of the uniform guideline into primary care. New Zealand has successfully integrated such tools across the vast majority of primary care settings. It is worth noting however, that decision support tools alone are unlikely to be the panacea. A cluster-randomized trial in Australia tested a computerized decision support tool for CVD management, and concluded that such tools offer only a partial solution to improving primary care CVD management [32]. Other countries should note that a computerized decision support tool is likely to be necessary but not sufficient for primary care CVD management; indeed previous research highlighted an abundance of risk prediction models that calculate a patient's absolute CVD risk, but little evidence of benefit to the patient [3]. The third factor is a systematic approach to CVD risk management, which has meant that New Zealand's collective outcomes are greater than the sum of their parts. The development of CVD risk management in New Zealand has been an on-going effort for over 25 years. The single unified CVD risk management guidelines that were established in 2003 are reinforced, rather than conflicted by drug reimbursement regulations from New Zealand's pharmaceutical management agency, PHARMAC. CVD risk monitoring was one of the New Zealand government's seven high priority health targets, with the aim of 90 per cent of eligible persons having completed a CVD risk assessment by 2015 [10]. The PREDICT decision support tool also collates patient data, and links to hospitalisation, pharmaceutical and death records so that the current Framingham-based risk equation can be regularly updated and better targeted to the New Zealand population [18]. Other countries should note the durable 'whole of system' approach to CVD risk management in New Zealand, with built-in data linkages, monitoring and revisions, and an on-going rather than ad-hoc program of work. Finally, while this durable approach has led to highly targeted statin initiation in New Zealand, overall statin use in high risk cohorts could be increased. Even in New Zealand, there is still room for improvement.

6. Conclusion

We have shown clearly that initial prescribing practices in New Zealand are consistent with the most appropriate absolute risk-based clinical approach. There is no compelling reason why Australia and other countries should not have the same consistent, absolute risk-based approach to targeted prescribing that we have revealed in New Zealand. Countries should have clear, uniform guidelines. Drug reimbursement rules should complement rather than contradict such guidelines. Computerized decision-support tools should be rolled out across primary care settings and capture data so that risk-equations can be improved over time, and governments should support such efforts by prioritizing CVD management and monitoring outcomes. The New Zealand example shows that this is readily achievable.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.healthpol.2017.09.022.

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