Co-prescribing of contraindicated and use-with-caution drugs in a national cohort of new users of simvastatin: how well are prescribing guidelines followed?

Joshua Quon, Lianne Parkin, Katrina Sharples, David Barson

ABSTRACT

AIM: To describe the use of contraindicated and use-with-caution medicines among new users of simvastatin.

METHODS: We used information from Ministry of Health national datasets to establish a cohort of all patients aged ≥18 years who initiated simvastatin use between January 2006 and December 2013 (n=349,371). We estimated the cumulative incidences of the first dispensing of contraindicated and use-with-caution medicines during simvastatin use, and explored factors associated with co-prescription, using Kaplan-Meir and Cox regression methods, respectively.

RESULTS: Eleven percent and 16% of patients were dispensed a contraindicated and use-with-caution medicine, respectively, during the first two years of simvastatin use; by seven years, the figures were 17% and 26%. Thirty-six percent of patients were co-prescribed a contraindicated medicine on >1 occasion; the corresponding proportion for use-with-caution medicines was 84%. For a substantial proportion of those co-prescribed a use-with-caution medicine, the concomitant daily dose of simvastatin exceeded the maximum dose recommended at the time of prescribing. In the majority of cases, the prescriber of simvastatin and the contraindicated or use-with-caution medicine were the same. Co-prescribing of contraindicated medicines varied by sex, age, ethnicity and comorbidity.

CONCLUSIONS: The prescription of contraindicated and use-with-caution drugs to patients taking simvastatin is not uncommon in New Zealand.

Statins play a vital role in the primary and secondary prevention of major cardiovascular events.[1] In recent years, the adoption of an absolute cardiovascular risk reduction approach to prevention has led to an increase in the use of these medicines in New Zealand.[2–7] In 2016, for example, over 1.8 million prescriptions for statins were dispensed.[7]

Three statins are fully funded by the New Zealand Pharmaceutical Management Agency (PHARMAC): simvastatin, atorvastatin, and pravastatin.[8] Simvastatin (and, to a lesser degree, atorvastatin) is metabolised by the isoenzyme cytochrome P450 3A4 (CYP3A4), and the concomitant use of medicines which inhibit CYP3A4 may increase plasma levels of simvastatin, thereby

increasing the risk of adverse events such as myopathy and rhabdomyolysis.[9] Some CYP3A4 inhibitors are completely contraindicated in users of simvastatin, while others should only be used with caution and careful management of simvastatin dose.

Researchers from several countries have reported concerning levels of exposure to CYP3A4 inhibitors among users of CYP3A4-metabolised statins;[10–16] however, the extent of any such co-prescribing in New Zealand is unknown. We undertook a nationwide study to describe the use of contraindicated medicines, and those which should be used with caution, among all patients who initiated simvastatin use in New Zealand between 1 January 2006 and 31 December 2013. The specific aims of the study were to: (i) calculate the proportion of patients for whom a prescription of a contraindicated medicine was filled while on simvastatin, (ii) calculate the proportion of patients for whom a prescription of a use-with-caution medicine was filled while on simvastatin, (iii) ascertain whether the prescribers of simvastatin and a contraindicated medicine were the same, (iv) ascertain whether the prescribers of simvastatin and a use-with-caution medicine were the same and (v) explore factors associated with co-prescription of contraindicated medicines, including age, sex, ethnicity, deprivation and comorbidity.

Methods

Data sources

The study was based on data from four national datasets held by the Ministry of Health: the Pharmaceutical Collection (claims for all publicly funded dispensings of prescription medicines from community pharmacies),[17] the National Health Index (NHI) Collection (demographic information indexed to a unique patient identifier, the NHI),[18] the National Minimum Dataset (NMDS, publicly funded hospital discharges from 1988)[19] and the Mortality Collection (hospital inpatient and community-based deaths).[20] Since 2005, NHIs have been recorded with most dispensing records in the Pharmaceutical Collection and this has allowed the linkage of person-level pharmaceutical, demographic and health information held in the national datasets.

Deriving the study cohort

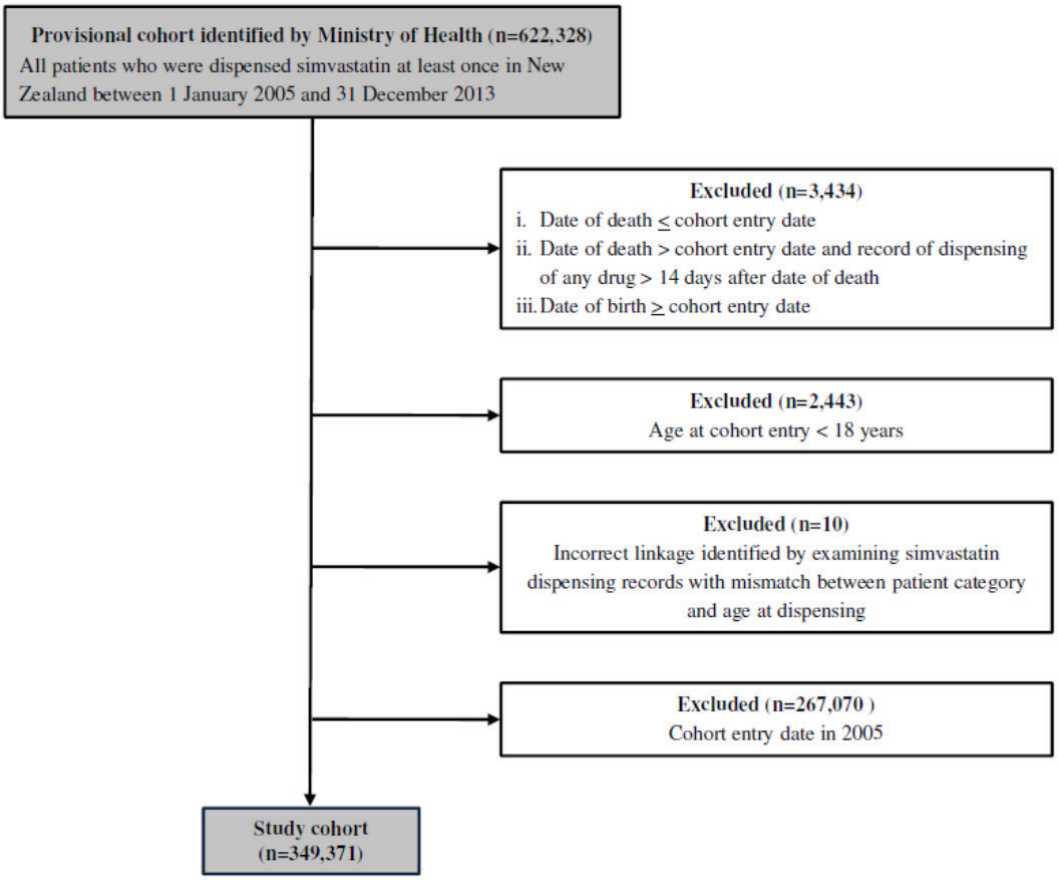
Analytical Services staff at the Ministry of Health searched the Pharmaceutical Collection to identify all patients who were dispensed simvastatin at least once between 1 January 2005 and 31 December 2013 (*the provisional cohort*). The date of the first simvastatin dispensing during that period was taken as the cohort entry date. For each patient, the Ministry provided us with the following data: demographic information (sex, date of birth, date of death, prioritised ethnicity [ie, patients with more than one recorded ethnic group were allocated to one group based on the following hierarchy: Māori, Pacific, Asian, Other, European][21] and an area-based measure of socioeconomic position, NZDep06[22]), details of all dispensings of simvastatin and other medicines (including subsequent dispensings of other statins) from cohort entry, details of any hospital discharges (back to 1988) and details of any deaths.

We undertook two steps to derive *the study cohort* from the provisional cohort identified by the Ministry (Figure 1). First, we excluded the small proportion of linked records where the pharmaceutical dispensing information and the health and demographic data clearly referred to different people. Second, we excluded patients with a cohort entry date in 2005 as we wanted to follow simvastatin users from the initiation of therapy (either as first-time users or as past users who were restarting after a break of at least one year).

Summarising simvastatin exposure

For each cohort member, we summarised simvastatin dispensing data into continuous episodes of use of the same daily dose, using an approach we have employed previously.[23,24] A continuous episode was defined as one in which the gap between the end date of one dispensed supply and the start date of the next was 30 days or less. Episodes were censored (truncated) at the earliest of any of the following: a different daily dose of simvastatin was dispensed, another statin was dispensed, the patient died or the end of the study period was reached (31 December 2013).

Figure 1: Deriving the study cohort.



Identifying exposure to contraindicated and use-with-caution medicines

We used the New Zealand Formulary (NZF)[8] to identify medicines which are contraindicated in simvastatin users, and those which should only be used with caution. Because prescribing advice regarding these medicines changed over time, we also examined archived hard copies of MIMs New Ethicals, which were current during the study period.[25] The contraindicated medicines included azole antifungals, ciclosporin (from January 2012), clarithromycin, danazol (from January 2012), erythromycin, gemfibrozil (from January 2012), omeprazole-amoxycillin-clarithromycin combination therapy and protease inhibitors. The use-with-caution medicines included amiodarone, amlodipine, bezafibrate, ciclosporin (January 2006 to December 2011), danazol (January 2006 to December 2011), diltiazem, gemfibrozil (January 2006 to December 2011), nicotinic acid and verapamil.

For each cohort member, we identified any dispensings of contraindicated and use-with-caution medicines which occurred during a continuous episode of simvastatin use (defined as co-prescribing). Any topical formulations were excluded from the count. In addition, we identified dispensings of amiodarone, amlodipine, bezafibrate, ciclosporin, danazol, diltiazem, gemfibrozil and verapamil to cohort members whose concomitant use of simvastatin exceeded the maximal daily dose recommended at the time of the dispensing. We did not have information about dispensed daily doses of nicotinic acid, so were unable to ascertain whether the dose of simvastatin was inappropriate.

Other information

We calculated a Charlson Comorbidity Score for each cohort member based on hospital discharge diagnoses in the five years before cohort entry, using an ICD-10 SAS macro developed by others.[26]

Statistical methods

Proportions and exact binomial 95% confidence intervals (95% CI)[27] were calculated to describe the crude proportions of simvastatin users who were co-prescribed each and any contraindicated and use-with-caution medicines during the follow-up period. Cumulative incidences of the first prescriptions of contraindicated and use-with-caution medicines were estimated using Kaplan-Meier methods,[28] with duration of simvastatin use as the measure of time. Cox regression methods[29] were used to estimate hazard ratios comparing demographic groups and comorbidity score using the same approach. Missing data were imputed for the Cox regression using chained equations[30] with age, sex, ethnicity, deprivation, Charlson score and outcome in the imputation models (n=10). R version 3.3.2 for Mac OSX and Stata v14 were used for statistical analyses.

Ethical approval

The study received approval from the Northern A Health and Disability Ethics Committee (14/NTA/178/A02).

Results

The study cohort

The provisional cohort identified by the Ministry of Health included 622,328 simvastatin users; a very small proportion had incorrectly linked records (0.9%, n=5,887), while 267,070 were prevalent users (Figure 1). In total, therefore, the study cohort included 349,371 patients who initiated simvastatin therapy in New Zealand between 1 January 2006 and 31 December 2013. The median duration of follow-up was 4.8 years, and the median duration on simvastatin was 2.1 years. The median age of cohort members was 59 years (interquartile range 50–69); just under half were female; 10.3% were Māori, 6.9% Pacific, 8.6% Asian, 66.9% European and 1.1% were classified as belonging to Other ethnic groups; and most had a Charlson Comorbidity Score less than 3 (Table 1). A socio-economic gradient was observed, with higher proportions of cohort members being found in the more deprived versus less deprived NZDep06 quintiles.

Table 1: Characteristics of the study cohort at entry. Values are numbers (%) unless stated otherwise.

Characteristic	Study cohort (n=349,371)
Female sex	157,325 (45.0)
Median age (interquartile range)	59 (50–69)
Ethnicity	
Māori	36,050 (10.3)
Pacific	24,045 (6.9)
Asian	29,893 (8.6)
European	233,757 (66.9)
Other	3,730 (1.1)
Missing	21,896 (6.3)
NZDep06 quintile	
1 (least disadvantaged)	55,825 (16.0)
2	56,805 (16.3)
3	71,862 (20.6)
4	81,611 (23.4)
5 (most disadvantaged)	82,113 (23.5)
Missing	1,155 (0.3)
Charlson Comorbidity Score	
0	271,229 (77.6)
1–2	60,825 (17.4)
3–4	11,279 (3.2)
5–6	3,290 (0.9)
≥7	2,748 (0.8)

Co-prescribing of contraindicated and use-with-caution medicines

Overall, 37,446 (10.72%) cohort members were dispensed at least one contraindicated medicine while they were using simvastatin (Table 2). Erythromycin was co-prescribed to 27,781 (7.95%) patients, while small proportions (between 0.6 and 0.8%) received clarithromycin (alone or in triple therapy), fluconazole, itraconazole and miconazole.

Table 2: Numbers and proportions of cohort members (n=349,371) who were co-prescribed contraindicated medicines on cohort entry date and/or during follow-up.

Medicine*	Cohort members co-prescribed contraindicated medicine	
	Number†	Percentage (95% CI)
Any contraindicated medicine	37,446	10.72 (10.62–10.82)
Clarithromycin	2,306	0.66 (0.63–0.69)
Erythromycin	27,781	7.95 (7.86–8.04)
Fluconazole	2,675	0.77 (0.74–0.80)
Itraconazole	1,992	0.57 (0.55–0.60)
Miconazole	2,593	0.74 (0.71–0.77)
Omeprazole, amoxicillin, clarithromycin combination therapy	2,197	0.63 (0.60–0.66)

*No cohort members were co-prescribed indinavir, nelfinavir or posaconazole, and very small numbers were co-prescribed atazanavir sulphate (n=10), ciclosporin (n=276), danazol (n=6), darunavir (n=3), gemfibrozil (n=100), ketoconazole (n=157), lopinavir with ritonavir (n=8), and ritonavir (n=11). The numbers for ciclosporin, danazol and gemfibrozil relate to dispensings from January 2012 onwards, when the concomitant use of these drugs with simvastatin became contraindicated.

†The number of cohort members co-prescribed at least one contraindicated medicine is less than the sum of the numbers for individual drugs because some people were co-prescribed more than one contraindicated medicine.

Co-prescription of ciclosporin, danazol, gemfibrozil, ketoconazole and protease inhibitors was very uncommon. Just over a third of patients (36.01%, n=13,484) who received a contraindicated medicine while taking simvastatin did so on more than one occasion, and 594 (1.59%) patients had at least 10 such co-prescribing events. The drug most likely to have been repeatedly dispensed was ciclosporin; of those who were dispensed ciclosporin, 96.01% had two or more dispensings, and 61.59% had 10 or more. A very small number (n=263) of patients were co-prescribed, at least once, two or more contraindicated medicines on the same day.

In total, 58,769 (16.82%) cohort members were dispensed at least one use-with-caution medicine during an episode of simvastatin use (Table 3). Amlodipine and diltiazem were the most common co-prescribed medicines (to 6.86% and 6.43% of patients, respectively). Overall, 83.74% (n=49,214) of cohort members who received a use-with-caution drug while taking simvastatin did so on more than one occasion; 46.14% (n=27,118) of patients had at least 10 such co-prescribing events, and 7.63% (n=4,485) had at least 50 events. Only 16 patients were co-prescribed, at least once, two or more use-with-caution medicines on the same day. Of the patients co-prescribed amiodarone, amlodipine, bezafibrate, diltiazem or verapamil, substantial proportions were taking simvastatin at a higher daily dose than recommended at the time of the dispensing.

Figure 2 shows the cumulative incidence of the first co-prescription of a contraindicated medicine, and of the first co-prescription of a use-with-caution medicine. The steep initial rise, particularly for use-with-caution drugs, is likely to be explained by repeats of previously prescribed medications. About 11% (11.2%, 95% CI: 11.1 to 11.3) of cohort members were dispensed a contraindicated medicine in the first two years of simvastatin use, and this increased to 16.7% (95% CI: 16.5 to 16.9) by seven years. The corresponding proportions for a use-with-caution medicine were 15.9% (95% CI: 15.8 to 16.0) and 25.8% (95% CI: 25.5 to 26.1), respectively.

For 21,546 (57.5%) of the first contraindicated medicine dispensings, the prescriber was the same clinician who had written the most recent prescription for simvastatin; just over a third (35.3%, n=7,610) of the dispensings from the same clinician occurred on the same day that simvastatin was dispensed. For 47,099 (80.1%) of the first use-with-caution dispensings, the

Table 3: Numbers and proportions of cohort members (n=349,371) who were co-prescribed use-with-caution medicines on cohort entry date and/or during follow-up, and numbers and proportions for whom concomitant use of simvastatin exceeded maximal daily dose recommendations.

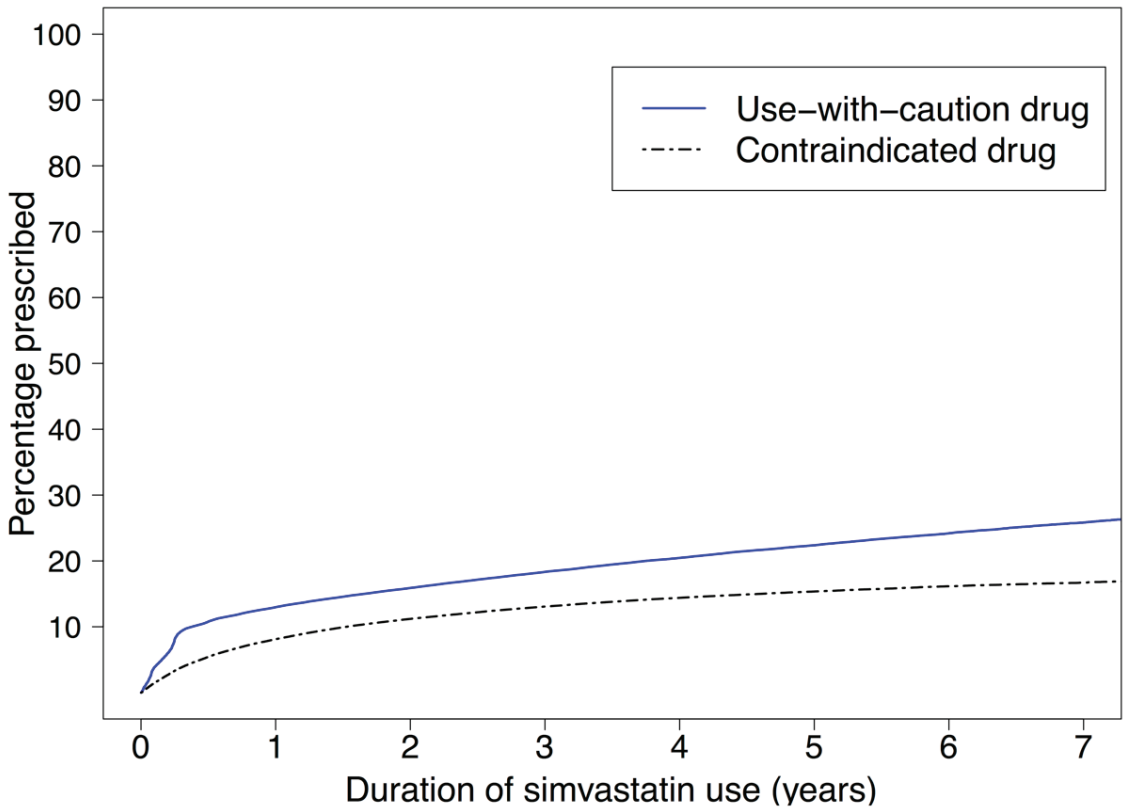
Medicine*	Cohort members co-prescribed use-with-caution medicine†		Cohort members co-prescribed use-with-caution medicine when concomitant use of simvastatin exceeded the recommended maximal daily dose	
	Number	Percentage (95% CI)	Number	Percentage (95% CI)‡
Any use-with-caution medicine	58,769	16.82 (16.70–16.95)	32,484	55.27 (54.87–55.67)
Amiodarone	5,663	1.62 (1.58–1.66)	3,491	61.65 (60.37–62.92)
Amlodipine	23,962	6.86 (6.78–6.94)	11,621	48.50 (47.87–49.14)
Bezafibrate	7,795	2.23 (2.18–2.28)	6,876	88.21 (87.47–88.91)
Diltiazem	22,448	6.43 (6.34–6.51)	11,584	51.60 (50.94–52.26)
Verapamil	2,933	0.84 (0.81–0.87)	1,277	43.54 (41.74–45.36)

*Very small numbers of cohort members were co-prescribed ciclosporin (n=448), danazol (n=21), gemfibrozil (n=50) and nicotinic acid (n=1,072). The numbers for ciclosporin, danazol and gemfibrozil relate to dispensings between January 2006 and December 2011, when it was advised that any co-prescribing of these drugs to patients taking simvastatin should be undertaken with caution.

†The number of cohort members co-prescribed at least one use-with-caution medicine is less than the sum of the numbers for individual drugs because some people were co-prescribed more than one contraindicated medicine.

‡The denominators for the percentages are the number of cohort members who were prescribed the use-with-caution medicines.

Figure 2: Cumulative incidence of co-prescription of contraindicated and use-with-caution medicines.



prescriber of the use-with-caution medicine and simvastatin were the same; for 36,836 (78.2%) of these dispensings the two medicines were dispensed on the same day.

Table 4 shows the results of the Cox regression analysis. Co-prescription of a contraindicated medicine was more common in women and in those with a higher Charlson Comorbidity Score, and less common in older age groups (for whom the time to the first co-prescribing event was longer). Compared with Māori, co-prescription was less common in Pacific and Asian patients, more common in the Other ethnic group and about the same in Europeans. There was no strong socio-economic gradient in co-prescribing.

Table 4: Numbers and proportions of cohort members (n=349,371) co-prescribed at least one contraindicated medicine according to demographic and clinical characteristics, with crude and adjusted hazard ratios.

Characteristic	Cohort members co-prescribed contraindicated medicine (no, %)*	Crude hazard ratio† (95% CI)	Adjusted hazard ratio (95% CI)†‡
Sex			
Female	19,003 (12.1)	1.43 (1.40–1.46)	1.44 (1.42–1.48)
Male	16,669 (8.7)	1.0	1.0
Age (years)			
18–39	1,900 (8.7)	1.0	1.0
40–59	14,957 (9.7)	0.93 (0.89–0.98)	0.89 (0.85–0.93)
60–79	15,956 (10.8)	0.97 (0.92–1.01)	0.86 (0.82–0.90)
≥80	2,860 (11.4)	1.12 (1.06–1.19)	0.83 (0.78–0.89)
Ethnicity			
Māori	3,871 (10.7)	1.0	1.0
Pacific	2,221 (9.2)	0.86 (0.81–0.90)	0.87 (0.82–0.91)
Asian	2,693 (9.0)	0.82 (0.78–0.86)	0.90 (0.86–0.95)
European	24,965 (10.7)	0.94 (0.91–0.97)	1.01 (0.98–1.05)
Other	463 (12.4)	1.22 (1.10–1.34)	1.31 (1.19–1.45)
NZDep06 quintile			
1 (least disadvantaged)	5,471 (9.8)	1.0	1.0
2	5,530 (9.7)	1.00 (0.97–1.04)	0.99 (0.95–1.03)
3	7,385 (10.3)	1.06 (1.02–1.10)	1.03 (1.00–1.07)
4	8,612 (10.6)	1.08 (1.05–1.12)	1.04 (1.01–1.08)
5 (most disadvantaged)	8,612 (10.5)	1.10 (1.06–1.14)	1.06 (1.02–1.10)
Charlson Comorbidity Score			
0	25,337 (9.3)	1.0	1.0
1–2	7,654 (12.6)	1.30 (1.26–1.33)	1.32 (1.28–1.35)
3–4	1,759 (15.6)	1.70 (1.62–1.78)	1.73 (1.65–1.82)
5–6	568 (17.3)	2.01 (1.85–2.18)	2.06 (1.89–2.24)
≥7	355 (12.9)	1.64 (1.47–1.82)	1.62 (1.46–1.80)

*Denominator is all cohort members in the category. Ethnicity was unknown for 1,460 cohort members prescribed a contraindicated medicine and NZDep06 quintile was unknown for six.

†Missing data were imputed for estimating the hazard ratios.

‡Adjusted for the other variables in the table.

Discussion

Principal findings

In this national study of all patients who initiated simvastatin use in New Zealand between 2006 and 2013, about 11% and 16% of patients were co-prescribed contraindicated and use-with-caution medicines, respectively, in the first two years of simvastatin use. These co-prescribing events were not always isolated incidents, with sizeable proportions of patients receiving a contraindicated or use-with-caution medicine on more than one occasion. For a substantial proportion of those co-prescribed a use-with-caution medicine, the concomitant daily dose of simvastatin exceeded the maximum dose recommended at the time. In the majority of cases, the prescriber of simvastatin and the contraindicated or use-with-caution medicine were the same. Female sex, younger age, greater comorbidity and ethnicity were all associated with co-prescribing of contraindicated medicines.

Strengths and limitations

The study had several strengths and some limitations which warrant further consideration. First, we were able to establish a national cohort of simvastatin users and follow those users from the initiation of therapy. Second, it is likely we identified virtually all dispensings of simvastatin, as well as contraindicated and use-with-caution medicines, from community pharmacies during the study period as pharmacists are not reimbursed for such dispensings unless they submit a claim. However, medicines dispensed to patients in hospital are not recorded in the Pharmaceutical Collection, so we cannot comment on the prevalence of co-prescribing in the hospital setting. Third, because the study was based on dispensing, rather than prescription, records, it is clear that cohort members recieved supplies of simvastatin and other medicines. However, we do not know whether they took those medicines as directed on the prescription; nor do we know whether patients who were prescribed a short course of a contraindicated or use-with-caution medicine were instructed to temporarily withhold simvastatin or reduce their daily dose. Hence it is possible that we might have overestimated the co-prescription of short-term medicines such as erythromycin, and therefore the overall proportion of cohort members co-prescribed any contraindicated medicine. By contrast, all of the use-with caution medicines which were dispensed to simvastatin users are drugs which are used long-term, so it seems less likely that patients would have been advised to stop or reduce their dose of simvastatin (while at the same time continuing to collect their usual simvastatin supplies from the pharmacy)—therefore our measures of co-prescription of use-with-caution medicines are less likely to be overestimates. For the same reason, we are unlikely to have substantially overestimated the proportions prescribed use-with-caution medicines in combination with daily doses of simvastatin exceeding the recommended levels.

Fourth, we focused on contraindicated and use-with-caution medicines, which were listed in prescribing information sources commonly used by prescribers during the study period (rather than the detailed simvastatin datasheets), so it is possible we might have underestimated the overall co-prescribing of both contraindicated and use-with-caution drugs.

Finally, our study cohort comprised new users of simvastatin who were identified for an earlier study,[24] so we were unable to examine co-prescribing of CYP3A4 inhibitors among users of atorvastatin. However, CYP3A4 inhibitors affect the metabolism of simvastatin more than atorvastatin, so our focus on simvastatin was justifiable. Moreover, because simvastatin was recommended as the first-line statin for the primary and secondary prevention of cardiovascular events during the study period[3,4] and the current guidelines still recommend simvastatin 40mg (or atorvastatin 20mg) for patients with a five-year combined cardiovascular risk of 10–20%,[5] simvastatin is widely used in New Zealand (in 2016, for example, it was the 14th most commonly dispensed medicine, with 650,000 dispensed prescriptions[7]).

Comparison with previous studies

This is the first study, internationally, to have examined the co-prescribing of contraindicated and use-with-caution medicines

in a national cohort of new users of simvastatin, so it is not possible to make direct comparisons with other investigations. In contrast to our study, previous investigations have been based on sub-groups of patients,[10,11,13,15,16] a mix of new and prevalent statin users,[10–16] and some have not differentiated between contraindicated and use-with-caution medicines.[11] However, despite these differences in design, our results are broadly consistent with reports of concomitant use of CYP3A4 inhibitors and CYP3A4-metablised statins in the UK,[13] US,[10,11] Australia,[15] Norway,[12] Sweden[14] and Korea.[16]

Conclusions

Despite the existence of prescribing guidelines and patient management software which alerts prescribers to potential drug interactions, the prescription of contraindicated and use-with-caution drugs to patients taking simvastatin is not uncommon in New Zealand. Further work is required to explore and address the reasons for such co-prescribing, and for the apparent differences in co-prescribing by demographic characteristics. Future studies could also examine the level of co-prescribing of contraindicated and use-with-caution medicines in users of atorvastatin.

Competing interests:
Nil.

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Author information:
Joshua Quon, Medical Student, Dunedin School of Medicine, University of Otago, Dunedin; Lianne Parkin, Senior Lecturer, Department of Preventive and Social Medicine, University of Otago, Dunedin; Katrina Sharples, Associate Professor, Department of Mathematics and Statistics, Department of Medicine, University of Otago, Dunedin;
David Barson, Data Manager, Department of Preventive and Social Medicine, University of Otago, Dunedin.

Corresponding author:
Dr Lianne Parkin, Senior Lecturer, Department of Preventive and Social Medicine, University of Otago, Dunedin.
lianne.parkin@otago.ac.nz

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