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MANUSCRIPT

Title Page

Title

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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Ethics Application

As all data were de-identified by encryption, ethics approval was confirmed as not required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006* (Upper South B Regional Ethics Committee, Ethics ref: URB/12/EXP/022).

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Conflict of Interest Statement

None

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None

Data Sharing

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

Key Words

Statins, diabetes, antihypertensives, metformin, primary care, electronic prescription.

Abbreviations

ACEi = angiotensin converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CCB = calcium channel blockers

Study Groups:

Antihypertensives TB = thiazides and beta-blockers.

Antihypertensive AAC = angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.

Abstract

Objective: Recent studies suggest statins increase the risk of subsequent diabetes with a clear dose response effect. However patients prescribed statins have a higher background risk of diabetes. This national cohort study aims to provide an estimate of the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, and those with already higher background risk on cardiovascular risk modifying drugs and a control drug.

Design: Longitudinal cohort study

Setting: Use of routinely collected data from a complete national primary care electronic prescription database in New Zealand.

Participants: 32,086 patients aged between 40 and 60 years in 2005 were eligible and assigned to four non-overlapping groups receiving their first prescription for:

1. diclofenac (healthy population) n=7140
2. antihypertensives thought likely to induce diabetes (thiazides and beta-blockers) n=5769
3. antihypertensives thought less likely to induce diabetes (ACEi, ARBs, CCBs) n= 6565
4. statins n= 12 612

Outcome: Numbers of first metformin prescriptions were compared between these groups from 2006 to 2011.

Results: Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01), followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribed

antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac.

Conclusions: Not all the risk of diabetes associated with statins can be attributed to increased background risk. It also suggests different risk levels may be associated with different antihypertensive drug classes. This provides important information for future research and for prescribers and patients when considering the risks and benefits of different types of cardiovascular risk modifying drugs.

Article Summary

Article focus:

- Estimates the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, other groups of cardiovascular risk modifying drugs indicating higher background risk and a control drug.

Key messages:

- Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01) when compared to control drug
- Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed thiazides and beta-blockers (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and ACEi, ARB and CCB (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins.

Strengths:

- A national cohort study using electronic prescription database
- First longitudinal study to compare incidence of subsequent diabetes between statins and antihypertensives with a control drug
- First study to measure outcome by proxy of first metformin prescription as indication of significant diabetes development, no longer amendable to lifestyle changes.

Limitations:

- Confounding factors like BMI, family history and socioeconomic status is not controlled for in this electronic database analysis. However, there is no indication that these factors are not unevenly distributed between the different “high risk” study groups.
- There is a small risk of misclassification for prescription of metformin for other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, but these are rare and is likely to only account for a small number of prescriptions.

Text

Introduction

Statins are widely used and have established benefits in the prevention of cardiovascular events.[1] However, recent studies suggested statins may also increase the risk of new-onset diabetes[2-8], which in turn increases risk of cardiovascular events. One meta-analysis reported the odds to be 9% (OR: 1.09; 95% Confidence Interval (CI) 1.02 to 1.17)[5], with other studies showing the association with pravastatin and rosuvastatin use.[3,4,7,9-11] More recent data indicates the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link.[6] Nevertheless, statins may still have an overall cardiovascular benefit.[5]

One of the difficulties in assessing the extent of this risk is that the patients with higher cardiovascular risk who are prescribed statins also carry an increased baseline risk of developing diabetes because of similar risk factors.[12-14] To understand the extent of the contributions of this increased baseline risk and the risk from the drugs themselves, we compared subsequent diabetes development in patients started on a statin with that in patients started on other drugs for cardiovascular risk management (antihypertensives) and with patients at low baseline risk. We used a complete national prescribing dataset[15] to create a population based cohort constructed of these three groups and compared the risk of subsequent development of clinically significant diabetes in each group.

Methods

Study design: Longitudinal cohort study using a national data set of de-identified routinely collected primary care electronic prescriptions of New Zealanders between ages 40 and 60, receiving first prescriptions of drugs studied (Appendix 1) in the year 2005.

Data source: Nationwide prescription data for the purpose of this study were sourced electronically from a complete national prescribing dataset, the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.[16] Community prescribing is electronic in primary care in New Zealand making this information accessible via NZHIS. Individual patients are assigned a unique identifier (NHI number) in

the New Zealand health system and this is attached to their prescriptions, allowing this to be the main data key linkage tool. All NHIs were de-identified at the point of data extraction, and automatically assigned a unique encrypted code.

Cohort construction: The cohort construction is illustrated in Figure 1 (Flow chart of cohort formation). The cohort included patients aged 40-60 in the year 2005 without prior prescription of excluded drugs and metformin (outcome drug) (Appendix 1), and all patients having received a prescription of at least one of the drug of interest between 2005 and 2011. These drugs were statins, antihypertensives, diclofenac (comparator drug) or metformin (outcome drug). Some antihypertensives are also associated with subsequent development of diabetes. Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,[14,17-19] whereas little association has been made with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB).[18,19] Following the literature, those in the antihypertensive drug group were further divided into "Antihypertensives TB" for antihypertensives thought likely to increase diabetes risk (T and BB), and "Antihypertensives AAC" for antihypertensives thought less likely to do so (ACEi, ARB and CCB). A total of 195,194 records listed at least one of the drugs in the drug groups under study: Diclofenac, Antihypertensives TB, Antihypertensives AAC, and Statin groups. Patients belonging to two study groups concurrently in 2005 were then excluded. Data were further examined and cleaned to identify duplicate individuals, exclusion drugs and data entry error. This left 32,086 unique individuals to form the 2005 study cohort with 7140, 5769, 6565 and 12,612 in Diclofenac, Antihypertensives TB, Antihypertensives AAC, Statin groups respectively.

Exclusion: Patients who had a prescription for oral hypoglycaemics, insulin, oral corticosteroids (known to increase the risk of diabetes), or any of the study group medications of interest (Appendix 1) prior to 2005. The upper age limit was chosen to limit the inclusion of cardiovascular drugs prescribed for treatment of other cardiovascular conditions (e.g. heart failure).

Exposure: New Zealand adults who received their first prescription of statins, antihypertensives, or diclofenac in the calendar year 2005 without prior prescription of exclusion drugs and metformin.

Primary Outcome Measure: The proportion of patients receiving their first prescription of metformin in the calendar years 2006-2011. Metformin is the recommended first line treatment for newly diagnosed type 2 diabetes mellitus in New Zealand.[20]

Analysis: Patient baseline demographics were summarised using simple descriptive statistics and differences between cohorts were assessed using chi-square statistics calculated on OpenEpi online[21]. Since these are routinely collected electronic records, loss to follow up cannot be measured directly, and will be measured by proxy of medication persistence, death and emigration rate. Persistence with medications was determined as having at least one prescription a year, and persons-years were calculated based on this data. Death and emigration rate were calculated by direct age standardisation based on information available on Statistics New Zealand life-tables to estimate loss to follow up for our cohorts.[22] Incidence rates and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated to compare the risk of new-onset diabetes between Diclofenac group and the other three cohorts. HR were calculated in SPSS 20.0 for Windows (SPSS Inc) using cox proportional hazards regression, and multivariable analysis was used to adjust for differences in the demographic structure of the cohorts. All analyses were 2-sided.

Results:

Patient characteristics: The baseline characteristics of the cohorts are summarised in Table 1 (Cohort demographic). The sex of the patients differed by groups with a higher proportion of females (68.8%, $\chi^2(1) = 447.86$, $p < 0.001$) in the Antihypertensives TB group, and of males (66.6%, $\chi^2(1) = 545.35$, $p < 0.001$) in the statin group. The age of patients also differed across groups with patients receiving cardiovascular risk modifying drugs tending to be older than those in the diclofenac group ($\chi^2(1) = 1016.39$, $p < 0.001$). New Zealand European was the major ethnicity in all study groups. There were more Maori in the Diclofenac group with only a few in the statin group ($\chi^2(1) = 301.86$, $p < 0.001$). These differences between groups are adjusted for in the multivariable analysis.

Cohort characteristics and follow up: A total of 32,086 unique patients were eligible for analysis from the recruitment: 7140 for the Diclofenac group, 5769 for Antihypertentives TB group, 6565 for

Antihypertensives AAC group, and 12,612 for the Statin group (Figure 1). Persistence with index medications for each group was 38.4%, 71.3%, 70.9% and 76.1% respectively (Appendix 2). The persistence within the control group was expectedly lower as diclofenac is not usually indicated for long term use. Loss of follow up due to deaths and emigration is estimated to be less than 2% of those who were not persistent with medications, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.

Primary analysis: Primary outcome results indicated that between 2006 and 2011, 710 patients within the four groups received their first prescription of metformin. This represents 1.2%, 1.5%, 2.3% and 3.1% of those exposed to Diclofenac, Antihypertensives TB, Antihypertensives AAC and Statin groups respectively. The incidence rates were 2.5, 2.8, 4.2 and 5.5 cases per 1,000 person years for first prescription of metformin (Table 2) accordingly. As known, patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac. In the multivariable analysis, patients commenced on statins had the highest risk of receiving a first prescription of metformin in 6 years after exposure compared to the Control group (HR: 3.31; 95% CI: 2.56-4.30; P < 0.01). In contrast to existing research, patients on

Antihypertensives AAC group have moderate risk of receiving their first prescription of metformin in 6 years (HR: 2.32; 95% CI: 1.74-3.09; P < 0.01), and patients in the Antihypertensives TB group had a slightly higher risk (HR: 1.59; 95% CI: 1.15-2.20; P < 0.01) (Table 3), when compared to patients on diclofenac. Our analysis indicates a duration-response: The HR of developing new-onset diabetes was approximately constant over the duration of the study as demonstrated by the plot for the cumulative hazard ratios for the first metformin prescription in each study cohort (Figure 2), adjusting for age, sex, and ethnicity.

Subgroup analyses: Patient demographics were analysed to assess other characteristics of recipients of first metformin prescription (Appendix 3). Cox regression model analysis revealed that females had a lower risk than males (HR = 0.85, 95% CI: 0.72-1.00, p = 0.05), and there was no difference in risk between age groups within our cohort age range. However, risks were increased with all other ethnicities when

compared to New Zealand European. Pacific Island and Asian ethnic group had the highest risk at HR 3.57 (95%CI: 2.63-4.85, P < 0.01) and HR 3.72 (95% CI: 3.00-4.62, P<0.01) respectively.

To assess whether those at risk of developing diabetes were prescribed higher doses of their prescribed medications, the drug doses of their first prescribed indexed medications in 2005 among those prescribed metformin were assessed. In the Statin group, 96.9% of patients were prescribed 40mg and less of both simvastatin and atorvastatin. For patients in the Antihypertensives TB group, 78.8% of patients were on beta blockers and 88% of those on thiazides were on 2.5mg of bendrofluazide. This indicates patients commenced on metformin were prescribed conservative dosing of cardiovascular risk modifying drugs.

There were 743 patients who swapped study cohorts during the study period. Of these, 220 were from the Diclofenac group, 206 from Antihypertensives TB group, 166 from Antihypertensives AAC group and 151 from Statin group (Appendix 4). Excluding these patients in a per-protocol analysis had little effect on the hazard ratios compared to the intention to treat analysis (results of analysis available but not included), which could indicate the effect is rare or that the exposure is steady.

Discussion

Patients receiving a first prescription for statins were at the highest risk of subsequently developing clinically significant diabetes, with a risk three times that of those prescribed diclofenac. Patients prescribed ACE inhibitors, ARBs or calcium channel blockers were the next highest risk, being twice as likely to receive a metformin prescription, while those prescribed thiazides and beta-blockers were only at slightly increased risk.

The association between new-onset diabetes, as estimated by first metformin prescriptions, and initiation of statins found in this study is consistent with recent reports. However, the risk in this population was lower (3.1%) than the 9% risk reported in meta-analyses.[23-25] More recent publications have identified the risks of new-onset diabetes with statin drug use ranging from 2.4% to 8.5%. [23-26] In contrast to our study, the diagnosis of diabetes in these other studies were identified by indicators such as disease classification recording, or intermediate indicators such as laboratory investigations of HbA1c and fasting serum glucose

readings. This will draw in milder levels of hyperglycemia where lifestyle changes can still be the first line of management and where laboratory threshold determines disease rates. This study is the first to identify the incident rate of clinically significant diabetes in patients prescribed statins as indicated by the first prescription of metformin in a non-research population. This is an outcome that matters to patients.

Our study is also the first to compare the risks of diabetes development in patients on statins against patients on other cardiovascular risk modifying drugs who might also be considered to be 'high risk'. Patients initiated on antihypertensive drugs were, like those prescribed statins, at greater risk of developing diabetes compared to those on diclofenac. Our findings therefore allow an assessment of the comparative risks of new-onset diabetes in patients with already higher risk on different classes of antihypertensives. There may be several explanations for the differences seen. Firstly, it may be a true association. Secondly, it may be that patients with risk factors for diabetes (such as obesity) are less likely to be prescribed treatment with associated increased risk of diabetes.[14,27] Hence, they are more likely to receive prescriptions of ACEi or ARBs for management of hypertension due to a lesser known risk of inducing diabetes. We also observed conservative dosing in patients on thiazides and beta-blockers, which may attenuate the risk. This study is not able to answer these questions, but raises these for future research.

Since all data collected are electronic records, patient persistence with medication can be grossly assessed. There were high rates of persistence with medications within the study groups, in particular to the antihypertensives and the statins. Given only a total of 743 patients (2.3% of 2005 cohort) swapped into different study groups during the study period, there were relatively clean groups for analyses of risks.

The development of clinically significant diabetes was estimated using a proxy measure, utilising the first prescription of metformin. The validity of using routinely collected and electronically stored prescription data for diagnosing diabetes has been previously demonstrated.[15,28] The use of routinely collected data also provides access to a complete national population based cohort. We were able to assess this cohort longitudinally over a period of 6 years in a representative primary care population rather than a trial population with tightly constrained entry criteria.

Limitations

Our study has several limitations. The nature of the electronic datasets available means it is not possible to obtain other factors contributing to cardiovascular and diabetes risks to more precisely define subgroups and allow direct comparison of the cohorts' baseline levels of risk of developing diabetes (e.g. body mass index and family history). These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study, however there is no indication to suggest that these risk factors would be unevenly distributed between the high risk prescription groups.

There is also the risk of misclassification. Metformin may also be prescribed for management of other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, however this is likely to account for only a small proportion of prescriptions.

It is also uncertain as to how frequently these patients are tested for diabetes mellitus in the primary care setting, as the electronic system is not currently linked to laboratory data. The study is also unable to control for the duration of mild hyperglycaemia prior to commencement of metformin.

In this study, we have not distinguished between the various statin doses and formulations.

Conclusions

Patients initiating treatment with any of the index cardiovascular risk modifying drugs have some risk of developing clinically significant new-onset diabetes compared to those prescribed diclofenac. However, patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Patients prescribed ACE inhibitors, angiotensin II receptor blockers and calcium channel blockers were also at moderately increased risk, while patients prescribed thiazides and beta-blockers only appeared to have a mildly increased risk. The effect seen carries an exposure duration-response groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers. This provides additional information on the comparative safety of these drugs in a real world setting in primary care, where the bulk of these prescriptions are likely to be initiated. This is useful information for doctors and patients considering the balance of harms against the

potential for benefit of both statins and different cardiovascular risk modifying medications in different populations.

Further Research

Whether there is an additive risk of inducing diabetes with combinations of different cardiovascular risk modifying drugs is currently unknown, and an important area for research to inform decision making on prescribing, given the prevalence of multi-morbidity and likely co-prescription. This is subject to a further study. It is also unclear what effect this additional risk of diabetes will have on morbidity and mortality for patients. Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely only as a risk factor for other disease, predominantly cardiovascular disease.

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Figures

Figure 1: Flow chart of cohort formation

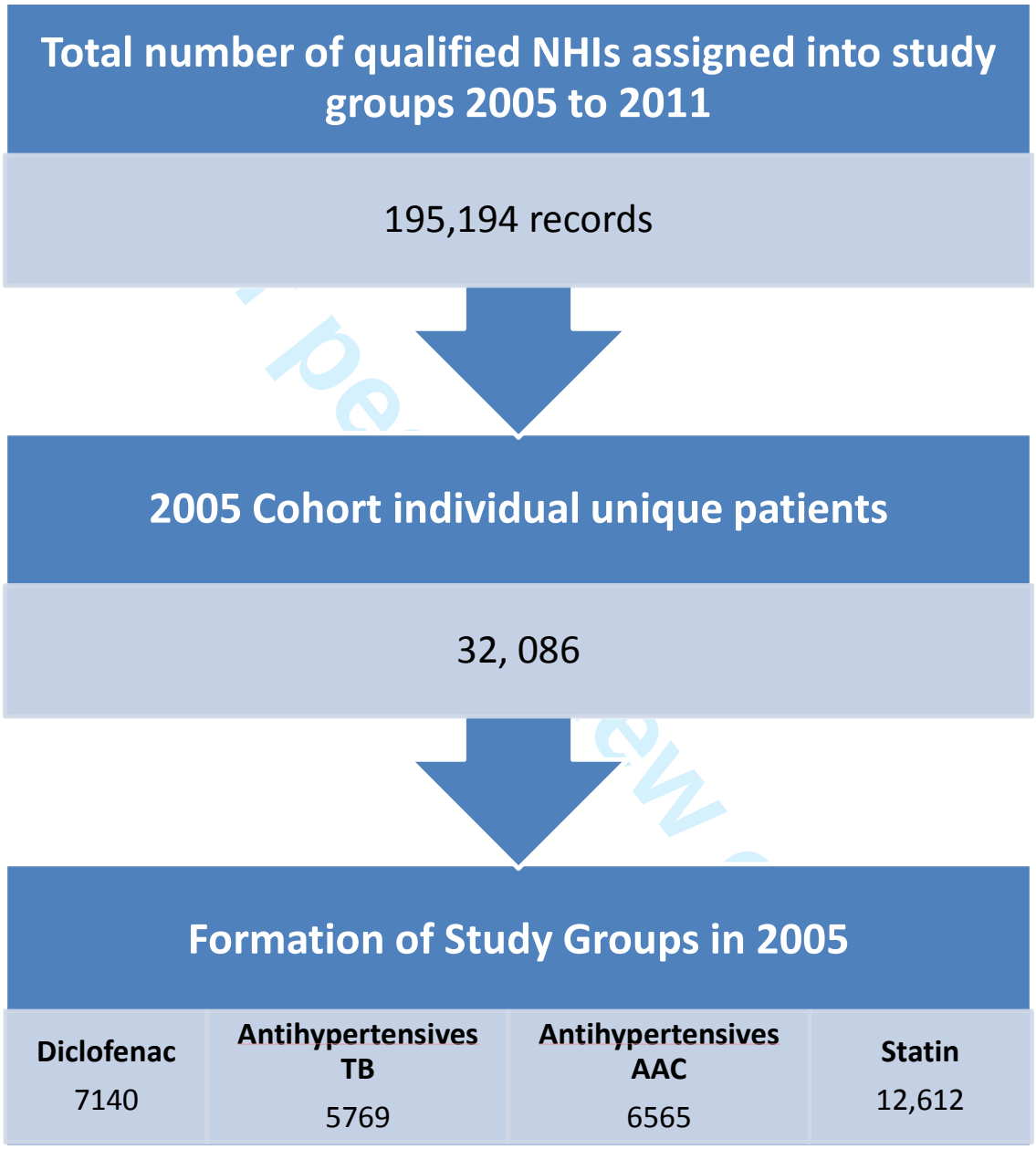
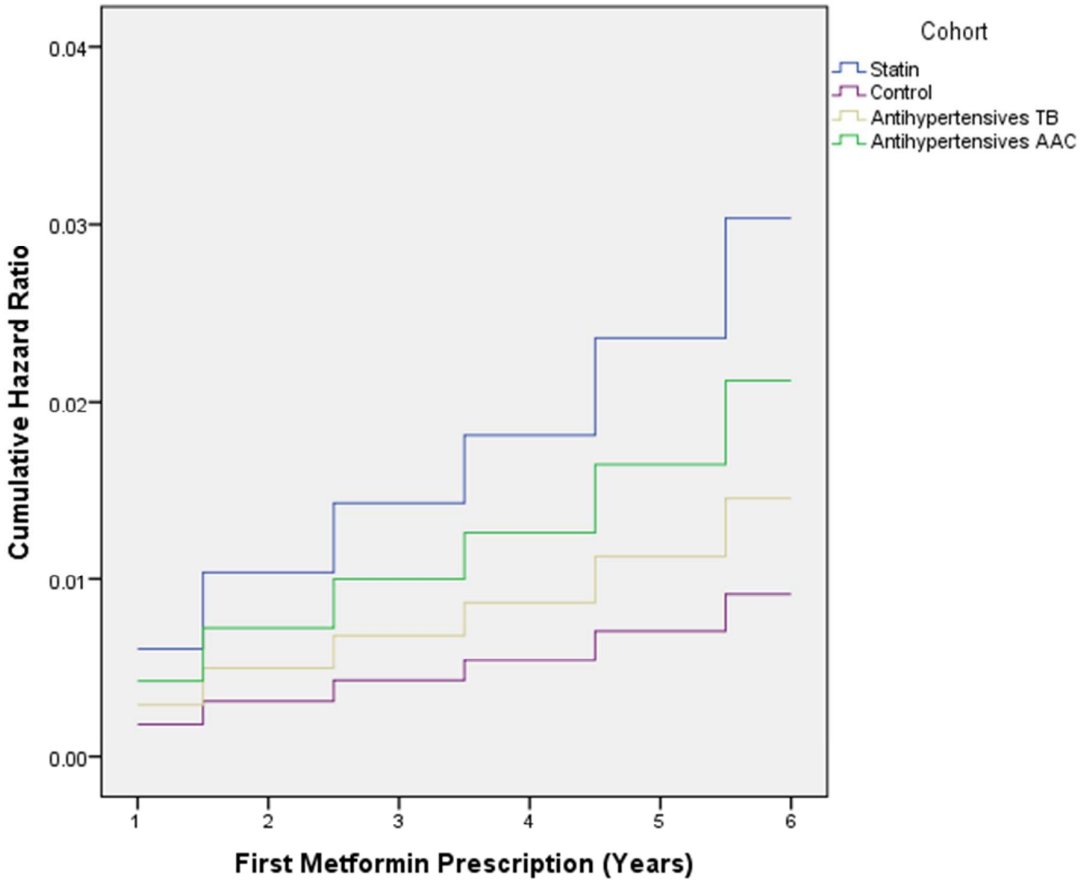


Figure 2: Hazard Ratio for first prescription of metformin in each year for different study groups



Tables

Table 1: Cohort Demographic

Characteristics	OVERALL	Diclofenac Group	Anti-hypertensives TB Group	Anti-hypertensives AAC Group	Statins Group
	% (n)	% (n)	% (n)	% (n)	% (n)
Recruited number of patients	100 (32086)	22.25 (7140)	17.98 (5769)	20.46 (6565)	39.31 (12612)
Sex					
Male	52.98 (16999)	49.69 (3548)	31.20 (1800)	49.52 (3251)	66.60 (8400)
Female	47.01 (15083)	50.29 (3591)	68.80 (3969)	50.46 (3313)	33.38 (4210)
Unknown	4	1	0	1	2
Age					
40-44	22.0 (7045)	33.8 (2415)	20.4 (1179)	19.1 (1255)	17.4 (2196)
45-49	22.7 (7289)	26.4 (1886)	22.4 (1295)	22.0 (1445)	21.1 (2663)
50-54	26.1 (8367)	21.1 (1509)	27.4 (1582)	27.3 (1794)	27.6 (3482)
55-59	29.2 (9385)	18.6 (1330)	29.7 (1713)	31.5 (2071)	33.9 (4271)
Ethnicity					
NZ European[+]	69.46 (22287)	61.3 (4377)	76.39 (4407)	69.23 (4545)	71.03 (8958)
Maori	7.05 (2261)	14.26 (1018)	5.91 (341)	7.75 (509)	3.12 (393)
Pacific Island*	3.48 (1116)	8.75 (625)	1.87 (108)	2.83 (186)	1.56 (197)
Asian[#]	5.31 (1703)	5.04 (360)	5.23 (302)	4.90 (322)	5.70 (719)
Others^	0.93 (298)	1.44 (103)	0.81 (47)	0.70 (46)	0.81 (102)
Unknown[@]	4421	657	564	957	2243

Table 2: Incidence rate for first prescription of metformin

Groups	Person-time	Number of new cases	Incidence rate cases per person year	Incidence rate cases per 1,000 person- years
Diclofenac	33190	84	0.00253	2.5
TB	30791	85	0.00276	2.8
AAC	35383	150	0.00424	4.2
Statin	70455	391	0.00555	5.5

Table 3: 6 year risk of first prescription of metformin in study groups compared to control group

			Univariable Analysis			Multivariable Analysis[1,2]		
	Total	**Metformin (%)**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Cohort								
Diclofenac	7140	84 (1.2)	1.00			1.00		
TB	5769	85 (1.5)	1.25	0.93-1.70	0.142	1.59	1.15-2.20	0.005
AAC	6565	150 (2.3)	1.95	1.50-2.55	<0.0001	2.32	1.74-3.09	<0.0001
Statin	12612	391 (3.1)	2.66	2.10-3.37	<0.0001	3.31	2.56-4.30	<0.0001

[1]Cox Regression
[2]Adjusting for: Age, sex, and ethnicity.

Appendices

Appendix 1: Summary of study analysis categories and drug lists

Groups	List of drugs	Sub group
Exclusion criteria Drugs (associated with increased risk of diabetes or are treatment for diabetes)	Insulin Neutral, Insulin Isophane, Insulin Isophane with Insulin Neural, Insulin Lispro with Insulin Lispro Protamine, Insulin Glargine, Insulin Aspart, Insulin Glulisine, Insulin lispro, Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone, Spironolactone, Cyproterone Acetate with Ethinyloestrodiol, Cyproterone acetate, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone tablets, Methylprednisone, Prednisone Sodium Phosphate, Prednisone	
Diclofenac group	Diclofenac Sodium enteric coated tablets, Diclofenac Sodium Long Acting Tablets	
Anti-hypertensives TB Group	Atenolol, Carvedilol, Celiprolol, Labetalol, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Propanolol, Sotalol, Labetalol	BB
	Bendrofluazide, Chlorthalidone, Indapamide, Chlorothiazide	T
Anti-hypertensives AAC Group	Captopril, Cilazapril, Enalapril, Lisinopril, Quinapril	ACEi
	Candersartan, Losartan	ARB
	Amlodipine, Felodipine, Isradipine, Nifedipine, Diltiazem Hydrochloride, Verapamil Hydrochloride	CC
Statin Group	Atorvastatin, Pravastatin, Simvastatin	
Outcome Group	Metformin Hydrochloride	

Appendix 2: Number of patients persistent with medications in each cohort in every study year

Cohort\Years	2006	2007	2008	2009	2010	2011	%
TB	5769	5202	4834	4547	4339	4115	71.3%
AAC	6565	5958	5583	5227	4955	4654	70.9%
STATIN	12612	11752	11186	10757	10187	9593	76.1%

Appendix 3: 6 year risk of first prescription of metformin in different patient demographics.

					Univariable Analyses			Multivariable Analyses[1,2]		
	Total	**%**	**Metformin**	**%**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex										
M	16999	53.0%	409	1.3%	1.00	-	-	1.00	-	-
F	15083	47.0%	301	0.9%	0.83	0.71-0.96	0.01	0.85	0.72-1.00	0.05
Unknown	4	0.00%	0	0.0%	-	-	-	-	-	-
Age										
40-44	7045	22.0%	163	0.5%	1.00	-	-	1.00	-	-
45-49	7289	22.7%	156	0.5%	0.93	0.74-1.15	0.49	0.87	0.69-1.10	0.25
50-54	8367	26.1%	185	0.6%	0.96	0.77-1.18	0.67	0.88	0.70-1.11	0.27
55-59	9385	29.2%	206	0.6%	0.95	0.77-1.17	0.61	0.96	0.77-1.20	0.71
Ethnicity										
European	22287	69.5%	384	1.2%	1.00	-	-	1.00	-	-
Maori	2261	7.0%	66	0.2%	1.70	1.31-2.21	<0.01	2.23	1.71-2.91	<0.01
PI	1116	3.5%	49	0.2%	2.57	1.91-3.47	<0.01	3.57	2.63-4.85	<0.01
Asian	1703	5.3%	106	0.3%	3.69	2.98-4.57	<0.01	3.72	3.00-4.62	<0.01
Other	298	0.9%	11	0.0%	2.17	1.18-3.93	0.01	2.43	1.33-4.43	<0.01

Note:

[+]European = NZ European, Other European, European NFD

*Pacific Island = Cook Island, Fijian, Niuean, Samoan, Tokelauan, Tongan, Pacific Island, Other Pacific Island

[#]Asian = Asian, Chinese, Other Asian, Indian, Southeast Asian

^Others = African, Latin American/Hispanic, Middle Eastern, other, other ethnicity

[1]Cox Regression

[2]Adjusting for: Age, sex, ethnicity, and study cohorts.

Appendix 4: 743 Patients who swapped study groups during study period

Group Swaps (From/To)	No Metformin	Metformin	Total Patient
Diclofenac Group	**207**	**13**	**220**
Antihypertensives TB Group	78	1	79
Antihypertensives AAC Group	56	1	57
Statin Group	73	11	84
Antihypertensives TB Group	**198**	**8**	**206**
Diclofenac Group	82	1	83
Antihypertensives AAC Group	98	6	104
Study Group	18	1	19
Antihypertensives AAC Group	**163**	**3**	**166**
Diclofenac Group	40	1	41
Antihypertensives TB Group	107	1	108
Statin Group	16	1	17
Statin Group	**149**	**2**	**151**
Diclofenac Group	104	1	105
Antihypertensives TB Group	24	0	24
Antihypertensives AAC Group	21	1	22
Total	**717**	**26**	**743**

Research Protocol

Project title: Drug Induced Diabetes: A Case of statins versus antihypertensives.
Date: April 2012
Principal investigator: Dr. Olivia Currie
Supervisor: Assoc. Professor Derelie Mangin

Project summary:

This is an observational prospective cohort study to assess whether the incidence of new onset diabetes is increased with the use of statin drugs; when compared to blood pressure drugs, and to a control group. The importance is indicated from previous experience with unwanted increased rate of cardiovascular events due to new onset diabetes with use of certain antihypertensives (1, 2). We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in 5 years. We will compare this with groups of patients with first prescription of drugs for high blood pressure (high diabetes risk control group), and patients with none of these prescriptions but who have attendance for an ACC-related condition (normal control group). We will use clinical data held electronically on drug prescriptions and laboratory tests on the Pegasus Health Community ePrescription system.

Background:

In modern cardiovascular risk management, statin drugs are popular and beneficial adjuncts for prevention of primary and secondary cardiovascular events. All forms of pharmacotherapy have side effects. Common to statin drugs are increases in liver transaminases, muscle aches, cognition impairment and rhabdomyolysis, albeit rare. However, there is now new evidence to suggest that statin drugs could have drug class effect in causing diabetes in previously non-diabetic individuals (3).

Statin induced diabetes was first observed in the JUPITER trial (4) with relation to Rosuvostatin use in non-diabetic subjects. It was reported by physicians involved in the trial as a secondary outcome and concluded that more evidence is needed to confirm the observed effect. Following that, multiple meta-analyses correlated an overall 9% increased risk of diabetes with statin use with newer evidence showing association with Pravastatin and Rosuvastatin use (5-8). The meta-analyses, should be interpreted with caution as diabetes is often not the primary outcome in the trials analysed. Recent evidence indicates the risk of new onset diabetes with statin use could also be dose dependent (9). These drugs may still have an overall cardiovascular benefit nonetheless (10).

One of the difficulties in assessing the extent of the risk is that patients of higher cardiovascular risk also carry an increased risk of developing diabetes. In order that the risks and benefits of these drugs to be properly considered by patients and doctors, decisions whether to use them, it is very important to understand the extend of this risk in already high risk patients as development of diabetes further increases cardiovascular risk and carries its own morbidity, reducing lifespan and quality of life.

Objective

To assess comparative rates of diabetes development in patients in primary care population started on statin drugs; by comparing them with rates of diabetes development in patients also at high risk of cardiovascular disease started on blood pressure medications but not on statins, and with normal control group.

Methodology:

We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in the subsequent 5 years. We will compare these rates in patients with first prescription of drugs for high blood pressure (high diabetes risk control group) and patients with none of these prescriptions (normal control group). Patients in the normal control group are those with without any of these prescriptions, and are recruited

from attendance for ACC-related conditions in the Canterbury region. We will use clinical data held electronically on drug prescriptions and laboratory tests on the Pegasus Health Community ePrescription system.

Study Design: Prospective cohort study using routinely collected data
Study population: Canterbury residents enrolled in Pegasus Health between ages 40 and 60, who are commenced on either on statin drugs, or on antihypertensives (high risk control group), or who have an ACC claim (low risk control goup) in the years 2005 to 2007.
Exclusion: Patients who previously have diabetes, glucose intolerance, polycystic ovarian syndrome, and those who are already on metformin, thiazides and corticosteroids (all known to increase diabetes risk).
Other variables: From the clinical records where available the age, gender and sex; family history of diabetes; body mass index; LDL level measured; blood glucose or HbA1c measured; and smoking status. The purpose is to describe other cardiovascular risk factors, if any, for groups of patients with prescription for statin drugs or drugs for high blood pressure.
Follow up: Cohort will be followed up for 5 years.
Outcome measure: First prescription of Meformin, or HbA1c result indicating diabetes.
Analysis: Proportions compared between statin started, antihypertensives known to have increased diabetes risk (thiazides and beta-blocker), antihypertensives known to have no increased diabetic risk (ACE-inhibitors, ARBs, calcium channel blockers) and ACC control group.

Ethical considerations:

No ethics committee is required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006*.
Pegasus Health has a method for anonymously electronically extracting and linking these data. Patients are aware when they sign their enrolment form for Pegasus Health that their data may be used anonymously for quality improvement. Data will be de-identified at the point of extraction from the clinical record. Collection of such data will be stored in de-identified manner. This study has been approved for support by the Pegasus Health Research, Audit and Evaluation committee.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ (refer Manuscript Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ (refer Manuscript Page 4)
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ (refer Manuscript Page 6)
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ (refer Manuscript Page 6)
Methods			
Study design	4	Present key elements of study design early in the paper	✓ (refer Manuscript Page 7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ (refer Manuscript Page 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✓ (refer Manuscript Page 7-8)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ (refer Manuscript Page 8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ (refer Manuscript Page 7)
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ (refer Manuscript Page 8)
Statistical	12	(*a*) Describe all statistical methods, including those used to control	✓

methods		for confounding	(refer Manuscript Page 8)
		(*b*) Describe any methods used to examine subgroups and interactions	✓ (refer Manuscript Page 8)
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✓ (refer Manuscript Page 8)
		(*e*) Describe any sensitivity analyses	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ (refer Manuscript Page 9)
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	✓ (Figure 1, page 17 Manuscript)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ (refer Manuscript Page 9, and table 1, page 19 Manuscript)
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✓ (refer Manuscript Page 9)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓ (refer Manuscript Page 9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ (refer Manuscript Page 9, Figure 2 and Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓ (refer Manuscript

			Page 10)
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ (refer Manuscript Page 11)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ (refer Manuscript Page 12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ (refer Manuscript Page 13)
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ (refer Manuscript Page 13)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ (refer Manuscript Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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MANUSCRIPT

Title Page

Title

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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Key Words

Statins, diabetes, antihypertensives, metformin, primary care, electronic prescription.

Abbreviations

ACEi = angiotensin converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CCB = calcium channel blockers

Study Groups:

Antihypertensives TB = thiazides and beta-blockers.

Antihypertensive AAC = angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.

Abstract

Objective: Recent studies suggest statins increase the risk of subsequent diabetes with a clear dose response effect. However patients prescribed statins have a higher background risk of diabetes. This national cohort study aims to provide an estimate of the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, and those with already higher background risk on cardiovascular risk modifying drugs and a control drug.

Design: Longitudinal cohort study

Setting: Use of routinely collected data from a complete national primary care electronic prescription database in New Zealand.

Participants: 32,086 patients aged between 40 and 60 years in 2005 were eligible and assigned to four non-overlapping groups receiving their first prescription for:

1. diclofenac (healthy population) n=7140
2. antihypertensives thought likely to induce diabetes (thiazides and beta-blockers) n=5769
3. antihypertensives thought less likely to induce diabetes (ACEi, ARBs, CCBs) n= 6565
4. statins n= 12 612

Outcome: Numbers of first metformin prescriptions were compared between these groups from 2006 to 2011.

Results: Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01), followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribed

antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac.

Conclusions: These findings further support the link between statin use and new-onset diabetes; and suggest the understanding of diabetes risk associated with different antihypertensive drug classes may bear practice modification. This provides important information for future research and for prescribers and patients when considering the risks and benefits of different types of cardiovascular risk modifying drugs.

Article Summary

Article focus:

- Estimates the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, other groups of cardiovascular risk modifying drugs indicating higher background risk and a control drug.

Key messages:

- Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01) when compared to control drug
- Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed ACEi, ARB and CCB (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and thiazides and beta-blockers (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins.

Strengths:

- A national cohort study using electronic prescription database
- First longitudinal study to compare incidence of subsequent diabetes between statins and antihypertensives with a control drug
- First study to measure outcome by proxy of first metformin prescription as indication of significant diabetes development.

Limitations:

- Confounding factors like BMI, family history and socioeconomic status is not controlled for in this electronic database analysis. However, there is no indication that these factors are not unevenly distributed between the different “high risk” study groups.
- There is a small risk of misclassification for prescription of metformin for other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, but these are rare and are likely to only account for a small number of prescriptions.

Text

Introduction

Statins are widely used and have established benefits in the prevention of cardiovascular events.[1] However, recent studies suggested statins may also increase the risk of new-onset diabetes[2-8], which in turn increases risk of cardiovascular events. One meta-analysis reported the odds to be 9% (OR: 1.09; 95% Confidence Interval (CI) 1.02 to 1.17)[5], with other studies showing the association with pravastatin and rosuvostatin use.[3,4,7,9-11] More recent data indicates the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link.[6] Nevertheless, statins may still have an overall cardiovascular benefit.[5]

One of the difficulties in assessing the extent of this risk is that the patients with higher cardiovascular risk who are prescribed statins also carry an increased baseline risk of developing diabetes because of similar risk factors.[12-14] To understand the extent of the contributions of this increased baseline risk and the risk from the drugs themselves, we compared subsequent diabetes development in patients started on a statin with that in patients started on other drugs for cardiovascular risk management (antihypertensives) and with patients at low baseline risk. We used a complete national prescribing dataset[15] to create a population based cohort constructed of these three groups and compared the risk of subsequent development of clinically significant diabetes in each group.

Methods

Study design: Longitudinal cohort study using a national data set of de-identified routinely collected primary care electronic prescriptions of New Zealanders between ages 40 and 60, receiving first prescriptions of drugs studied (Appendix 1) in the year 2005.

Data source: Nationwide prescription data for the purpose of this study were sourced electronically from a complete national prescribing dataset, the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.[16] Community prescribing is electronic in primary care in New Zealand making this information accessible via NZHIS. Individual patients are assigned a unique identifier (NHI number) in

the New Zealand health system and this is attached to their prescriptions, allowing this to be the main data key linkage tool. All NHIs were de-identified at the point of data extraction, and automatically assigned a unique encrypted code.

Cohort construction: The cohort construction is illustrated in Figure 1 (Flow chart of cohort formation). The cohort included patients aged 40-60 in the year 2005 without prior prescription of excluded drugs and metformin (outcome drug) (Appendix 1), and all patients having received a prescription of at least one of the drugs of interest between 2005 and 2011. These drugs were statins, antihypertensives, diclofenac (comparator drug) or metformin (outcome drug). Diclofenac was chosen as the comparator drug to represent low diabetic risk patients presenting to primary care services with musculoskeletal injuries. Some antihypertensives are associated with subsequent development of diabetes. Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,[14,17-19] whereas little association has been made with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB).[18,19] Following the literature, those in the antihypertensive drug group were further divided into “Antihypertensives TB” for antihypertensives thought likely to increase diabetes risk (T and BB), and “Antihypertensives AAC” for antihypertensives thought less likely to do so (ACEi, ARB and CCB). A total of 195,194 records listed at least one of the drugs in the drug groups under study: Diclofenac, Antihypertensives TB, Antihypertensives AAC, and Statin groups. Patients belonging to two study groups concurrently in 2005 were then excluded. Data were further examined and cleaned to identify duplicate individuals, exclusion drugs and data entry error. This left 32,086 unique individuals to form the 2005 study cohort with 7140, 5769, 6565 and 12,612 in Diclofenac, Antihypertensives TB, Antihypertensives AAC, Statin groups respectively.

Exclusion: Patients who had a prescription for oral hypoglycaemics, insulin, oral corticosteroids (known to increase the risk of diabetes), or any of the study group medications of interest (Appendix 1) prior to 2005. The upper age limit was chosen to limit the inclusion of cardiovascular drugs prescribed for treatment of other cardiovascular conditions (e.g. heart failure).

Exposure: New Zealand adults who received their first prescription of statins, antihypertensives, or diclofenac in the calendar year 2005 without prior prescription of exclusion drugs and metformin.

Primary Outcome Measure: The proportion of patients receiving their first prescription of metformin in the calendar years 2006-2011. Metformin is the recommended first line treatment for newly diagnosed type 2 diabetes mellitus in New Zealand.[20]

Analysis: Patient baseline demographics were summarised using simple descriptive statistics and differences between cohorts were assessed using chi-square statistics calculated on OpenEpi online[21]. Since these are routinely collected electronic records, loss to follow up cannot be measured directly, and will be measured by proxy of medication persistence, death and emigration rate. Persistence with medications was determined as having at least one prescription a year, and persons-years were calculated based on this data. Death and emigration rate were calculated by direct age standardisation based on information available on Statistics New Zealand life-tables to estimate loss to follow up for our cohorts.[22] Incidence rates and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated to compare the risk of new-onset diabetes between Diclofenac group and the other three cohorts. HR were calculated in SPSS 20.0 for Windows (SPSS Inc) using cox proportional hazards regression, and multivariable analysis was used to adjust for differences in the demographic structure of the cohorts. All analyses were 2-sided.

Results:

Patient characteristics: The baseline characteristics of the cohorts are summarised in Table 1 (Cohort demographic). The sex of the patients differed by groups with a higher proportion of females (68.8%, $\chi^2(1) = 447.86$, $p < 0.001$) in the Antihypertensives TB group, and of males (66.6%, $\chi^2(1) = 545.35$, $p < 0.001$) in the statin group. The age of patients also differed across groups with patients receiving cardiovascular risk modifying drugs tending to be older than those in the diclofenac group ($\chi^2(1) = 1016.39$, $p < 0.001$). New Zealand European was the major ethnicity in all study groups. There were more Maori in the Diclofenac group with only a few in the statin group ($\chi^2(1) = 301.86$, $p < 0.001$). These differences between groups are adjusted for in the multivariable analysis.

Cohort characteristics and follow up: A total of 32,086 unique patients were eligible for analysis from the recruitment: 7140 for the Diclofenac group, 5769 for Antihypertentives TB group, 6565 for Antihypertensives AAC group, and 12,612 for the Statin group (Figure 1). Persistence with index medications for each group was 38.4%, 71.3%, 70.9% and 76.1% respectively (Appendix 2). The persistence within the control group was expectedly lower as diclofenac is not usually indicated for long term use. Loss of follow up due to deaths and emigration is estimated to be less than 2% of those who were not persistent with medications, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.

Primary analysis: Primary outcome results indicated that between 2006 and 2011, 710 patients within the four groups received their first prescription of metformin. This represents 1.2%, 1.5%, 2.3% and 3.1% of those exposed to Diclofenac, Antihypertensives TB, Antihypertensives AAC and Statin groups respectively. The incidence rates were 2.5, 2.8, 4.2 and 5.5 cases per 1,000 person years for first prescription of metformin (Table 2) accordingly. In the multivariable analysis, patients commenced on statins had the highest risk of receiving a first prescription of metformin in 6 years after exposure compared to the Control group (HR: 3.31; 95% CI: 2.56-4.30elevated; P < 0.01). In contrast to existing research, when compared to patients on diclofenac, patients on Antihypertensives AAC group have moderate risk of receiving their first prescription of metformin in 6 years (HR: 2.32; 95% CI: 1.74-3.09; P < 0.01), and patients in the Antihypertensives TB group had a slightly elevated risk (HR: 1.59; 95% CI: 1.15-2.20; P < 0.01) (Table 3). Our analysis indicates a duration-response: The HR of developing new-onset diabetes was approximately constant over the duration of the study as demonstrated by the plot for the cumulative hazard ratios for the first metformin prescription in each study cohort (Figure 2), adjusting for age, sex, and ethnicity.

Subgroup analyses: Patient demographics were analysed to assess other characteristics of recipients of first metformin prescription (Appendix 3). Cox regression model analysis revealed that females had a lower risk than males (HR = 0.85, 95% CI: 0.72-1.00, p = 0.05), and there was no difference in risk between age groups within our cohort age range. However, risks were increased with all other ethnicities when

compared to New Zealand European. Pacific Island and Asian ethnic group had the highest risk at HR 3.57 (95%CI: 2.63-4.85, P < 0.01) and HR 3.72 (95% CI: 3.00-4.62, P<0.01) respectively.

To assess whether those at risk of developing diabetes were prescribed higher doses of their prescribed medications, the drug doses of their first prescribed indexed medications in 2005 among those prescribed metformin were assessed. In the Statin group, 96.9% of patients were prescribed 40mg and less of both simvastatin and atorvastatin. For patients in the Antihypertensives TB group, 78.8% of patients were on beta blockers and 88% of those on thiazides were on 2.5mg of bendrofluazide. This indicates patients commenced on metformin were prescribed conservative dosing of cardiovascular risk modifying drugs.

There were 743 patients who swapped study cohorts during the study period. Of these, 220 were from the Diclofenac group, 206 from Antihypertensives TB group, 166 from Antihypertensives AAC group and 151 from Statin group (Appendix 4). Excluding these patients in a per-protocol analysis had little effect on the hazard ratios compared to the intention to treat analysis (results of analysis available but not included), which could indicate the effect is rare or that the exposure is steady.

Discussion

Patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac. Patients receiving a first prescription for statins were at the highest risk of subsequently developing clinically significant diabetes, with a risk three times that of those prescribed diclofenac. Patients prescribed ACE inhibitors, ARBs or calcium channel blockers were the next highest risk, being twice as likely to receive a metformin prescription, while those prescribed thiazides and beta-blockers were only at slightly increased risk.

The association between new-onset diabetes, as estimated by first metformin prescriptions, and initiation of statins found in this study is consistent with recent reports. However, the risk in this population was lower (3.1%) than the 9% risk reported in meta-analyses.[23-25] More recent publications have identified the risks of new-onset diabetes with statin drug use ranging from 2.4% to 8.5%. [23-26] In contrast to our study, the diagnosis of diabetes in these other studies were identified by indicators such as disease classification

recording, or intermediate indicators such as laboratory investigations of HbA1c and fasting serum glucose readings. This will draw in milder levels of hyperglycemia where lifestyle changes can still be the first line of management and where laboratory threshold determines disease rates. This study is the first to identify the incident rate of clinically significant diabetes in patients prescribed statins as indicated by the first prescription of metformin in a non-research population. This is an outcome that matters to patients.

Our study is also the first to compare the risks of diabetes development in patients on statins against patients on other cardiovascular risk modifying drugs who might also be considered to be 'high risk'. Patients initiated on antihypertensive drugs were, like those prescribed statins, at greater risk of developing diabetes compared to those on diclofenac. Our findings therefore allow an assessment of the comparative risks of new-onset diabetes in patients with already higher risk on different classes of antihypertensives. There may be several explanations for the differences seen. Firstly, it may be a true association. Secondly, it may be that patients with risk factors for diabetes (such as obesity) are less likely to be prescribed treatment with associated increased risk of diabetes.[14,27] Hence, they are more likely to receive prescriptions of ACEi or ARBs for management of hypertension due to a lesser known risk of inducing diabetes. We also observed conservative dosing in patients on thiazides and beta-blockers, which may attenuate the risk. Presence of metabolic syndrome risk factors also increased the risk of subsequent glucose elevation, on as well as off statin use.[28] This study is not able to answer these questions, but raises these for future research.

Since all data collected are electronic records, patient persistence with medication can be grossly assessed. There were high rates of persistence with medications within the study groups, in particular to the antihypertensives and the statins. Given only a total of 743 patients (2.3% of 2005 cohort) swapped into different study groups during the study period, there were relatively clean groups for analyses of risks.

The development of clinically significant diabetes was estimated using a proxy measure, utilising the first prescription of metformin. The validity of using routinely collected and electronically stored prescription data for diagnosing diabetes has been previously demonstrated.[15,29] The use of routinely collected data also provides access to a complete national population based cohort. We were able to assess this cohort

longitudinally over a period of 6 years in a representative primary care population rather than a trial population with tightly constrained entry criteria.

Limitations

Our study has several limitations. The nature of the electronic datasets available means it is not possible to obtain other factors contributing to cardiovascular and diabetes risks to more precisely define subgroups and allow direct comparison of the cohorts' baseline levels of risk of developing diabetes (e.g. body mass index and family history). These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study.

There is also the risk of misclassification. Metformin may also be prescribed for management of other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, however this is likely to account for only a small proportion of prescriptions. With first prescription of metformin, we have also excluded patients who present infrequently to their primary health care providers for well-checks and routine follow up (missing new-onset diabetes) and those who may have presented acutely with diabetic emergency (as they will be commenced on alternate hypoglycaemic agents).

It is also uncertain as to how frequently these patients are tested for diabetes mellitus in the primary care setting, as the electronic system is not currently linked to laboratory data. The study is also unable to control for the duration of mild hyperglycaemia prior to commencement of metformin.

In this study, we have not distinguished between the various statin doses and formulations.

Conclusions

Patients initiating treatment with any of the index cardiovascular risk modifying drugs have some risk of developing clinically significant new-onset diabetes compared to those prescribed diclofenac. However, patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Patients prescribed ACE inhibitors, angiotensin II receptor blockers and calcium channel blockers were also at moderately increased risk, while patients prescribed thiazides and beta-

blockers only appeared to have a mildly increased risk. The effect seen carries an exposure duration-response groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers. This provides additional information on the comparative safety of these drugs in a real world setting in primary care, where the bulk of these prescriptions are likely to be initiated. This is useful information for doctors and patients considering the balance of harms against the potential for benefit of both statins and different cardiovascular risk modifying medications in different populations.

Further Research

Whether there is an additive risk of inducing diabetes with combinations of different cardiovascular risk modifying drugs is currently unknown, and an important area for research to inform decision making on prescribing, given the prevalence of multi-morbidity and likely co-prescription. This is subject to a further study. It is also unclear what effect this additional risk of diabetes will have on morbidity and mortality for patients. Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely only as a risk factor for other disease, predominantly cardiovascular disease.

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Prior Presentations

None

Ethics Application

As all data were de-identified by encryption, ethics approval was confirmed as not required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006* (Upper South B Regional Ethics Committee, Ethics ref: URB/12/EXP/022).

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Conflict of Interest Statement

None

Prior Publication

None

Data Sharing

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

Contributorship

Olivia Currie, Dee Mangin, Bianca McKinnon-Gee and Paul Bridgford design the study. Bianca McKinnon-Gee ran the search for electronic prescription data according to study protocol. Olivia Currie designed data

collection tools, monitored data collection for the whole study, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. Olivia Currie and Jonathan Williman analysed the data. Olivia Currie, Dee Mangin and Jonathan Williman revised the draft paper.

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MANUSCRIPT

Title Page

Title

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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Ethics Application

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Acknowledgements

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Conflict of Interest Statement

None

Prior Publication

None

Data Sharing

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

Key Words

Statins, diabetes, antihypertensives, metformin, primary care, electronic prescription.

Abbreviations

ACEi = angiotensin converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CCB = calcium channel blockers

Study Groups:

Antihypertensives TB = thiazides and beta-blockers.

Antihypertensive AAC = angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.

Abstract

Objective: Recent studies suggest statins increase the risk of subsequent diabetes with a clear dose response effect. However patients prescribed statins have a higher background risk of diabetes. This national cohort study aims to provide an estimate of the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, and those with already higher background risk on cardiovascular risk modifying drugs and a control drug.

Design: Longitudinal cohort study

Setting: Use of routinely collected data from a complete national primary care electronic prescription database in New Zealand.

Participants: 32,086 patients aged between 40 and 60 years in 2005 were eligible and assigned to four non-overlapping groups receiving their first prescription for:

1. diclofenac (healthy population) n=7140
2. antihypertensives thought likely to induce diabetes (thiazides and beta-blockers) n=5769
3. antihypertensives thought less likely to induce diabetes (ACEi, ARBs, CCBs) n= 6565
4. statins n= 12 612

Outcome: Numbers of first metformin prescriptions were compared between these groups from 2006 to 2011.

Results: Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01), followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribed

antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac.

Conclusions: These findings further support the link between statin use and new-onset diabetes; and suggest the understanding of diabetes risk associated with different antihypertensive drug classes may bear practice modification. This provides important information for future research and for prescribers and patients when considering the risks and benefits of different types of cardiovascular risk modifying drugs.

Article Summary

Article focus:

- Estimates the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, other groups of cardiovascular risk modifying drugs indicating higher background risk and a control drug.

Key messages:

- Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01) when compared to control drug
- Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed ACEi, ARB and CCB (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and thiazides and beta-blockers (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins.

Strengths:

- A national cohort study using electronic prescription database
- First longitudinal study to compare incidence of subsequent diabetes between statins and antihypertensives with a control drug
- First study to measure outcome by proxy of first metformin prescription as indication of significant diabetes development.

Limitations:

- Confounding factors like BMI, family history and socioeconomic status is not controlled for in this electronic database analysis. However, there is no indication that these factors are not unevenly distributed between the different “high risk” study groups.
- There is a small risk of misclassification for prescription of metformin for other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, but these are rare and are likely to only account for a small number of prescriptions.

Text

Introduction

Statins are widely used and have established benefits in the prevention of cardiovascular events.[1] However, recent studies suggested statins may also increase the risk of new-onset diabetes[2-8], which in turn increases risk of cardiovascular events. One meta-analysis reported the odds to be 9% (OR: 1.09; 95% Confidence Interval (CI) 1.02 to 1.17)[5], with other studies showing the association with pravastatin and rosuvostatin use.[3,4,7,9-11] More recent data indicates the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link.[6] Nevertheless, statins may still have an overall cardiovascular benefit.[5]

One of the difficulties in assessing the extent of this risk is that the patients with higher cardiovascular risk who are prescribed statins also carry an increased baseline risk of developing diabetes because of similar risk factors.[12-14] To understand the extent of the contributions of this increased baseline risk and the risk from the drugs themselves, we compared subsequent diabetes development in patients started on a statin with that in patients started on other drugs for cardiovascular risk management (antihypertensives) and with patients at low baseline risk. We used a complete national prescribing dataset[15] to create a population based cohort constructed of these three groups and compared the risk of subsequent development of clinically significant diabetes in each group.

Methods

Study design: Longitudinal cohort study using a national data set of de-identified routinely collected primary care electronic prescriptions of New Zealanders between ages 40 and 60, receiving first prescriptions of drugs studied (Appendix 1) in the year 2005.

Data source: Nationwide prescription data for the purpose of this study were sourced electronically from a complete national prescribing dataset, the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.[16] Community prescribing is electronic in primary care in New Zealand making this information accessible via NZHIS. Individual patients are assigned a unique identifier (NHI number) in

the New Zealand health system and this is attached to their prescriptions, allowing this to be the main data key linkage tool. All NHIs were de-identified at the point of data extraction, and automatically assigned a unique encrypted code.

Cohort construction: The cohort construction is illustrated in Figure 1 (Flow chart of cohort formation). The cohort included patients aged 40-60 in the year 2005 without prior prescription of excluded drugs and metformin (outcome drug) (Appendix 1), and all patients having received a prescription of at least one of the drugs of interest between 2005 and 2011. These drugs were statins, antihypertensives, diclofenac (comparator drug) or metformin (outcome drug). Diclofenac was chosen as the comparator drug to represent low diabetic risk patients presenting to primary care services with musculoskeletal injuries. Some antihypertensives are associated with subsequent development of diabetes. Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,[14,17-19] whereas little association has been made with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB).[18,19] Following the literature, those in the antihypertensive drug group were further divided into "Antihypertensives TB" for antihypertensives thought likely to increase diabetes risk (T and BB), and "Antihypertensives AAC" for antihypertensives thought less likely to do so (ACEi, ARB and CCB). A total of 195,194 records listed at least one of the drugs in the drug groups under study: Diclofenac, Antihypertensives TB, Antihypertensives AAC, and Statin groups. Patients belonging to two study groups concurrently in 2005 were then excluded. Data were further examined and cleaned to identify duplicate individuals, exclusion drugs and data entry error. This left 32,086 unique individuals to form the 2005 study cohort with 7140, 5769, 6565 and 12,612 in Diclofenac, Antihypertensives TB, Antihypertensives AAC, Statin groups respectively.

Exclusion: Patients who had a prescription for oral hypoglycaemics, insulin, oral corticosteroids (known to increase the risk of diabetes), or any of the study group medications of interest (Appendix 1) prior to 2005. The upper age limit was chosen to limit the inclusion of cardiovascular drugs prescribed for treatment of other cardiovascular conditions (e.g. heart failure).

Exposure: New Zealand adults who received their first prescription of statins, antihypertensives, or diclofenac in the calendar year 2005 without prior prescription of exclusion drugs and metformin.

Primary Outcome Measure: The proportion of patients receiving their first prescription of metformin in the calendar years 2006-2011. Metformin is the recommended first line treatment for newly diagnosed type 2 diabetes mellitus in New Zealand.[20]

Analysis: Patient baseline demographics were summarised using simple descriptive statistics and differences between cohorts were assessed using chi-square statistics calculated on OpenEpi online[21]. Since these are routinely collected electronic records, loss to follow up cannot be measured directly, and will be measured by proxy of medication persistence, death and emigration rate. Persistence with medications was determined as having at least one prescription a year, and persons-years were calculated based on this data. Death and emigration rate were calculated by direct age standardisation based on information available on Statistics New Zealand life-tables to estimate loss to follow up for our cohorts.[22] Incidence rates and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated to compare the risk of new-onset diabetes between Diclofenac group and the other three cohorts. HR were calculated in SPSS 20.0 for Windows (SPSS Inc) using cox proportional hazards regression, and multivariable analysis was used to adjust for differences in the demographic structure of the cohorts. All analyses were 2-sided.

Results:

Patient characteristics: The baseline characteristics of the cohorts are summarised in Table 1 (Cohort demographic). The sex of the patients differed by groups with a higher proportion of females (68.8%, $\chi^2(1) = 447.86$, $p < 0.001$) in the Antihypertensives TB group, and of males (66.6%, $\chi^2(1) = 545.35$, $p < 0.001$) in the statin group. The age of patients also differed across groups with patients receiving cardiovascular risk modifying drugs tending to be older than those in the diclofenac group ($\chi^2(1) = 1016.39$, $p < 0.001$). New Zealand European was the major ethnicity in all study groups. There were more Maori in the Diclofenac group with only a few in the statin group ($\chi^2(1) = 301.86$, $p < 0.001$). These differences between groups are adjusted for in the multivariable analysis.

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Subgroup analyses: Patient demographics were analysed to assess other characteristics of recipients of first metformin prescription (Appendix 3). Cox regression model analysis revealed that females had a lower risk than males (HR = 0.85, 95% CI: 0.72-1.00, p = 0.05), and there was no difference in risk between age groups within our cohort age range. However, risks were increased with all other ethnicities when

compared to New Zealand European. Pacific Island and Asian ethnic group had the highest risk at HR 3.57 (95%CI: 2.63-4.85, P < 0.01) and HR 3.72 (95% CI: 3.00-4.62, P<0.01) respectively.

To assess whether those at risk of developing diabetes were prescribed higher doses of their prescribed medications, the drug doses of their first prescribed indexed medications in 2005 among those prescribed metformin were assessed. In the Statin group, 96.9% of patients were prescribed 40mg and less of both simvastatin and atorvastatin. For patients in the Antihypertensives TB group, 78.8% of patients were on beta blockers and 88% of those on thiazides were on 2.5mg of bendrofluazide. This indicates patients commenced on metformin were prescribed conservative dosing of cardiovascular risk modifying drugs.

There were 743 patients who swapped study cohorts during the study period. Of these, 220 were from the Diclofenac group, 206 from Antihypertensives TB group, 166 from Antihypertensives AAC group and 151 from Statin group (Appendix 4). Excluding these patients in a per-protocol analysis had little effect on the hazard ratios compared to the intention to treat analysis (results of analysis available but not included), which could indicate the effect is rare or that the exposure is steady.

Discussion

Patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac. Patients receiving a first prescription for statins were at the highest risk of subsequently developing clinically significant diabetes, with a risk three times that of those prescribed diclofenac. Patients prescribed ACE inhibitors, ARBs or calcium channel blockers were the next highest risk, being twice as likely to receive a metformin prescription, while those prescribed thiazides and beta-blockers were only at slightly increased risk.

The association between new-onset diabetes, as estimated by first metformin prescriptions, and initiation of statins found in this study is consistent with recent reports. However, the risk in this population was lower (3.1%) than the 9% risk reported in meta-analyses.[23-25] More recent publications have identified the risks of new-onset diabetes with statin drug use ranging from 2.4% to 8.5%. [23-26] In contrast to our study, the diagnosis of diabetes in these other studies were identified by indicators such as disease classification

recording, or intermediate indicators such as laboratory investigations of HbA1c and fasting serum glucose readings. This will draw in milder levels of hyperglycemia where lifestyle changes can still be the first line of management and where laboratory threshold determines disease rates. This study is the first to identify the incident rate of clinically significant diabetes in patients prescribed statins as indicated by the first prescription of metformin in a non-research population. This is an outcome that matters to patients.

Our study is also the first to compare the risks of diabetes development in patients on statins against patients on other cardiovascular risk modifying drugs who might also be considered to be 'high risk'. Patients initiated on antihypertensive drugs were, like those prescribed statins, at greater risk of developing diabetes compared to those on diclofenac. Our findings therefore allow an assessment of the comparative risks of new-onset diabetes in patients with already higher risk on different classes of antihypertensives. There may be several explanations for the differences seen. Firstly, it may be a true association. Secondly, it may be that patients with risk factors for diabetes (such as obesity) are less likely to be prescribed treatment with associated increased risk of diabetes.[14,27] Hence, they are more likely to receive prescriptions of ACEi or ARBs for management of hypertension due to a lesser known risk of inducing diabetes. We also observed conservative dosing in patients on thiazides and beta-blockers, which may attenuate the risk. Presence of metabolic syndrome risk factors also increased the risk of subsequent glucose elevation, on as well as off statin use.[28] This study is not able to answer these questions, but raises these for future research.

Since all data collected are electronic records, patient persistence with medication can be grossly assessed. There were high rates of persistence with medications within the study groups, in particular to the antihypertensives and the statins. Given only a total of 743 patients (2.3% of 2005 cohort) swapped into different study groups during the study period, there were relatively clean groups for analyses of risks.

The development of clinically significant diabetes was estimated using a proxy measure, utilising the first prescription of metformin. The validity of using routinely collected and electronically stored prescription data for diagnosing diabetes has been previously demonstrated.[15,29] The use of routinely collected data also provides access to a complete national population based cohort. We were able to assess this cohort

longitudinally over a period of 6 years in a representative primary care population rather than a trial population with tightly constrained entry criteria.

Limitations

Our study has several limitations. The nature of the electronic datasets available means it is not possible to obtain other factors contributing to cardiovascular and diabetes risks to more precisely define subgroups and allow direct comparison of the cohorts' baseline levels of risk of developing diabetes (e.g. body mass index and family history). These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study.

There is also the risk of misclassification. Metformin may also be prescribed for management of other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, however this is likely to account for only a small proportion of prescriptions. With first prescription of metformin, we have also excluded patients who present infrequently to their primary health care providers for well-checks and routine follow up (missing new-onset diabetes) and those who may have presented acutely with diabetic emergency (as they will be commenced on alternate hypoglycaemic agents).

It is also uncertain as to how frequently these patients are tested for diabetes mellitus in the primary care setting, as the electronic system is not currently linked to laboratory data. The study is also unable to control for the duration of mild hyperglycaemia prior to commencement of metformin.

In this study, we have not distinguished between the various statin doses and formulations.

Conclusions

Patients initiating treatment with any of the index cardiovascular risk modifying drugs have some risk of developing clinically significant new-onset diabetes compared to those prescribed diclofenac. However, patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Patients prescribed ACE inhibitors, angiotensin II receptor blockers and calcium channel blockers were also at moderately increased risk, while patients prescribed thiazides and beta-

blockers only appeared to have a mildly increased risk. The effect seen carries an exposure duration-response groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers. This provides additional information on the comparative safety of these drugs in a real world setting in primary care, where the bulk of these prescriptions are likely to be initiated. This is useful information for doctors and patients considering the balance of harms against the potential for benefit of both statins and different cardiovascular risk modifying medications in different populations.

Further Research

Whether there is an additive risk of inducing diabetes with combinations of different cardiovascular risk modifying drugs is currently unknown, and an important area for research to inform decision making on prescribing, given the prevalence of multi-morbidity and likely co-prescription. This is subject to a further study. It is also unclear what effect this additional risk of diabetes will have on morbidity and mortality for patients. Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely only as a risk factor for other disease, predominantly cardiovascular disease.

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Figures

Figure 1: Flow chart of cohort formation

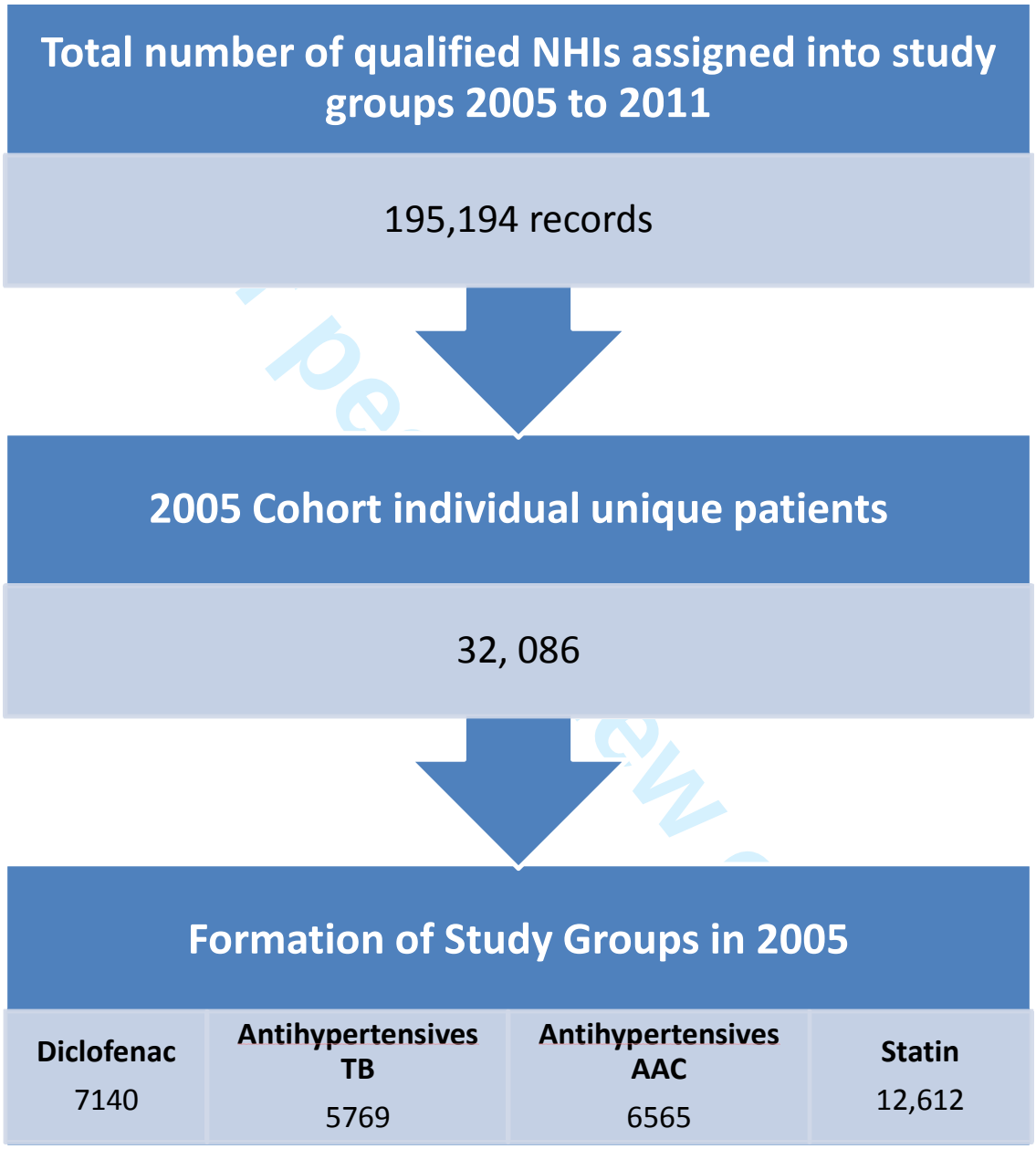
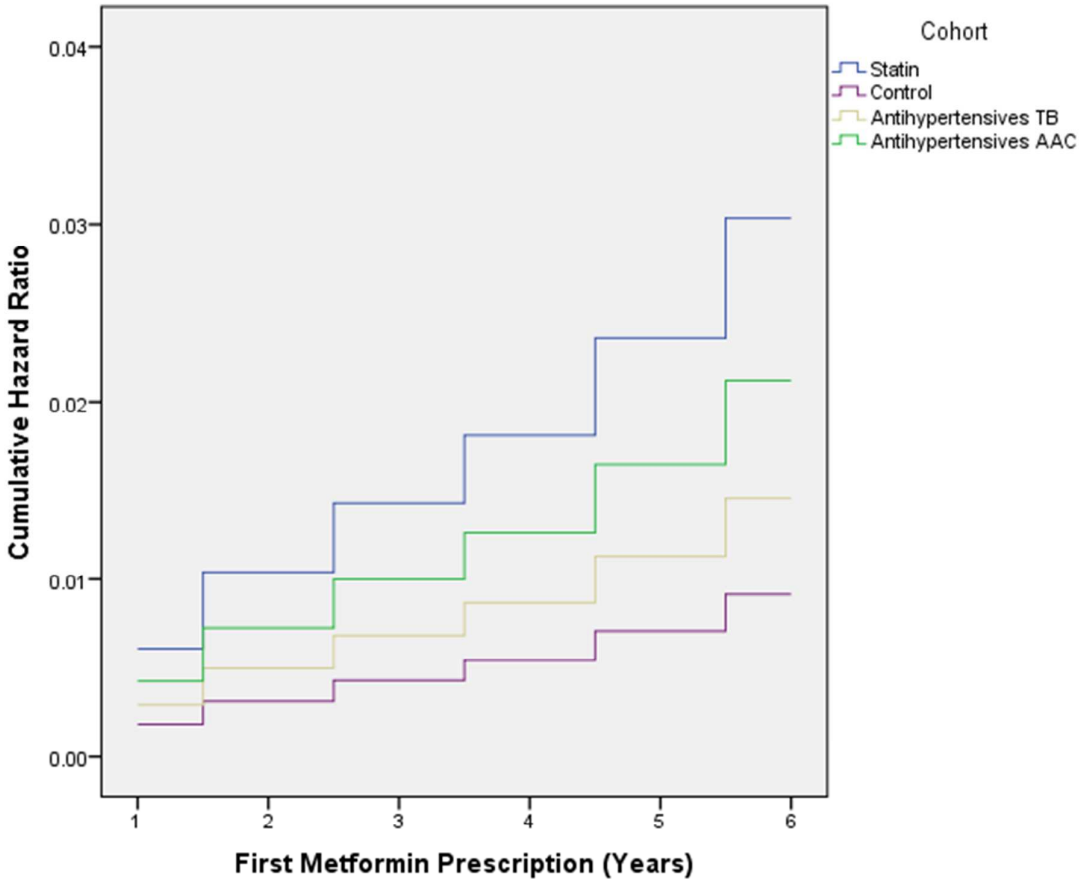


Figure 2: Hazard Ratio for first prescription of metformin in each year for different study groups



Tables

Table 1: Cohort Demographic

Characteristics	OVERALL	Diclofenac Group	Anti-hypertensives TB Group	Anti-hypertensives AAC Group	Statins Group
	% (n)	% (n)	% (n)	% (n)	% (n)
Recruited number of patients	100 (32086)	22.25 (7140)	17.98 (5769)	20.46 (6565)	39.31 (12612)
Sex					
Male	52.98 (16999)	49.69 (3548)	31.20 (1800)	49.52 (3251)	66.60 (8400)
Female	47.01 (15083)	50.29 (3591)	68.80 (3969)	50.46 (3313)	33.38 (4210)
Unknown	4	1	0	1	2
Age					
40-44	22.0 (7045)	33.8 (2415)	20.4 (1179)	19.1 (1255)	17.4 (2196)
45-49	22.7 (7289)	26.4 (1886)	22.4 (1295)	22.0 (1445)	21.1 (2663)
50-54	26.1 (8367)	21.1 (1509)	27.4 (1582)	27.3 (1794)	27.6 (3482)
55-59	29.2 (9385)	18.6 (1330)	29.7 (1713)	31.5 (2071)	33.9 (4271)
Ethnicity					
NZ European[+]	69.46 (22287)	61.3 (4377)	76.39 (4407)	69.23 (4545)	71.03 (8958)
Maori	7.05 (2261)	14.26 (1018)	5.91 (341)	7.75 (509)	3.12 (393)
Pacific Island*	3.48 (1116)	8.75 (625)	1.87 (108)	2.83 (186)	1.56 (197)
Asian[#]	5.31 (1703)	5.04 (360)	5.23 (302)	4.90 (322)	5.70 (719)
Others^	0.93 (298)	1.44 (103)	0.81 (47)	0.70 (46)	0.81 (102)
Unknown[@]	4421	657	564	957	2243

Table 2: Incidence rate for first prescription of metformin

Groups	Person-time	Number of new cases	Incidence rate cases per person year	Incidence rate cases per 1,000 person- years
Diclofenac	33190	84	0.00253	2.5
TB	30791	85	0.00276	2.8
AAC	35383	150	0.00424	4.2
Statin	70455	391	0.00555	5.5

Table 3: 6 year risk of first prescription of metformin in study groups compared to control group

			Univariable Analysis			Multivariable Analysis[1,2]		
	Total	**Metformin (%)**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Cohort								
Diclofenac	7140	84 (1.2)	1.00			1.00		
TB	5769	85 (1.5)	1.25	0.93-1.70	0.142	1.59	1.15-2.20	0.005
AAC	6565	150 (2.3)	1.95	1.50-2.55	<0.0001	2.32	1.74-3.09	<0.0001
Statin	12612	391 (3.1)	2.66	2.10-3.37	<0.0001	3.31	2.56-4.30	<0.0001

[1]Cox Regression
[2]Adjusting for: Age, sex, and ethnicity.

Appendices

Appendix 1: Summary of study analysis categories and drug lists

Groups	List of drugs	Sub group
Exclusion criteria Drugs (associated with increased risk of diabetes or are treatment for diabetes)	Insulin Neutral, Insulin Isophane, Insulin Isophane with Insulin Neural, Insulin Lispro with Insulin Lispro Protamine, Insulin Glargine, Insulin Aspart, Insulin Glulisine, Insulin lispro, Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone, Spironolactone, Cyproterone Acetate with Ethinyloestrodiol, Cyproterone acetate, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone tablets, Methylprednisone, Prednisone Sodium Phosphate, Prednisone	
Diclofenac group	Diclofenac Sodium enteric coated tablets, Diclofenac Sodium Long Acting Tablets	
Anti-hypertensives TB Group	Atenolol, Carvedilol, Celiprolol, Labetalol, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Propanolol, Sotalol, Labetalol	BB
	Bendrofluazide, Chlorthalidone, Indapamide, Chlorothiazide	T
Anti-hypertensives AAC Group	Captopril, Cilazapril, Enalapril, Lisinopril, Quinapril	ACEi
	Candersartan, Losartan	ARB
	Amlodipine, Felodipine, Isradipine, Nifedipine, Diltiazem Hydrochloride, Verapamil Hydrochloride	CC
Statin Group	Atorvastatin, Pravastatin, Simvastatin	
Outcome Group	Metformin Hydrochloride	

Appendix 2: Number of patients persistent with medications in each cohort in every study year

Cohort\Years	2006	2007	2008	2009	2010	2011	%
TB	5769	5202	4834	4547	4339	4115	71.3%
AAC	6565	5958	5583	5227	4955	4654	70.9%
STATIN	12612	11752	11186	10757	10187	9593	76.1%

Appendix 3: 6 year risk of first prescription of metformin in different patient demographics.

					Univariable Analyses			Multivariable Analyses[1,2]		
	Total	%	Metformin	%	HR	95% CI	P	HR	95% CI	P
Sex										
M	16999	53.0%	409	1.3%	1.00	-	-	1.00	-	-
F	15083	47.0%	301	0.9%	0.83	0.71-0.96	0.01	0.85	0.72-1.00	0.05
Unknown	4	0.00%	0	0.0%	-	-	-	-	-	-
Age										
40-44	7045	22.0%	163	0.5%	1.00	-	-	1.00	-	-
45-49	7289	22.7%	156	0.5%	0.93	0.74-1.15	0.49	0.87	0.69-1.10	0.25
50-54	8367	26.1%	185	0.6%	0.96	0.77-1.18	0.67	0.88	0.70-1.11	0.27
55-59	9385	29.2%	206	0.6%	0.95	0.77-1.17	0.61	0.96	0.77-1.20	0.71
Ethnicity										
European	22287	69.5%	384	1.2%	1.00	-	-	1.00	-	-
Maori	2261	7.0%	66	0.2%	1.70	1.31-2.21	<0.01	2.23	1.71-2.91	<0.01
PI	1116	3.5%	49	0.2%	2.57	1.91-3.47	<0.01	3.57	2.63-4.85	<0.01
Asian	1703	5.3%	106	0.3%	3.69	2.98-4.57	<0.01	3.72	3.00-4.62	<0.01
Other	298	0.9%	11	0.0%	2.17	1.18-3.93	0.01	2.43	1.33-4.43	<0.01

Note:

[+]European = NZ European, Other European, European NFD

*Pacific Island = Cook Island, Fijian, Niuean, Samoan, Tokelauan, Tongan, Pacific Island, Other Pacific Island

[#]Asian = Asian, Chinese, Other Asian, Indian, Southeast Asian

^Others = African, Latin American/Hispanic, Middle Eastern, other, other ethnicity

[1]Cox Regression

[2]Adjusting for: Age, sex, ethnicity, and study cohorts.

Appendix 4: 743 Patients who swapped study groups during study period

Group Swaps (From/To)	No Metformin	Metformin	Total Patient
Diclofenac Group	**207**	**13**	**220**
Antihypertensives TB Group	78	1	79
Antihypertensives AAC Group	56	1	57
Statin Group	73	11	84
Antihypertensives TB Group	**198**	**8**	**206**
Diclofenac Group	82	1	83
Antihypertensives AAC Group	98	6	104
Study Group	18	1	19
Antihypertensives AAC Group	**163**	**3**	**166**
Diclofenac Group	40	1	41
Antihypertensives TB Group	107	1	108
Statin Group	16	1	17
Statin Group	**149**	**2**	**151**
Diclofenac Group	104	1	105
Antihypertensives TB Group	24	0	24
Antihypertensives AAC Group	21	1	22
Total	**717**	**26**	**743**

Research Protocol

Project title: Drug Induced Diabetes: A Case of statins versus antihypertensives.
Date: April 2012
Principal investigator: Dr. Olivia Currie
Supervisor: Assoc. Professor Derelie Mangin

Project summary:

This is an observational prospective cohort study to assess whether the incidence of new onset diabetes is increased with the use of statin drugs; when compared to blood pressure drugs, and to a control group. The importance is indicated from previous experience with unwanted increased rate of cardiovascular events due to new onset diabetes with use of certain antihypertensives (1, 2). We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in 5 years. We will compare this with groups of patients with first prescription of drugs for high blood pressure (high diabetes risk control group), and patients with none of these prescriptions but who have attendance for an ACC-related condition (normal control group). We will use clinical data held electronically on drug prescriptions and laboratory tests on the Pegasus Health Community ePrescription system.

Background:

In modern cardiovascular risk management, statin drugs are popular and beneficial adjuncts for prevention of primary and secondary cardiovascular events. All forms of pharmacotherapy have side effects. Common to statin drugs are increases in liver transaminases, muscle aches, cognition impairment and rhabdomyolysis, albeit rare. However, there is now new evidence to suggest that statin drugs could have drug class effect in causing diabetes in previously non-diabetic individuals (3).

Statin induced diabetes was first observed in the JUPITER trial (4) with relation to Rosuvostatin use in non-diabetic subjects. It was reported by physicians involved in the trial as a secondary outcome and concluded that more evidence is needed to confirm the observed effect. Following that, multiple meta-analyses correlated an overall 9% increased risk of diabetes with statin use with newer evidence showing association with Pravastatin and Rosuvastatin use (5-8). The meta-analyses, should be interpreted with caution as diabetes is often not the primary outcome in the trials analysed. Recent evidence indicates the risk of new onset diabetes with statin use could also be dose dependent (9). These drugs may still have an overall cardiovascular benefit nonetheless (10).

One of the difficulties in assessing the extent of the risk is that patients of higher cardiovascular risk also carry an increased risk of developing diabetes. In order that the risks and benefits of these drugs to be properly considered by patients and doctors, decisions whether to use them, it is very important to understand the extend of this risk in already high risk patients as development of diabetes further increases cardiovascular risk and carries its own morbidity, reducing lifespan and quality of life.

Objective

To assess comparative rates of diabetes development in patients in primary care population started on statin drugs; by comparing them with rates of diabetes development in patients also at high risk of cardiovascular disease started on blood pressure medications but not on statins, and with normal control group.

Methodology:

We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in the subsequent 5 years. We will compare these rates in patients with first prescription of drugs for high blood pressure (high diabetes risk control group) and patients with none of these prescriptions (normal control group). Patients in the normal control group are those with without any of these prescriptions, and are recruited

from attendance for ACC-related conditions in the Canterbury region. We will use clinical data held electronically on drug prescriptions and laboratory tests on the Pegasus Health Community ePrescription system.

Study Design: Prospective cohort study using routinely collected data
Study population: Canterbury residents enrolled in Pegasus Health between ages 40 and 60, who are commenced on either on statin drugs, or on antihypertensives (high risk control group), or who have an ACC claim (low risk control goup) in the years 2005 to 2007.
Exclusion: Patients who previously have diabetes, glucose intolerance, polycystic ovarian syndrome, and those who are already on metformin, thiazides and corticosteroids (all known to increase diabetes risk).
Other variables: From the clinical records where available the age, gender and sex; family history of diabetes; body mass index; LDL level measured; blood glucose or HbA1c measured; and smoking status. The purpose is to describe other cardiovascular risk factors, if any, for groups of patients with prescription for statin drugs or drugs for high blood pressure.
Follow up: Cohort will be followed up for 5 years.
Outcome measure: First prescription of Meformin, or HbA1c result indicating diabetes.
Analysis: Proportions compared between statin started, antihypertensives known to have increased diabetes risk (thiazides and beta-blocker), antihypertensives known to have no increased diabetic risk (ACE-inhibitors, ARBs, calcium channel blockers) and ACC control group.

Ethical considerations:

No ethics committee is required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006*.
Pegasus Health has a method for anonymously electronically extracting and linking these data. Patients are aware when they sign their enrolment form for Pegasus Health that their data may be used anonymously for quality improvement. Data will be de-identified at the point of extraction from the clinical record. Collection of such data will be stored in de-identified manner. This study has been approved for support by the Pegasus Health Research, Audit and Evaluation committee.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ (refer Manuscript Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ (refer Manuscript Page 4)
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ (refer Manuscript Page 6)
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ (refer Manuscript Page 6)
Methods			
Study design	4	Present key elements of study design early in the paper	✓ (refer Manuscript Page 7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ (refer Manuscript Page 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✓ (refer Manuscript Page 7-8)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ (refer Manuscript Page 8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ (refer Manuscript Page 7)
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	✓ (See Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ (refer Manuscript Page 8)

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓ (refer Manuscript Page 8)
		(*b*) Describe any methods used to examine subgroups and interactions	✓ (refer Manuscript Page 8)
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✓ (refer Manuscript Page 8)
		(*e*) Describe any sensitivity analyses	Not applicable
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ (refer Manuscript Page 9)
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	✓ (Figure 1, page 17 Manuscript)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ (refer Manuscript Page 9, and table 1, page 19 Manuscript)
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✓ (refer Manuscript Page 9)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓ (refer Manuscript Page 9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ (refer Manuscript Page 9, Figure 2 and Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	✓ (refer

		sensitivity analyses	Manuscript Page 10)
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ (refer Manuscript Page 11)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ (refer Manuscript Page 12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ (refer Manuscript Page 13)
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ (refer Manuscript Page 13)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ (refer Manuscript Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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MANUSCRIPT

Title Page

Title

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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Key Words

Statins, diabetes, antihypertensives, metformin, primary care, electronic prescription.

Abbreviations

ACEi = angiotensin converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CCB = calcium channel blockers

Study Groups:

Antihypertensives TB = thiazides and beta-blockers.

Antihypertensive AAC = angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.

Abstract

Objective: Recent studies suggest statins increase the risk of subsequent diabetes with a clear dose response effect. However patients prescribed statins have a higher background risk of diabetes. This national cohort study aims to provide an estimate of the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, and those with already higher background risk on cardiovascular risk modifying drugs and a control drug.

Design: Longitudinal cohort study

Setting: Use of routinely collected data from a complete national primary care electronic prescription database in New Zealand.

Participants: 32,086 patients aged between 40 and 60 years in 2005 were eligible and assigned to four non-overlapping groups receiving their first prescription for:

1. diclofenac (healthy population) n=7140
2. antihypertensives thought likely to induce diabetes (thiazides and beta-blockers) n=5769
3. antihypertensives thought less likely to induce diabetes (ACEi, ARBs, CCB) n= 6565
4. statins n= 12 612

Outcome: Numbers of first metformin prescriptions were compared between these groups from 2006 to 2011.

Results: Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01), followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribed

antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac.

Conclusions: These findings further support the link between statin use and new-onset diabetes; and suggest the understanding of diabetes risk associated with different antihypertensive drug classes may bear practice modification. This provides important information for future research, and for prescribers and patients when considering the risks and benefits of different types of cardiovascular risk modifying drugs.

Article Summary

Article focus:

- Estimates the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, other groups of cardiovascular risk modifying drugs indicating higher background risk and a control drug.

Key messages:

- Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01) when compared to control drug.
- Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed ACEi, ARB and CCB (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and thiazides and beta-blockers (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins.

Strengths:

- A national cohort study using electronic prescription database.
- First longitudinal study to compare incidence of subsequent diabetes between statins and antihypertensives with a control drug.
- First study to measure outcome by proxy of first metformin prescription as indication of significant diabetes development.

Limitations:

- Confounding factors like BMI, family history and socioeconomic status are not controlled for in this electronic database analysis. However, there is no indication that these factors are unevenly distributed between the different “high risk” study groups.
- There is a small risk of misclassification for prescription of metformin for other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, but these are rare and are likely to only account for a small number of prescriptions.

Text

Introduction

Statins are widely used and have established benefits in the prevention of cardiovascular events.[1] However, recent studies suggested statins may also increase the risk of new-onset diabetes[2-8], which in turn increases risk of cardiovascular events. One meta-analysis reported the odds to be 9% (OR: 1.09; 95% Confidence Interval (CI) 1.02 to 1.17)[5], with other studies showing the association with pravastatin and rosuvostatin use.[3,4,7,9-11] More recent data indicates the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link.[6] Nevertheless, statins may still have an overall cardiovascular benefit.[5]

One of the difficulties in assessing the extent of this risk is that patients with higher cardiovascular risk prescribed statins also carry an increased baseline risk of developing diabetes because of similar risk factors.[12-14] To understand the extent of the contributions of this increased baseline risk and the risk from the drugs themselves, we compared subsequent diabetes development in patients started on a statin with patients started on other drugs for cardiovascular risk management (antihypertensives) and patients at low baseline risk. We used a complete national prescribing dataset[15] to create a population based cohort constructed of these three groups and compared the risk of subsequent development of clinically significant diabetes in each group.

Methods

Study design: Longitudinal cohort study using a national data set of de-identified routinely collected primary care electronic prescriptions of New Zealanders between ages 40 and 60, receiving first prescriptions of drugs studied (Appendix 1) in the year 2005.

Data source: Nationwide prescription data for the purpose of this study were sourced electronically from a complete national prescribing dataset, the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.[16] Community prescribing is electronic in primary care in New Zealand making this information accessible via NZHIS. Individual patients are assigned a unique identifier (NHI number) in

the New Zealand health system and this is attached to their prescriptions, allowing this to be the main data key linkage tool. All NHIs were de-identified at the point of data extraction, and automatically assigned a unique encrypted code.

Cohort construction: The cohort construction is illustrated in Figure 1 (Flow chart of cohort formation). The cohort included patients aged 40-60 in the year 2005 without prior prescription of excluded drugs and metformin (outcome drug) (Appendix 1), and all patients having received a prescription of at least one of the drugs of interest between 2005 and 2011. These drugs were statins, antihypertensives, diclofenac (comparator drug) or metformin (outcome drug). Diclofenac was chosen as the comparator drug to represent low diabetic risk patients presenting to primary care services with musculoskeletal injuries. Some antihypertensives are associated with subsequent development of diabetes. Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,[14,17-19] whereas little association has been made with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB).[18,19] Following the literature, those in the antihypertensive drug group were further divided into “Antihypertensives TB” for antihypertensives thought likely to increase diabetes risk (T and BB), and “Antihypertensives AAC” for antihypertensives thought less likely to do so (ACEi, ARB and CCB). A total of 195,194 records listed at least one of the drugs in the drug groups under study: Diclofenac, Antihypertensives TB, Antihypertensives AAC, and Statin groups. Patients belonging to two study groups concurrently in 2005 were then excluded. Data were further examined and cleaned to identify duplicate individuals, exclusion drugs and data entry error. This left 32,086 unique individuals to form the 2005 study cohort with 7140, 5769, 6565 and 12,612 in Diclofenac, Antihypertensives TB, Antihypertensives AAC, Statin groups respectively.

Exclusion: Patients who had a prescription for oral hypoglycaemics, insulin, oral corticosteroids (known to increase the risk of diabetes), or any of the study group medications of interest (Appendix 1) prior to 2005. The upper age limit was chosen to limit the inclusion of cardiovascular drugs prescribed for treatment of other cardiovascular conditions (e.g. heart failure).

Exposure: New Zealand adults who received their first prescription of statins, antihypertensives, or diclofenac in the calendar year 2005 without prior prescription of exclusion drugs and metformin.

Primary Outcome Measure: The proportion of patients receiving their first prescription of metformin in the calendar years 2006-2011. Metformin is the recommended first line treatment for newly diagnosed type 2 diabetes mellitus in New Zealand.[20]

Analysis: Patient baseline demographics were summarised using simple descriptive statistics and differences between cohorts were assessed using chi-square statistics calculated on OpenEpi online[21]. Since these are routinely collected electronic records, loss to follow up cannot be measured directly, and will be measured by proxy of medication persistence, death and emigration rate. Persistence with medications was determined as having at least one prescription a year, and persons-years were calculated based on this data. Death and emigration rate were calculated by direct age standardisation based on information available on Statistics New Zealand life-tables to estimate loss to follow up for our cohorts.[22] Incidence rates and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated to compare the risk of new-onset diabetes between Diclofenac group and the other three cohorts. HR were calculated in SPSS 20.0 for Windows (SPSS Inc) using cox proportional hazards regression, and multivariable analysis was used to adjust for differences in the demographic structure of the cohorts. All analyses were 2-sided.

Results:

Patient characteristics: The baseline characteristics of the cohorts are summarised in Table 1 (Cohort demographic). The sex of the patients differed by groups with a higher proportion of females (68.8%, $\chi^2(1) = 447.86$, $p < 0.001$) in the Antihypertensives TB group, and of males (66.6%, $\chi^2(1) = 545.35$, $p < 0.001$) in the statin group. The age of patients also differed across groups with patients receiving cardiovascular risk modifying drugs tending to be older than those in the diclofenac group ($\chi^2(1) = 1016.39$, $p < 0.001$). New Zealand European was the major ethnicity in all study groups. There were more Maori in the Diclofenac group with only a few in the statin group ($\chi^2(1) = 301.86$, $p < 0.001$). These differences between groups are adjusted for in the multivariable analysis.

Cohort characteristics and follow up: A total of 32,086 unique patients were eligible for analysis from the recruitment: 7140 for the Diclofenac group, 5769 for Antihypertentives TB group, 6565 for Antihypertensives AAC group, and 12,612 for the Statin group (Figure 1). Persistence with index medications for each group was 38.4%, 71.3%, 70.9% and 76.1% respectively (Appendix 2). The persistence within the control group was expectedly lower as diclofenac is not usually indicated for long term use. Loss of follow up due to deaths and emigration is estimated to be less than 2% of those who were not persistent with medications, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.

Primary analysis: Primary outcome results indicated that between 2006 and 2011, 710 patients within the four groups received their first prescription of metformin. This represents 1.2%, 1.5%, 2.3% and 3.1% of those exposed to Diclofenac, Antihypertensives TB, Antihypertensives AAC and Statin groups respectively. The incidence rates were 2.5, 2.8, 4.2 and 5.5 cases per 1,000 person years for first prescription of metformin (Table 2) accordingly. In the multivariable analysis, patients commenced on statins had the highest risk of receiving a first prescription of metformin in 6 years after exposure compared to the Control group (HR: 3.31; 95% CI: 2.56-4.30; P < 0.01). In contrast to existing research, when compared to patients on diclofenac, patients on Antihypertensives AAC group have moderate risk of receiving their first prescription of metformin in 6 years (HR: 2.32; 95% CI: 1.74-3.09; P < 0.01), and patients in the Antihypertensives TB group have slightly elevated risk (HR: 1.59; 95% CI: 1.15-2.20; P < 0.01) (Table 3). Our analysis indicates a duration-response: The HR of developing new-onset diabetes was approximately constant over the duration of the study as demonstrated by the plot for the cumulative hazard ratios for the first metformin prescription in each study cohort (Figure 2), adjusting for age, sex, and ethnicity.

Subgroup analyses: Patient demographics were analysed to assess other characteristics of recipients of first metformin prescription (Appendix 3). Cox regression model analysis revealed that females had a lower risk than males (HR = 0.85, 95% CI: 0.72-1.00, p = 0.05), and there was no difference in risk between age groups within our cohort age range. However, risks were increased with all other ethnicities when

compared to New Zealand European. Pacific Island and Asian ethnic group had the highest risk at HR 3.57 (95% CI: 2.63-4.85, P < 0.01) and HR 3.72 (95% CI: 3.00-4.62, P<0.01) respectively.

To assess whether those at risk of developing diabetes were prescribed higher doses of their prescribed medications, the drug doses of their first prescribed indexed medications in 2005 among those prescribed metformin were assessed. In the Statin group, 96.9% of patients were prescribed 40mg and less of both simvastatin and atorvastatin. For patients in the Antihypertensives TB group, 78.8% of patients were on beta blockers and 88% of those on thiazides were on 2.5mg of bendrofluazide. This indicates patients commenced on metformin were prescribed conservative doses of cardiovascular risk modifying drugs.

There were 743 patients who swapped study cohorts during the study period. Of these, 220 were from the Diclofenac group, 206 from Antihypertensives TB group, 166 from Antihypertensives AAC group and 151 from Statin group (Appendix 4). Excluding these patients in a per-protocol analysis had little effect on the hazard ratios compared to the intention to treat analysis (results of analysis available but not included), which could indicate the effect is rare or that the exposure is steady.

Discussion

Patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac. Patients receiving first prescription for statins were at the highest risk of subsequently developing clinically significant diabetes, with a risk three times that of those prescribed diclofenac. Patients prescribed ACEi, ARBs or CCB were the next highest risk, being twice as likely to receive a metformin prescription, while those prescribed thiazides and beta-blockers were only at slightly increased risk.

The association between new-onset diabetes, as estimated by first metformin prescriptions, and initiation of statins found in this study is consistent with recent reports. However, the risk in this population was lower (3.1%) than the 9% risk reported in meta-analyses.[23-25] More recent publications have identified the risks of new-onset diabetes with statin drug use ranging from 2.4% to 8.5%.[23-26] In contrast to our study, the diagnosis of diabetes in these other studies were identified by indicators such as disease classification

recording, or intermediate indicators such as laboratory investigations of HbA1c and fasting serum glucose readings. This will draw in milder levels of hyperglycemia where lifestyle changes can still be the first line of management and where laboratory threshold determines disease rates. This study is the first to identify the incident rate of clinically significant diabetes as indicated by the first prescription of metformin in a non-research population. This is an outcome that matters to patients.

Our study is also the first to compare the risks of diabetes development in patients on statins against patients on other cardiovascular risk modifying drugs who might also be considered to be "high risk". Patients initiated on antihypertensive drugs were, like those prescribed statins, at greater risk of developing diabetes compared to those on diclofenac. Our findings therefore allow an assessment of the comparative risks of new-onset diabetes in patients with already higher risk on different classes of antihypertensives. There may be several explanations for the differences seen. Firstly, it may be a true association. Secondly, patients already with risk factors for diabetes (such as obesity) are less likely to be prescribed medications that will further increase this risk.[14,27] Hence, they are more likely to receive prescriptions of ACEi or ARBs for management of hypertension due to a lesser known risk of inducing diabetes. We also observed conservative dosing in patients on thiazides and beta-blockers, which may attenuate the risk. Finally, higher baseline risk factors (dyslipidaemia and hypertension) that leads to prescription of the study drugs also increases the risk of subsequent glucose elevation, and this effect is observed in patients on as well as off statin use.[28] Our study is not able to answer these questions, but raises these for future research.

Since all data collected are electronic records, patient persistence with medication can be grossly assessed. There were high rates of persistence with medications within the study groups, in particular for the antihypertensives and statins. Given only a total of 743 patients (2.3% of 2005 cohort) swapped into different study groups during the study period, these were relatively clean groups for analyses of risks.

The development of clinically significant diabetes was estimated using a proxy measure, utilising the first prescription of metformin. The validity of using routinely collected and electronically stored prescription data for diagnosing diabetes has been previously demonstrated.[15,29] The use of routinely collected data

also provides access to a complete national population based cohort. We were able to assess this cohort longitudinally over a period of 6 years in a representative primary care population rather than a trial population with tightly constrained entry criteria.

Limitations

Our study has several limitations. The nature of the electronic datasets available means it is not possible to obtain other factors contributing to cardiovascular and diabetes risks to more precisely define subgroups and allow direct comparison of the cohorts' baseline levels of risk of developing diabetes (e.g. body mass index and family history). These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study.

There is also the risk of misclassification. Metformin may also be prescribed for management of other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, however this is likely to account for only a small proportion of prescriptions. With first prescription of metformin, we have also excluded patients who present infrequently to their primary health care providers for well-checks and routine follow up (missing new-onset diabetes) and those who may have presented acutely with diabetic emergency (as they will be commenced on alternate hypoglycaemic agents).

It is also uncertain as to how frequently these patients are tested for diabetes mellitus in the primary care setting, as the electronic system is not currently linked to laboratory data. The study is also unable to control for the duration of mild hyperglycaemia prior to commencement of metformin.

In this study, we have not distinguished between the various statin doses and formulations.

Conclusions

Patients initiating treatment with any of the index cardiovascular risk modifying drugs have some risk of developing clinically significant new-onset diabetes compared to those prescribed diclofenac. However, patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Patients prescribed ACEi, ARBs and CCB were also at moderately increased risk,

while patients prescribed thiazides and beta-blockers only appeared to have a mildly increased risk. The effect seen carries an exposure and duration-response between groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers. This provides additional information on the comparative safety of these drugs in a real world setting in primary care, where the bulk of these prescriptions are likely to be initiated. This is useful information for doctors and patients considering the balance of harms against the potential for benefit of both statins and different cardiovascular risk modifying medications in different populations.

Further Research

Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely as a risk factor for other disease, predominantly cardiovascular disease. Whether there is an additive risk of inducing diabetes with combinations of different cardiovascular risk modifying drugs is currently unknown, and an important area for research to inform decision making on prescribing, given the prevalence of multi-morbidity and likely co-prescription. This is subject to a further study. It is also unclear what effect this additional risk of diabetes will have on morbidity and mortality for patients.

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Prior Presentations

None

Ethics Application

As all data were de-identified by encryption, ethics approval was confirmed as not required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006* (Upper South B Regional Ethics Committee, Ethics ref: URB/12/EXP/022).

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Conflict of Interest Statement

None

Prior Publication

None

Data Sharing

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

Contributorship

Olivia Currie, Dee Mangin, Bianca McKinnon-Gee and Paul Bridgford design the study. Bianca McKinnon-Gee ran the search for electronic prescription data according to study protocol. Olivia Currie designed data

collection tools, monitored data collection for the whole study, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. Olivia Currie and Jonathan Williman analysed the data. Olivia Currie, Dee Mangin and Jonathan Williman revised the draft paper.

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MANUSCRIPT

Title Page

Title

The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.

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Statins, diabetes, antihypertensives, metformin, primary care, electronic prescription.

Abbreviations

ACEi = angiotensin converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CCB = calcium channel blockers

Study Groups:

Antihypertensives TB = thiazides and beta-blockers.

Antihypertensive AAC = angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers.

Abstract

Objective: Recent studies suggest statins increase the risk of subsequent diabetes with a clear dose response effect. However patients prescribed statins have a higher background risk of diabetes. This national cohort study aims to provide an estimate of the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, and those with already higher background risk on cardiovascular risk modifying drugs and a control drug.

Design: Longitudinal cohort study

Setting: Use of routinely collected data from a complete national primary care electronic prescription database in New Zealand.

Participants: 32,086 patients aged between 40 and 60 years in 2005 were eligible and assigned to four non-overlapping groups receiving their first prescription for:

1. diclofenac (healthy population) n=7140
2. antihypertensives thought likely to induce diabetes (thiazides and beta-blockers) n=5769
3. antihypertensives thought less likely to induce diabetes (ACEi, ARBs, CCB) n= 6565
4. statins n= 12 612

Outcome: Numbers of first metformin prescriptions were compared between these groups from 2006 to 2011.

Results: Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01), followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribed

antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac.

Conclusions: These findings further support the link between statin use and new-onset diabetes; and suggest the understanding of diabetes risk associated with different antihypertensive drug classes may bear practice modification. This provides important information for future research, and for prescribers and patients when considering the risks and benefits of different types of cardiovascular risk modifying drugs.

Article Summary

Article focus:

- Estimates the comparative risks for subsequent development of new-onset diabetes in adults prescribed statins, other groups of cardiovascular risk modifying drugs indicating higher background risk and a control drug.

Key messages:

- Patients prescribed statins have the highest risk of receiving a subsequent metformin prescription (HR: 3.31; 95% CI: 2.56 to 4.30; P < 0.01) when compared to control drug.
- Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed ACEi, ARB and CCB (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and thiazides and beta-blockers (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins.

Strengths:

- A national cohort study using electronic prescription database.
- First longitudinal study to compare incidence of subsequent diabetes between statins and antihypertensives with a control drug.
- First study to measure outcome by proxy of first metformin prescription as indication of significant diabetes development.

Limitations:

- Confounding factors like BMI, family history and socioeconomic status are not controlled for in this electronic database analysis. However, there is no indication that these factors are unevenly distributed between the different “high risk” study groups.
- There is a small risk of misclassification for prescription of metformin for other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, but these are rare and are likely to only account for a small number of prescriptions.

Text

Introduction

Statins are widely used and have established benefits in the prevention of cardiovascular events.[1] However, recent studies suggested statins may also increase the risk of new-onset diabetes[2-8], which in turn increases risk of cardiovascular events. One meta-analysis reported the odds to be 9% (OR: 1.09; 95% Confidence Interval (CI) 1.02 to 1.17)[5], with other studies showing the association with pravastatin and rosuvostatin use.[3,4,7,9-11] More recent data indicates the risk of new-onset diabetes with statin use could also be dose dependent, further supporting a causal link.[6] Nevertheless, statins may still have an overall cardiovascular benefit.[5]

One of the difficulties in assessing the extent of this risk is that patients with higher cardiovascular risk prescribed statins also carry an increased baseline risk of developing diabetes because of similar risk factors.[12-14] To understand the extent of the contributions of this increased baseline risk and the risk from the drugs themselves, we compared subsequent diabetes development in patients started on a statin with patients started on other drugs for cardiovascular risk management (antihypertensives) and patients at low baseline risk. We used a complete national prescribing dataset[15] to create a population based cohort constructed of these three groups and compared the risk of subsequent development of clinically significant diabetes in each group.

Methods

Study design: Longitudinal cohort study using a national data set of de-identified routinely collected primary care electronic prescriptions of New Zealanders between ages 40 and 60, receiving first prescriptions of drugs studied (Appendix 1) in the year 2005.

Data source: Nationwide prescription data for the purpose of this study were sourced electronically from a complete national prescribing dataset, the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.[16] Community prescribing is electronic in primary care in New Zealand making this information accessible via NZHIS. Individual patients are assigned a unique identifier (NHI number) in

the New Zealand health system and this is attached to their prescriptions, allowing this to be the main data key linkage tool. All NHIs were de-identified at the point of data extraction, and automatically assigned a unique encrypted code.

Cohort construction: The cohort construction is illustrated in Figure 1 (Flow chart of cohort formation). The cohort included patients aged 40-60 in the year 2005 without prior prescription of excluded drugs and metformin (outcome drug) (Appendix 1), and all patients having received a prescription of at least one of the drugs of interest between 2005 and 2011. These drugs were statins, antihypertensives, diclofenac (comparator drug) or metformin (outcome drug). Diclofenac was chosen as the comparator drug to represent low diabetic risk patients presenting to primary care services with musculoskeletal injuries. Some antihypertensives are associated with subsequent development of diabetes. Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,[14,17-19] whereas little association has been made with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB).[18,19] Following the literature, those in the antihypertensive drug group were further divided into “Antihypertensives TB” for antihypertensives thought likely to increase diabetes risk (T and BB), and “Antihypertensives AAC” for antihypertensives thought less likely to do so (ACEi, ARB and CCB). A total of 195,194 records listed at least one of the drugs in the drug groups under study: Diclofenac, Antihypertensives TB, Antihypertensives AAC, and Statin groups. Patients belonging to two study groups concurrently in 2005 were then excluded. Data were further examined and cleaned to identify duplicate individuals, exclusion drugs and data entry error. This left 32,086 unique individuals to form the 2005 study cohort with 7140, 5769, 6565 and 12,612 in Diclofenac, Antihypertensives TB, Antihypertensives AAC, Statin groups respectively.

Exclusion: Patients who had a prescription for oral hypoglycaemics, insulin, oral corticosteroids (known to increase the risk of diabetes), or any of the study group medications of interest (Appendix 1) prior to 2005. The upper age limit was chosen to limit the inclusion of cardiovascular drugs prescribed for treatment of other cardiovascular conditions (e.g. heart failure).

Exposure: New Zealand adults who received their first prescription of statins, antihypertensives, or diclofenac in the calendar year 2005 without prior prescription of exclusion drugs and metformin.

Primary Outcome Measure: The proportion of patients receiving their first prescription of metformin in the calendar years 2006-2011. Metformin is the recommended first line treatment for newly diagnosed type 2 diabetes mellitus in New Zealand.[20]

Analysis: Patient baseline demographics were summarised using simple descriptive statistics and differences between cohorts were assessed using chi-square statistics calculated on OpenEpi online[21]. Since these are routinely collected electronic records, loss to follow up cannot be measured directly, and will be measured by proxy of medication persistence, death and emigration rate. Persistence with medications was determined as having at least one prescription a year, and persons-years were calculated based on this data. Death and emigration rate were calculated by direct age standardisation based on information available on Statistics New Zealand life-tables to estimate loss to follow up for our cohorts.[22] Incidence rates and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated to compare the risk of new-onset diabetes between Diclofenac group and the other three cohorts. HR were calculated in SPSS 20.0 for Windows (SPSS Inc) using cox proportional hazards regression, and multivariable analysis was used to adjust for differences in the demographic structure of the cohorts. All analyses were 2-sided.

Results:

Patient characteristics: The baseline characteristics of the cohorts are summarised in Table 1 (Cohort demographic). The sex of the patients differed by groups with a higher proportion of females (68.8%, $\chi^2(1) = 447.86$, $p < 0.001$) in the Antihypertensives TB group, and of males (66.6%, $\chi^2(1) = 545.35$, $p < 0.001$) in the statin group. The age of patients also differed across groups with patients receiving cardiovascular risk modifying drugs tending to be older than those in the diclofenac group ($\chi^2(1) = 1016.39$, $p < 0.001$). New Zealand European was the major ethnicity in all study groups. There were more Maori in the Diclofenac group with only a few in the statin group ($\chi^2(1) = 301.86$, $p < 0.001$). These differences between groups are adjusted for in the multivariable analysis.

Cohort characteristics and follow up: A total of 32,086 unique patients were eligible for analysis from the recruitment: 7140 for the Diclofenac group, 5769 for Antihypertentives TB group, 6565 for Antihypertensives AAC group, and 12,612 for the Statin group (Figure 1). Persistence with index medications for each group was 38.4%, 71.3%, 70.9% and 76.1% respectively (Appendix 2). The persistence within the control group was expectedly lower as diclofenac is not usually indicated for long term use. Loss of follow up due to deaths and emigration is estimated to be less than 2% of those who were not persistent with medications, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.

Primary analysis: Primary outcome results indicated that between 2006 and 2011, 710 patients within the four groups received their first prescription of metformin. This represents 1.2%, 1.5%, 2.3% and 3.1% of those exposed to Diclofenac, Antihypertensives TB, Antihypertensives AAC and Statin groups respectively. The incidence rates were 2.5, 2.8, 4.2 and 5.5 cases per 1,000 person years for first prescription of metformin (Table 2) accordingly. In the multivariable analysis, patients commenced on statins had the highest risk of receiving a first prescription of metformin in 6 years after exposure compared to the Control group (HR: 3.31; 95% CI: 2.56-4.30; P < 0.01). In contrast to existing research, when compared to patients on diclofenac, patients on Antihypertensives AAC group have moderate risk of receiving their first prescription of metformin in 6 years (HR: 2.32; 95% CI: 1.74-3.09; P < 0.01), and patients in the Antihypertensives TB group have slightly elevated risk (HR: 1.59; 95% CI: 1.15-2.20; P < 0.01) (Table 3). Our analysis indicates a duration-response: The HR of developing new-onset diabetes was approximately constant over the duration of the study as demonstrated by the plot for the cumulative hazard ratios for the first metformin prescription in each study cohort (Figure 2), adjusting for age, sex, and ethnicity.

Subgroup analyses: Patient demographics were analysed to assess other characteristics of recipients of first metformin prescription (Appendix 3). Cox regression model analysis revealed that females had a lower risk than males (HR = 0.85, 95% CI: 0.72-1.00, p = 0.05), and there was no difference in risk between age groups within our cohort age range. However, risks were increased with all other ethnicities when

compared to New Zealand European. Pacific Island and Asian ethnic group had the highest risk at HR 3.57 (95% CI: 2.63-4.85, P < 0.01) and HR 3.72 (95% CI: 3.00-4.62, P<0.01) respectively.

To assess whether those at risk of developing diabetes were prescribed higher doses of their prescribed medications, the drug doses of their first prescribed indexed medications in 2005 among those prescribed metformin were assessed. In the Statin group, 96.9% of patients were prescribed 40mg and less of both simvastatin and atorvastatin. For patients in the Antihypertensives TB group, 78.8% of patients were on beta blockers and 88% of those on thiazides were on 2.5mg of bendrofluazide. This indicates patients commenced on metformin were prescribed conservative doses of cardiovascular risk modifying drugs.

There were 743 patients who swapped study cohorts during the study period. Of these, 220 were from the Diclofenac group, 206 from Antihypertensives TB group, 166 from Antihypertensives AAC group and 151 from Statin group (Appendix 4). Excluding these patients in a per-protocol analysis had little effect on the hazard ratios compared to the intention to treat analysis (results of analysis available but not included), which could indicate the effect is rare or that the exposure is steady.

Discussion

Patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac. Patients receiving first prescription for statins were at the highest risk of subsequently developing clinically significant diabetes, with a risk three times that of those prescribed diclofenac. Patients prescribed ACEi, ARBs or CCB were the next highest risk, being twice as likely to receive a metformin prescription, while those prescribed thiazides and beta-blockers were only at slightly increased risk.

The association between new-onset diabetes, as estimated by first metformin prescriptions, and initiation of statins found in this study is consistent with recent reports. However, the risk in this population was lower (3.1%) than the 9% risk reported in meta-analyses.[23-25] More recent publications have identified the risks of new-onset diabetes with statin drug use ranging from 2.4% to 8.5%.[23-26] In contrast to our study, the diagnosis of diabetes in these other studies were identified by indicators such as disease classification

recording, or intermediate indicators such as laboratory investigations of HbA1c and fasting serum glucose readings. This will draw in milder levels of hyperglycemia where lifestyle changes can still be the first line of management and where laboratory threshold determines disease rates. This study is the first to identify the incident rate of clinically significant diabetes as indicated by the first prescription of metformin in a non-research population. This is an outcome that matters to patients.

Our study is also the first to compare the risks of diabetes development in patients on statins against patients on other cardiovascular risk modifying drugs who might also be considered to be "high risk". Patients initiated on antihypertensive drugs were, like those prescribed statins, at greater risk of developing diabetes compared to those on diclofenac. Our findings therefore allow an assessment of the comparative risks of new-onset diabetes in patients with already higher risk on different classes of antihypertensives. There may be several explanations for the differences seen. Firstly, it may be a true association. Secondly, patients already with risk factors for diabetes (such as obesity) are less likely to be prescribed medications that will further increase this risk.[14,27] Hence, they are more likely to receive prescriptions of ACEi or ARBs for management of hypertension due to a lesser known risk of inducing diabetes. We also observed conservative dosing in patients on thiazides and beta-blockers, which may attenuate the risk. Finally, higher baseline risk factors (dyslipidaemia and hypertension) that leads to prescription of the study drugs also increases the risk of subsequent glucose elevation, and this effect is observed in patients on as well as off statin use.[28] Our study is not able to answer these questions, but raises these for future research.

Since all data collected are electronic records, patient persistence with medication can be grossly assessed. There were high rates of persistence with medications within the study groups, in particular for the antihypertensives and statins. Given only a total of 743 patients (2.3% of 2005 cohort) swapped into different study groups during the study period, these were relatively clean groups for analyses of risks.

The development of clinically significant diabetes was estimated using a proxy measure, utilising the first prescription of metformin. The validity of using routinely collected and electronically stored prescription data for diagnosing diabetes has been previously demonstrated.[15,29] The use of routinely collected data

also provides access to a complete national population based cohort. We were able to assess this cohort longitudinally over a period of 6 years in a representative primary care population rather than a trial population with tightly constrained entry criteria.

Limitations

Our study has several limitations. The nature of the electronic datasets available means it is not possible to obtain other factors contributing to cardiovascular and diabetes risks to more precisely define subgroups and allow direct comparison of the cohorts' baseline levels of risk of developing diabetes (e.g. body mass index and family history). These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study.

There is also the risk of misclassification. Metformin may also be prescribed for management of other conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans, however this is likely to account for only a small proportion of prescriptions. With first prescription of metformin, we have also excluded patients who present infrequently to their primary health care providers for well-checks and routine follow up (missing new-onset diabetes) and those who may have presented acutely with diabetic emergency (as they will be commenced on alternate hypoglycaemic agents).

It is also uncertain as to how frequently these patients are tested for diabetes mellitus in the primary care setting, as the electronic system is not currently linked to laboratory data. The study is also unable to control for the duration of mild hyperglycaemia prior to commencement of metformin.

In this study, we have not distinguished between the various statin doses and formulations.

Conclusions

Patients initiating treatment with any of the index cardiovascular risk modifying drugs have some risk of developing clinically significant new-onset diabetes compared to those prescribed diclofenac. However, patients prescribed statins have the highest risk of new-onset diabetes, strengthening the recent signal from current literature. Patients prescribed ACEi, ARBs and CCB were also at moderately increased risk,

while patients prescribed thiazides and beta-blockers only appeared to have a mildly increased risk. The effect seen carries an exposure and duration-response between groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers. This provides additional information on the comparative safety of these drugs in a real world setting in primary care, where the bulk of these prescriptions are likely to be initiated. This is useful information for doctors and patients considering the balance of harms against the potential for benefit of both statins and different cardiovascular risk modifying medications in different populations.

Further Research

Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely as a risk factor for other disease, predominantly cardiovascular disease. Whether there is an additive risk of inducing diabetes with combinations of different cardiovascular risk modifying drugs is currently unknown, and an important area for research to inform decision making on prescribing, given the prevalence of multi-morbidity and likely co-prescription. This is subject to a further study. It is also unclear what effect this additional risk of diabetes will have on morbidity and mortality for patients.

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Prior Presentations

None

Ethics Application

As all data were de-identified by encryption, ethics approval was confirmed as not required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006* (Upper South B Regional Ethics Committee, Ethics ref: URB/12/EXP/022).

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Conflict of Interest Statement

None

Prior Publication

None

Data Sharing

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

Contributorship

Olivia Currie, Dee Mangin, Bianca McKinnon-Gee and Paul Bridgford design the study. Bianca McKinnon-Gee ran the search for electronic prescription data according to study protocol. Olivia Currie designed data

collection tools, monitored data collection for the whole study, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. Olivia Currie and Jonathan Williman analysed the data. Olivia Currie, Dee Mangin and Jonathan Williman revised the draft paper.

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Figures

Figure 1: Flow chart of cohort formation

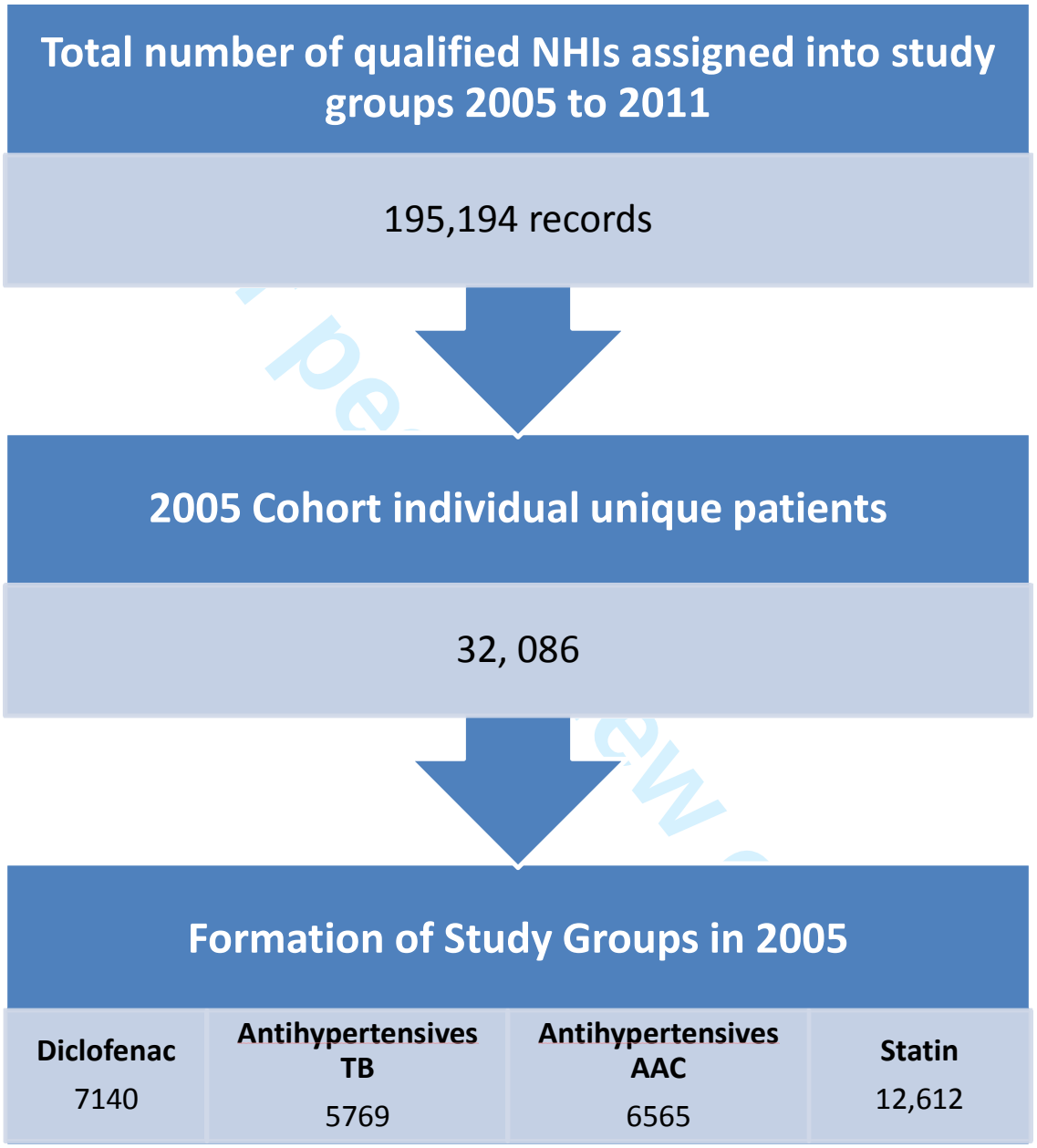
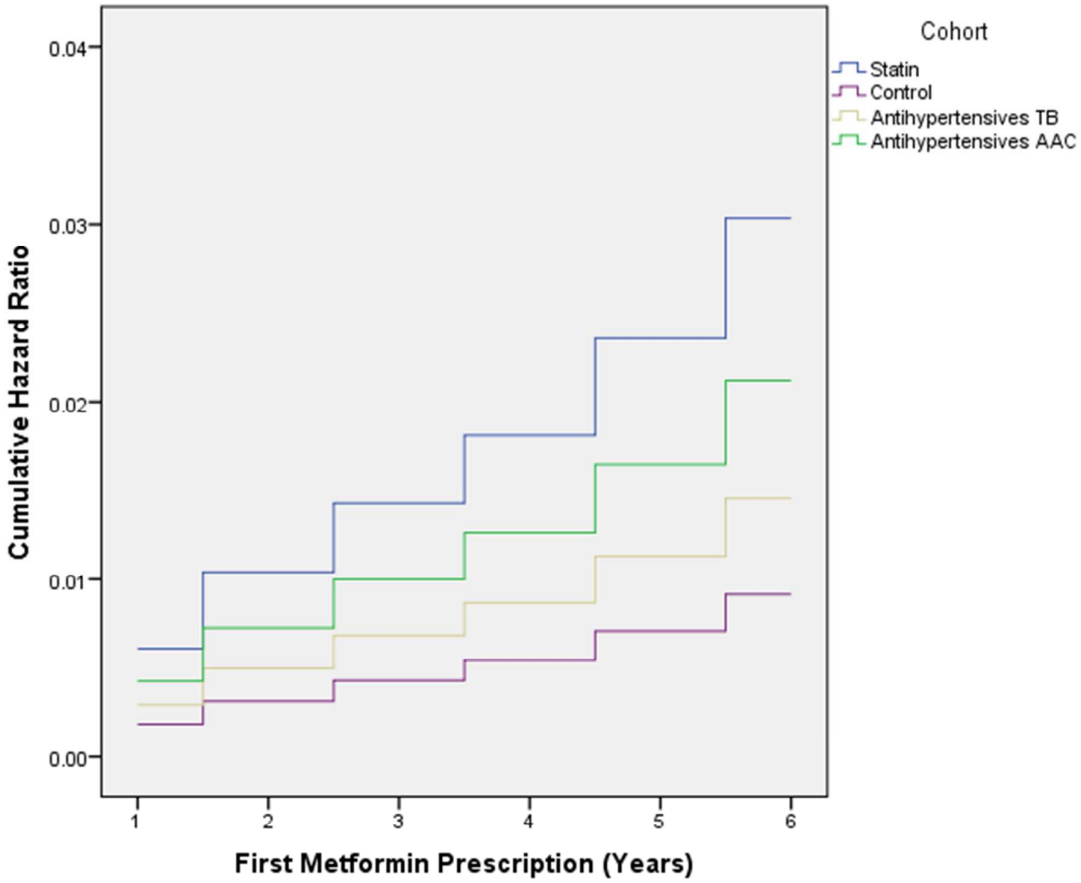


Figure 2: Hazard Ratio for first prescription of metformin in each year for different study groups



Tables

Table 1: Cohort Demographic

Characteristics	OVERALL	Diclofenac Group	Anti-hypertensives TB Group	Anti-hypertensives AAC Group	Statins Group
	% (n)	% (n)	% (n)	% (n)	% (n)
Recruited number of patients	100 (32086)	22.25 (7140)	17.98 (5769)	20.46 (6565)	39.31 (12612)
Sex					
Male	52.98 (16999)	49.69 (3548)	31.20 (1800)	49.52 (3251)	66.60 (8400)
Female	47.01 (15083)	50.29 (3591)	68.80 (3969)	50.46 (3313)	33.38 (4210)
Unknown	4	1	0	1	2
Age					
40-44	22.0 (7045)	33.8 (2415)	20.4 (1179)	19.1 (1255)	17.4 (2196)
45-49	22.7 (7289)	26.4 (1886)	22.4 (1295)	22.0 (1445)	21.1 (2663)
50-54	26.1 (8367)	21.1 (1509)	27.4 (1582)	27.3 (1794)	27.6 (3482)
55-59	29.2 (9385)	18.6 (1330)	29.7 (1713)	31.5 (2071)	33.9 (4271)
Ethnicity					
NZ European[+]	69.46 (22287)	61.3 (4377)	76.39 (4407)	69.23 (4545)	71.03 (8958)
Maori	7.05 (2261)	14.26 (1018)	5.91 (341)	7.75 (509)	3.12 (393)
Pacific Island*	3.48 (1116)	8.75 (625)	1.87 (108)	2.83 (186)	1.56 (197)
Asian[#]	5.31 (1703)	5.04 (360)	5.23 (302)	4.90 (322)	5.70 (719)
Others^	0.93 (298)	1.44 (103)	0.81 (47)	0.70 (46)	0.81 (102)
Unknown[@]	4421	657	564	957	2243

Table 2: Incidence rate for first prescription of metformin

Groups	Person-time	Number of new cases	Incidence rate cases per person year	Incidence rate cases per 1,000 person- years
Diclofenac	33190	84	0.00253	2.5
TB	30791	85	0.00276	2.8
AAC	35383	150	0.00424	4.2
Statin	70455	391	0.00555	5.5

Table 3: 6 year risk of first prescription of metformin in study groups compared to control group

			Univariable Analysis			Multivariable Analysis[1,2]		
	Total	**Metformin (%)**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Cohort								
Diclofenac	7140	84 (1.2)	1.00			1.00		
TB	5769	85 (1.5)	1.25	0.93-1.70	0.142	1.59	1.15-2.20	0.005
AAC	6565	150 (2.3)	1.95	1.50-2.55	<0.0001	2.32	1.74-3.09	<0.0001
Statin	12612	391 (3.1)	2.66	2.10-3.37	<0.0001	3.31	2.56-4.30	<0.0001

[1]Cox Regression
[2]Adjusting for: Age, sex, and ethnicity.

Appendices

Appendix 1: Summary of study analysis categories and drug lists

Groups	List of drugs	Sub group
Exclusion criteria Drugs (associated with increased risk of diabetes or are treatment for diabetes)	Insulin Neutral, Insulin Isophane, Insulin Isophane with Insulin Neural, Insulin Lispro with Insulin Lispro Protamine, Insulin Glargine, Insulin Aspart, Insulin Glulisine, Insulin lispro, Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone, Spironolactone, Cyproterone Acetate with Ethinyloestrodiol, Cyproterone acetate, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone tablets, Methylprednisone, Prednisone Sodium Phosphate, Prednisone	
Diclofenac group	Diclofenac Sodium enteric coated tablets, Diclofenac Sodium Long Acting Tablets	
Anti-hypertensives TB Group	Atenolol, Carvedilol, Celiprolol, Labetalol, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Propanolol, Sotalol, Labetalol	BB
	Bendrofluazide, Chlorthalidone, Indapamide, Chlorothiazide	T
Anti-hypertensives AAC Group	Captopril, Cilazapril, Enalapril, Lisinopril, Quinapril	ACEi
	Candersartan, Losartan	ARB
	Amlodipine, Felodipine, Isradipine, Nifedipine, Diltiazem Hydrochloride, Verapamil Hydrochloride	CC
Statin Group	Atorvastatin, Pravastatin, Simvastatin	
Outcome Group	Metformin Hydrochloride	

Appendix 2: Number of patients persistent with medications in each cohort in every study year

Cohort\Years	2006	2007	2008	2009	2010	2011	%
TB	5769	5202	4834	4547	4339	4115	71.3%
AAC	6565	5958	5583	5227	4955	4654	70.9%
STATIN	12612	11752	11186	10757	10187	9593	76.1%

Appendix 3: 6 year risk of first prescription of metformin in different patient demographics.

					Univariable Analyses			Multivariable Analyses[1,2]		
	Total	**%**	**Metformin**	**%**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex										
M	16999	53.0%	409	1.3%	1.00	-	-	1.00	-	-
F	15083	47.0%	301	0.9%	0.83	0.71-0.96	0.01	0.85	0.72-1.00	0.05
Unknown	4	0.00%	0	0.0%	-	-	-	-	-	-
Age										
40-44	7045	22.0%	163	0.5%	1.00	-	-	1.00	-	-
45-49	7289	22.7%	156	0.5%	0.93	0.74-1.15	0.49	0.87	0.69-1.10	0.25
50-54	8367	26.1%	185	0.6%	0.96	0.77-1.18	0.67	0.88	0.70-1.11	0.27
55-59	9385	29.2%	206	0.6%	0.95	0.77-1.17	0.61	0.96	0.77-1.20	0.71
Ethnicity										
European	22287	69.5%	384	1.2%	1.00	-	-	1.00	-	-
Maori	2261	7.0%	66	0.2%	1.70	1.31-2.21	<0.01	2.23	1.71-2.91	<0.01
PI	1116	3.5%	49	0.2%	2.57	1.91-3.47	<0.01	3.57	2.63-4.85	<0.01
Asian	1703	5.3%	106	0.3%	3.69	2.98-4.57	<0.01	3.72	3.00-4.62	<0.01
Other	298	0.9%	11	0.0%	2.17	1.18-3.93	0.01	2.43	1.33-4.43	<0.01

Note:

[+]European = NZ European, Other European, European NFD

*Pacific Island = Cook Island, Fijian, Niuean, Samoan, Tokelauan, Tongan, Pacific Island, Other Pacific Island

[#]Asian = Asian, Chinese, Other Asian, Indian, Southeast Asian

^Others = African, Latin American/Hispanic, Middle Eastern, other, other ethnicity

[1]Cox Regression

[2]Adjusting for: Age, sex, ethnicity, and study cohorts.

Appendix 4: 743 Patients who swapped study groups during study period

Group Swaps (From/To)	No Metformin	Metformin	Total Patient
Diclofenac Group	**207**	**13**	**220**
Antihypertensives TB Group	78	1	79
Antihypertensives AAC Group	56	1	57
Statin Group	73	11	84
Antihypertensives TB Group	**198**	**8**	**206**
Diclofenac Group	82	1	83
Antihypertensives AAC Group	98	6	104
Study Group	18	1	19
Antihypertensives AAC Group	**163**	**3**	**166**
Diclofenac Group	40	1	41
Antihypertensives TB Group	107	1	108
Statin Group	16	1	17
Statin Group	**149**	**2**	**151**
Diclofenac Group	104	1	105
Antihypertensives TB Group	24	0	24
Antihypertensives AAC Group	21	1	22
Total	**717**	**26**	**743**

Research Protocol

Project title: The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study

Date: April 2012

Principal investigator: Dr. Olivia Currie

Supervisor: Assoc. Professor Derelie Mangin

Project summary:

This is an observational prospective cohort study to assess whether the incidence of new onset diabetes is increased with the use of statin drugs; when compared to blood pressure drugs, and to a control group. The importance is indicated from previous experience with unwanted increased rate of cardiovascular events due to new onset diabetes with use of certain antihypertensives (1, 2). We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in 6 years. We will compare this with groups of patients with first prescription of drugs for high blood pressure (high diabetes risk control group), and patients with prescription for diclofenac (normal control group). We will use prescription data held electronically in the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.

Background:

In modern cardiovascular risk management, statin drugs are popular and beneficial adjuncts for prevention of primary and secondary cardiovascular events. All forms of pharmacotherapy have side effects. Common to statin drugs are increases in liver transaminases, muscle aches, cognition impairment and rhabdomyolysis, albeit rare. However, there is now new evidence to suggest that statin drugs could have drug class effect in causing diabetes in previously non-diabetic individuals (3).

Statin induced diabetes was first observed in the JUPITER trial (4) with relation to rosuvostatin use in non-diabetic subjects. It was reported by physicians involved in the trial as a secondary outcome and concluded that more evidence is needed to confirm the observed effect. Following that, multiple meta-analyses correlated an overall 9% increased risk of diabetes with statin use with newer evidence showing association with pravastatin and rosuvastatin use (5-8). The meta-analyses, should be interpreted with caution as diabetes is often not the primary outcome in the trials analysed. Recent evidence indicates the risk of new onset diabetes with statin use could also be dose dependent (9). These drugs may still have an overall cardiovascular benefit nonetheless (10).

One of the difficulties in assessing the extent of the risk is that patients of higher cardiovascular risk also carry an increased risk of developing diabetes. In order that the risks and benefits of these drugs to be properly considered by patients and doctors, decisions whether to use them, it is very important to understand the extend of this risk in already high risk patients as development of diabetes further increases cardiovascular risk and carries its own morbidity, reducing lifespan and quality of life.

Objective

To assess comparative rates of diabetes development in patients in primary care population started on statin drugs; by comparing them with rates of diabetes development in patients also at high risk of cardiovascular disease started on blood pressure medications but not on statins, and with normal control group.

Methodology:

We will look at patients with first prescription of statin drugs and assess the proportion of users who develop diabetes in the subsequent 6 years. We will compare these rates in patients with first prescription of drugs for high blood pressure (high diabetes risk control group) and patients with prescriptions for diclofenac (normal control group). We will use

electronic prescription data from the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection.

Study Design: Prospective cohort study using routinely collected data
Study population: New Zealanders between ages 40 and 60, who are commenced on either on statin drugs, or on antihypertensives (high risk control group), or diclofenac (low risk control goup) in the year 2005.
Exclusion: Patients who previously have diabetes, glucose intolerance, polycystic ovarian syndrome, and those who are already on metformin, thiazides and corticosteroids (all known to increase diabetes risk).
Follow up: Cohort will be followed up for 6 years.
Outcome measure: First prescription of meformin.
Analysis: Proportions compared between statin started, antihypertensives known to have increased diabetes risk (thiazides and beta-blocker), antihypertensives known to have no increased diabetic risk (ACE-inhibitors, ARBs, calcium channel blockers) and diclofenac.

Ethical considerations:

No ethics committee is required by the National Ethics Advisory Committee, New Zealand as stated in the *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities, NEAC, December 2006*.
Pegasus Health has a method for anonymously electronically extracting and linking these data from the New Zealand Health Information Service' (NZHIS) Pharmaceutical Collection. Data will be de-identified at the point of extraction from the clinical record. Collection of such data will be stored in de-identified manner. This study has been approved for support by the Pegasus Health Research, Audit and Evaluation committee.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ (refer Manuscript Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ (refer Manuscript Page 4)
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ (refer Manuscript Page 6)
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ (refer Manuscript Page 6)
Methods			
Study design	4	Present key elements of study design early in the paper	✓ (refer Manuscript Page 7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ (refer Manuscript Page 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✓ (refer Manuscript Page 7-8)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ (refer Manuscript Page 8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ (refer Manuscript Page 7)
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	✓ (See Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ (refer Manuscript Page 8)

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓ (refer Manuscript Page 8)
		(*b*) Describe any methods used to examine subgroups and interactions	✓ (refer Manuscript Page 8)
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✓ (refer Manuscript Page 8)
		(*e*) Describe any sensitivity analyses	Not applicable
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ (refer Manuscript Page 9)
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	✓ (Figure 1, page 17 Manuscript)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ (refer Manuscript Page 9, and table 1, page 19 Manuscript)
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✓ (refer Manuscript Page 9)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓ (refer Manuscript Page 9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ (refer Manuscript Page 9, Figure 2 and Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	✓ (refer

		sensitivity analyses	Manuscript Page 10)
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ (refer Manuscript Page 11)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ (refer Manuscript Page 12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ (refer Manuscript Page 13)
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ (refer Manuscript Page 13)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ (refer Manuscript Page 1)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.