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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Interrogation of a longitudinal, national pharmacy claims dataset to explore factors that predict the need for add-on therapy in older and socioeconomically disadvantaged Australians with type 2 diabetes mellitus patients (T2DM)

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Abstract

Purpose The management of type 2 diabetes mellitus (T2DM) is complex. The aim of this work is to explore factors that predict the need for add-on therapy in patients with T2DM in the community.

Methods We accessed longitudinal, pharmacy payment claim records from the national Pharmaceutical Benefits Scheme (PBS) (Subsidises costs of medicines: government pays difference between patient co-payments, lower in concessional patients, and additional cost of drug.) for the period January 2006 to September 2014 (EREC/MI3127) from a 10% random sample of the Australian population validated to be representative of the population by the Australian Bureau of Statistics (ABS). Likely, T2DM patients were identified as those having been dispensed a single anti-hyperglycaemic drug (monotherapy). The time taken and possible factors that might lead to the addition of a second therapy were examined. An examination was made of trends in the co-prescription of either antihypertensive or anti-hyperlipidaemic agents in relation to the time (± 3 years) of initiating an anti-hyperglycaemic agent.

Results Most (83%) presumed T2DM patients were initiated with metformin. The average time until the second agent was added was 4.8 years (95% CI 4.7–4.9). Satisfactory adherence, age, male gender, initiating therapy after 2012 and initiating with a sulphonylurea drug all were significant risks for add-on therapy. There was no overall trend in the initiation of antihypertensive and/or anti-hyperlipidaemic agents with respect to the time of anti-hyperglycaemic initiation.

Conclusion The usefulness of a longitudinal dataset of pharmacy-claim records is demonstrated. Over half of all older and socioeconmically disadvantaged T2DM patients captured in this longitudinal claims database will be prescribed a second anti-hyperglycaemic agent within 5 years of their first drug therapy. Several factors can predict the risk of prescription of add-on therapy, and these should be considered when prescribing medications to treat T2DM.

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Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) in 2014 was 422 million [1]. In Australia in 2014–2015, it was estimated that one million people had T2DM, and of these, approximately 750,000 were over the age of 65 [2]. The economic burden of T2DM is substantial, valued at $14.6 billion per annum [3]. Patients with T2DM are at high risk of developing cardiovascular [4] and end-stage kidney disease [5]. It is estimated that diabetes resulted in 3.7 million deaths globally in 2012 largely due to the increased risk of cardiovascular diseases [1]. Optimal management of T2DM can prevent/delay these outcomes [6]. As the risk of cardiovascular disease in T2DM patients is high [4], early attention to other risk factors is a strong recommendation. The pharmacotherapies suggested for hypertension are angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) initially, followed by the addition of calcium channel blockers (CCBs) or low-dose thiazide diuretics if blood pressure targets are not met [7–11]. Statins are recommended as first-line therapy for hyperlipidaemia [7–11].

Pharmacotherapy of type 2 diabetes mellitus (T2DM) generally commences with metformin with additional therapies prescribed if haemoglobin A1c (HbA1c), a marker of long-term glucose control, has not fallen sufficiently. This initiation scheme reflects the consensus in several different countries [7–11]. Factors other than HbA1c that have been shown to influence the need for add-on therapy have included age [12–14], prescription of sulphonylurea as first choice antihyperglycaemic medicine, co-morbidities [13, 14], female sex [13] and race [12].

The overall aim of the present study was to interrogate a longitudinal, national pharmacy claims dataset to explore factors that predict the need for add-on therapy in older and socioeconomically disadvantaged, de-identified Australians with highly likely type 2 diabetes mellitus patients (T2DM) based upon prescription of medications overwhelmingly used for T2DM. Given the guideline advice to attend to risk factors for accelerated cardiovascular and renal disease early, we also examined the concomitant use of antihypertensive and anti-hyperlipidaemic agents in these subjects.

Methods

Data sources

We accessed longitudinal, pharmacy payment claim records from the national Pharmaceutical Benefits Scheme (PBS)[1] for the period January 2006 to September 2014 (EREC/MI3127) from a 10% random sample of the Australian population validated to be representative of the population by the Australian Bureau of Statistics (ABS). Patients with T2DM were identified by prescriptions of a single anti-hyperglycaemic agent based on a unique PBS item code (Supplementary Table 1). Our data set consisted of concession cardholders[2] only i.e. eligible people > 65 years old or socioeconomically disadvantaged (non-concessional prescriptions data were not available at the time we conducted this analysis).

Time and factors effecting the addition of a second therapy

The inclusion criteria for this analysis was any patient with more than one dispensation of a single anti-hyperglycaemic agent (identified by a single PBS item code, Supplementary Table 1) commencing in the period January 1 2007 to September 30, 2014. Data from 2006 were excluded in order to ensure that only the first script of an anti-hyperglycaemic agent was being captured, as many patients progress to concessional status at age 65 having received prescriptions as non-concessional patients prior to that time. Patients with inconsistent concessional access (< 70% concessional possession ratio[3]) and/or patients missing demographic data were also excluded from analysis.

The time to add-on therapy was defined as the time until a second anti-hyperglycaemic agent (or class; identified by PBS item code, Supplementary Table 2) was dispensed, or when a fixed dose, anti-hyperglycaemic combination (identified by PBS item code, Supplementary Table 1) was dispensed. The decision to start an add-on therapy was at the discretion of the clinician, and the rationale for this was not recorded in this data set. Our assumption was that in the majority of cases, this was because glycaemic control was not satisfactory.

A Kaplan-Meier analysis was used to estimate the median time to add-on therapy in adherent and non-adherent patients. A patient was considered 'non-adherent' to therapy if their average quantity of dispensed medication per unit time frame

[1] Subsidises costs of medicines: government pays difference between patient co-payments, lower in concessional patients, and additional cost of drug.
[2] Concessional status: cost of drugs are further subsidised for those patients aged over 65 years, those with sickness benefits and those from a low socio-economic background by a reduction in co-payments
[3] Concessional possession ratio is the ratio of concessional scripts accessed by a patient over the expected number of concessional scripts to be accessed by that patient if the prescription of the drug for this patient is unchanged.

(based on up to 12 months), fell below the 25th percentile of dispensed medication for the study population.[4] Data were censored for the following reasons: death, lost to follow up (> 180 days since last claim) or the 'cohort censored' date (September 30, 2014) was reached. Univariate and multivariate Cox proportional hazards regression analysis was performed to determine variables that influenced the time to add-on therapy. The variables examined included, adherence, sex, 'calendar year of initiation of treatment' (< 2012 or ≥ 2012), age (< 30, 30–39, 40–49, 50–59, 60–69 ≥ 70) and 'class of initiating anti-hyperglycaemic agent'. The division at the commencement of 2012 was chosen as guidelines advising specific HbA1C targets were released at that time. All covariates were retained in multivariate models and as such, only multivariate results are presented.

Treatment of hypertension and hyperlipidaemia

This analysis focused on patients dispensed any oral hyperglycaemic agent script in the period January 2009 through September 2011. We then determined whether either an anti-hypertensive or anti-hyperlipidaemic agents (including fixed-dose combinations, PBS item codes in Supplementary Table 2) were dispensed within 3 years of the first dispensing of an anti-hyperglycaemic medication. The proportion of patients on anti-hypertensive and/or anti-hyperlipidaemic agents was calculated. The trends to commencing these treatments before or after the first dispensation of an oral hyperglycaemic agent were also examined.

Results

Time to add-on therapy

The dataset consisted of 18,637 patients, with median age of 66 years at the time of the first anti-hyperglycaemic prescribed (IQR 57–73, Table 1).[5] Overall, 83% of patients were initiated with metformin monotherapy while 12% were commenced on sulphonylureas (Table 1). Of the remaining 5%, some will have commenced on insulin but the majority of these will be type I diabetes mellitus patients.

The median time to the addition of a second anti-hyperglycaemic agent was 4.71 years (95% CI 4.66–4.76). Figure 1 shows the median time to addition of a second anti-hyper glycaemic agent for adherent and non-adherent patients. All the covariates tested in the multivariate analysis were significant predictors of add-on therapy ($P < 0.001$, Table 2). Patients initiated on sulphonylureas were about twice as likely to start a second anti- hyperglycaemic agent compared to patients starting metformin (Table 2). Approximately 58% of the patient cohort were deemed to be non-adherent, a surprisingly high proportion. Again surprisingly, patients that were non-adherent were less likely to require add-on therapy (HR 0.71, 95% CI 0.67–0.75, Table 2).

Table 1 Cohort characteristics and initiating anti-hyperglycaemic agent ($n = 18,637$; first prescription Jan 1, 2007)

Characteristic	Value
Age (median, IQR)	66 (57–73)
Male (%)	47.3
Initiating anti-hyperglycaemic agent	
Metformin (%)	83.1
Sulphonylurea (%)	12.1
Other (%)[a]	4.8

[a] Other includes acarbose, thiazolidinediones, DPP4 inhibitors, insulin and dapagliflozin

Treatment of hypertension and hyperlipidaemia

During the period January 2009 to September 2011, a total of 14,578 patients received an anti-hyperglycaemic agent. Of these, 56.6% were prescribed either an antihypertensive or an anti-hyperlipidaemic agent within 3 years of starting an oral anti-hyperglycaemic medication (Fig. 2). There was no overall difference in the likelihood of initiating either of these classes of medications according to whether the patient had or had not already started an oral anti-hyperglycaemic agent, although slightly more patients were treated for hypertension and/or hyperlipidaemia in the first year before or after starting an oral anti-hyperglycaemic agent compared to years 2 and 3 after initiating anti-hyperglycaemic medication (Fig. 2). Interestingly, a proportion (12.4%) of patients who received an anti-hyperglycaemic, also received either an antihypertensive and/or an anti-hyperlipidaemic on the same day.

Discussion

These data have provided some insights into the actions of patients and prescribers with respect to the pharmacological management of T2DM through the ability to track the medication history of de-identified patients over a number of years. The longitudinal analyses of these data allowed us to estimate an adherence rate of 42%, a value lying within the range of previous estimates (30–85%) for patients with T2DM taking oral anti-hyperglycaemic agents [15, 16]. An association between adherence to medication and lower haemoglobin A1c (HbA1c) concentrations is expected and has been reported

[4] This metric was implemented as a moving average.

[5] 2158 patients were excluded because their concessional possession ratio was less than 70% and 167 patients because of missing demographic data leaving 18,704 patients in the data set.

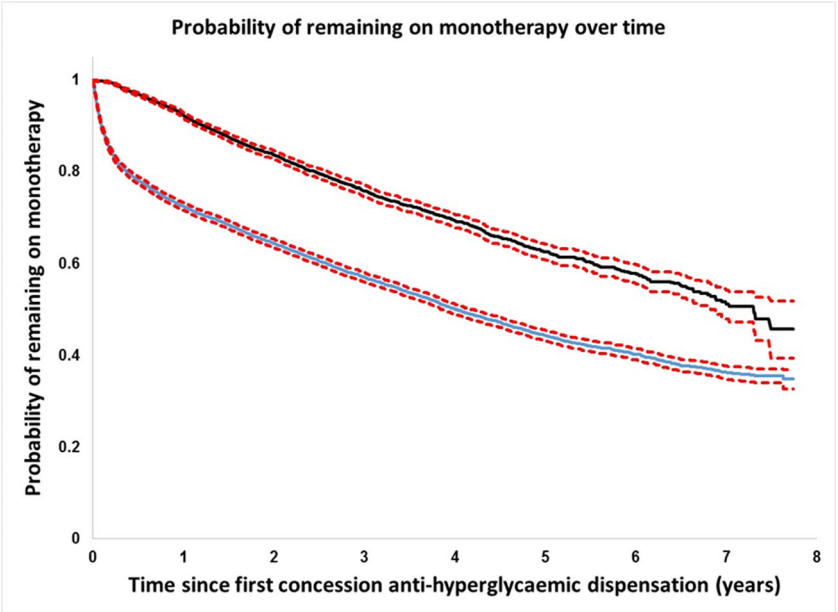

Fig. 1 Time to the addition of a second anti-hyperglycaemic drug by adherence. Solid blue line—adherent patients. Solid black line—non-adherent patients. Dashed red lines—95% CI

[17], and the ability to obtain these data longitudinally and linked to the prescribing data would be preferred. On a population scale, the effectiveness of interventions to improve adherence to medication, however, can be assessed using the methodology we have applied.

Table 2 Multivariate Cox proportional hazard models for the factors affecting the time to addition of a second agent

Variable	Hazard ratio	95% CI	*P* value
Adherence			
Adherent	1	–	–
Non-adherent	0.41	0.391–0.437	< 0.001
Age (*n*)			
< 30 (72)	0.49	0.384–0.620	< 0.001
30–39 (187)	0.85	0.720–0.996	0.045
40–49 (538)	1	–	–
50–59 (1025)	0.895	0.810–0.988	0.029
60–69 (2074)	0.721	0.658–0.790	< 0.001
> 70 (2214)	0.582	0.531–0.637	< 0.001
Sex			
Female	1	–	–
Male	1.19	1.13–1.25	< 0.001
Year of initiating therapy			
< 2012	1	–	–
≥ 2012	1.14	1.07–1.22	< 0.001
Initiating anti-hyperglycaemic agent			
Metformin 500 mg IR	0.637	0.536–0.754	< 0.001
Metformin 500 mg XR	0.723	0.610–0.856	< 0.001
Metformin 850 mg IR	1.05	0.839–1.31	0.682
Metformin 1000 mg IR	1.24	1.02–1.51	0.032
Metformin 1000 mg XR	1	–	–
Glibenclamide	1.51	1.02–2.24	0.042
Gliclazide	0.915	0.761–1.10	0.342
Glimepiride	1.36	1.03–1.79	0.031

We identified several factors that influenced the probability of the addition of a second hypoglycaemic drug. These factors included adherence to therapy, male sex, whether therapy was initiated prior to 2012 or commenced after 2012, and if the initiating agent was a sulphonylurea. As noted, HbA1c values were not included in the claims data base. It may be possible that in a multivariate analysis that included HbA1C, some of the factors we have identified may no longer be significant. However, there are studies that have included HbA1c in their analyses and still found demographic factors to be significant influences on the prescription of add-on therapy [12, 14].

A rather counter-intuitive result was that patients deemed to be non-adherent were found to be less likely to require add-on therapy given the known relationship between adherence and HbA1c [17]. One hypothesis is that patients more adherent to therapy consulted their general practitioner (GP) more frequently so that the need for more anti-hyperglycaemic therapy would more likely be identified. This hypothesis would be amenable to testing by linking the pharmacy payment claim records of the PBS to the Medicare Data base that records episodes of care such as GP visits; however, this was beyond the scope of the present study. If patients attending their GP more often were not meeting their HbA1c targets, a second agent might then be prescribed sooner than in the poorly adherent group who did not attend their GP as often. Another possible explanation might be that the GP may have been less likely to prescribe a second medication if they thought it was less likely to be taken. Possibly also, the 'non-adherent' group had less threatening blood glucose and HbA1C concentrations because of less severe T2DM. Add-on therapy occurred more

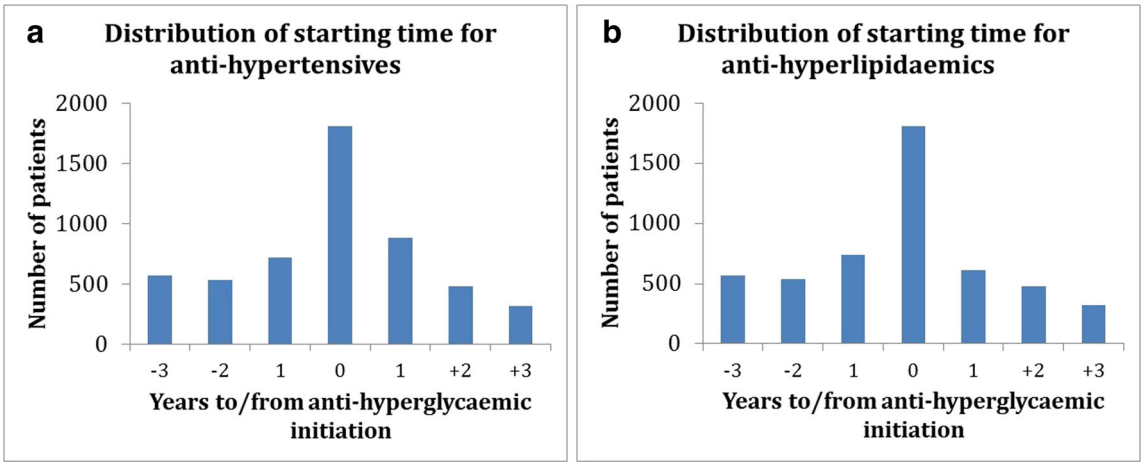

Fig. 2 Distribution of starting times for concomitant drugs. Top panel—anti-hypertensive agents. Bottom panel—anti-hyperlipidaemic agents. 'Time' is with respect to the first dispensation of an anti-hyperglycaemic agent. Data is not mutually exclusive i.e. a patient may have started both drugs before or after the first dispensation of an anti-hyperglycaemic agent

often in the first 6 months of treatment in the adherent group, but the rates of add-on therapy between the groups were similar thereafter. Without actual HbA1c concentrations, there is no way of determining which of these hypotheses is correct. The ability to link de-identified, individual, longitudinal PBS data to specific pathology tests performed would also allow these hypotheses to be tested.

Male sex was associated with an increased rate of add-on therapy; this is in line with a previous paper that demonstrated the inverse sex association i.e. females were less likely to require a change to their initial therapy [13]. Patients claiming their first anti-hyperglycaemic script after 2012 were more likely to require add-on therapy. The likely explanation for this result was the introduction of individualised HbA1c targets around this time [18]. In line with the results of the ADOPT study [19], we also found that patients initiated with sulphonylureas were more likely to be prescribed a second anti-hyperglycaemic drug. The reason for selection of a sulphonylurea drug first cannot be discerned from our data set but possible reasons might include concerns some prescribers have about renal impairment and prescription of metformin.

The differences in rate for add-on therapy observed between the drug classes used likely can be attributed to the various mechanisms of actions of the individual drugs. In contrast to metformin, sulphonylureas increase the amount of circulating insulin that in turn can cause weight gain and hypoglycaemic attacks. Metformin reduces hepatic insulin resistance and is not associated with these adverse effects.

There was no overall trend when comparing patients starting antihypertensives and/or anti-hyperlipidaemics prior to or after initiating an oral anti-hyperglycaemic drug. There was, however, a higher number of patients prescribed these drugs within the first year of initiating a prescription of the oral anti-hyperglycaemic compared to within years 2 and 3 of the index hypoglycaemic prescription. This indicates that a proportion of these patients have at least two of these disorders diagnosed within a similar, short timeframe. This result is expected as the AusDiab study demonstrated that patients with T2DM are three times more likely to have hypertension and 2.5 times more likely to have elevated triglycerides compared to non-diabetic individuals [20]. Additionally, the diagnosis of T2DM changes the targets for cholesterol and blood pressure [7–11], and the diagnosis should now trigger identification and treatment for these conditions.

To date, only one other study has looked at the time to the addition of a second therapy, namely the ADOPT study [19]. However, our results are not directly comparable as ADOPT was a randomised, prospective study. The ADOPT study monitored HbA1c levels and had a strict dose escalation protocol that was implemented prior to the addition of a second agent. In contrast to ADOPT, we do not know the duration of diabetes pre-entry to our study or the degree of glycaemic control in our patients. Additionally, we were unable to delineate what dose escalations, if any, may have taken place prior to the addition of the second agent.

There were some limitations to our analysis. Firstly, we cannot generalise our results to all T2DM patients, as the patients in our cohort could not be selected unless and until they reached concessionary status (mainly $\geq$65 years). Additionally, these results may not be generalised to other countries because of differences in health insurance mechanisms. The reason for add-on therapy was not recorded, nor were any biochemical results such as HbA1c available. It would be useful to be able to link actual HbA1c values to individual patients as variations in the thresholds for intensifying therapy between prescribers are likely. Finally, the results from this study cannot be generalised to all hypoglycaemic drug classes as the majority of the

patients were initiated on metformin. Accordingly, we were not able to calculate the time until add-on therapy for each anti-hyperglycaemic drug class.

Conclusion

This study demonstrated that large longitudinal claims datasets are powerful tools and can provide meaningful data in order to answer important clinical questions pertaining to the 'real world' of community health care. However, we have had to infer the clinical state of the patient based on these pharmacy claim records and then the potential clinical decisions around these inferences. De-identified data linkage with, for example, pathology data, would overcome some of these issues and needs to be facilitated in Australia given the potential of this approach to improve health outcomes through targeting public health interventions.

Author contributions Study conception: SSK, HM, TR, KMW, PC, ROD
Data acquisition: HM, TR
Data analysis: SK, HM, TR
Data interpretation: All authors
Manuscript drafting and editing: All authors
Final approval: All authors

Compliance with ethical standards

Conflict of interest Authors Kumar, Viardot, Greenfield, Williams and Day declare no conflict of interest. Authors McManus and Radovich were employees of Prospection Pty Ltd., the software used in the analyses in this work. Author Cronin is founder and Chief Executive of Prospection Pty Ltd.

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