Exploring inequity in access to medications for Type 2 Diabetes in primary care in the Waikato region

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FINAL REPORT

Background

Type 2 diabetes (T2D) is a growing health issue in New Zealand (NZ)[1] that disproportionately affects twice as many Māori as non-Māori[2] and an increasing number of younger people.[3] T2D is associated with a range of microvascular and macrovascular complications,[4] chronic kidney disease[5] and cardiovascular disease (CVD),[6] the latter being the greatest cause of morbidity and mortality in this patient group. However, complications are reduced in patients that have improved glycaemic control.[7,8] To achieve optimal outcomes and reduce the chance of diabetes-related complications, patients should aim to have their glycated haemoglobin (HbA1c) measurement less than 53 mmol/mol if possible.[9]

Diabetes is primarily managed in primary care, and a number of recent publications suggest that there is considerable inequity in the management of diabetes in New Zealand, particularly for Māori. In an earlier piece of work we have shown that Maori are significantly less likely than non-Maori to be prescribed metformin,[10] but that once prescribed it they are equally likely to have the medication dispensed. This suggests that there may be issues that can be addressed within primary care that are influencing the use of diabetes medications.

Thus, the aim of this small piece of work was to characterise diabetes medication use in a Waikato primary care population, and to report on medication adherence and association with HbA1c levels.

Our objectives, as outlined in our initial proposal were as follows:

1) Characterise diabetes medication use by those with diabetes (including metformin, insulin, sulfonylureas etc)
2) Evaluate equity in access to medications for diabetes
3) Determine prescription adherence by linking prescription to pharmaceutical dispensing data.
4) Evaluate how medication and prescription adherence correlates to clinical outcomes (eg HbA1c levels)

We have primarily met these objectives, but have focussed on key medications. We have also had a summer student (Christopher Mayo) working with us who has supported these data analyses.

Methods

Data Sources

Primary care data were sourced directly from Hauraki Primary Healthcare Organisation (PHO; 17 practices), and then additionally from the electronic patient management systems of 14 general practices affiliated with Pinnacle PHO during September – December 2020.

National Health Index (NHI)-identified patient information was extracted for all patients who had a confirmed diagnosis (≥ 12 months) of diabetes (read code C10) and were aged ≥ 20 years as at October 1 2017. Extracted data included age (at time of data collection), gender, ethnicity, and HbA1c levels (Oct 01 2017 – Sept 30 2018). Patient records were also checked against the Waikato District Health Board clinical records to retrieve missing demographic and diagnosis information. Patients with Type 1 Diabetes were then excluded from the dataset. Additional NHI-matched HbA1c data were obtained from Pathlab New Zealand for the same time period, and these were combined and then averaged to provide a mean value for each patient for the study period.

NHI-matched medication dispensing data was obtained from the Ministry of Health Pharmaceutical Collection (PHARMS) database (Oct 01 2017 – Dec 31 2019). Medications of interest in our studies included, Metformin, insulin, sulfonylureas, pioglitazone, vildagliptin and

Data Processing

For inclusion in the data analysis, all patients with type 2 diabetes had to have received at least two dispensings of the particular glucose lowering therapy (oral hypoglycaemic agents and/or insulin) during the study period. For specific sub-studies, patients were later excluded if they had received medications outside of particular time periods (ie if they had received unfunded vildagliptin prior to the open access approval in October 2018). These details are given in more detail below.

General practices were coded as VLCA or non-VCLA based on their published patient fee structures. HbA1c levels were categorised as < 53 mmol/mol (current glycaemic target),[11,12] 53-64 mmol/mol (previous Ministry of Health Target)[13,14] and > 64 mmol/mol.

Medication adherence was assessed using the PHARMS data, and calculating a medication possession ratio (MPR) for specific timepoints of interest. For these studies, patients needed to have at least two dispensings of a specific medication within the 2018 calendar year, and MPR was calculated as the number of days supply divided by the number of days left in the year after the date of the first prescription. An MPR of ≥ 0.8 was considered to be 'good' adherence.

Statistical analyses

For the various sub-studies, the T2D population of interest was analysed by gender, age group, ethnicity, VLCA status, and diabetes medication regimen. For initiation of new therapies (e.g vildagliptin and/or insulin), the date of the first dispensing was recorded for each patient, and

the cumulative uptake (time to first dispensing) were plotted in a series of cox-regression plots by age, gender, VLCA status, ethnicity, medication adherence and HbA1c levels. Subgroup differences were analysed with chi-squared test and student *t*-tests.

Cross-sectional logistic regression analyses were used to estimate the odds ratio of a patient being dispensed a particular medication, or having a specific medication possession ratio. Linear regression was used to determine the effects of the different parameters on HbA1c levels.

All data analyses were performed in Python 3.7 using the Pandas 0.25.3, Scipy 1.3.2, and Statsmodels 0.10.2 libraries with significance accepted at $P < 0.05$.

Results:

Data from 5577 T2D patients was sourced from Hauraki PHO (n=2676) and directly from the PMS of Pinnacle practices (n=2901). Those without available PHARMS data or with significant missing data were excluded, giving a final dataset of n=5404.

Project 1: Evaluating medication adherence using PHARMS data and MPR

A modified cohort of patients with at least two dispensings of diabetes medications during the 2018 calendar year (n=3885) was used for this sub-study. Of this group, 49.0% were European, 31.2% were Māori, 12.0% were Asian, 6.5% were Pacific.

Table 1 gives the number (proportion) of patients who had been using specific diabetes medication during the study period. Medication use was highest in those patients aged 60-74 years, though metformin, insulin and sulfonylurea use was similar between males and females and between the two PHOs studied.

The proportion of patients using metformin was similar between European (83.7%), Māori (81.8%) and Pacific (81.4%) though all three were significantly lower than Asian (88.7%; all $P < 0.001$). In contrast, Asian were less likely than European and Māori to be using insulin (25.9% vs 33.1% and 31.0%, respectively). No other differences for insulin use were observed. Sulfonylurea use was comparable for all ethnic groups (41.7%, 39.7%, 42.0% and 42.7% for Asian, European, Māori and Pacific). Results are not reported for MELAA and other ethnic groups (other than in the table) due to the small sample sizes.

Table 1: Proportion of patients using metformin, insulin and/or sulphonylureas during the study period.

		Metformin User 2018				Insulin User 2018				Sulfonylurea User 2018			
		NO	**YES**	**Total**	**P-Value**	**NO**	**YES**	**Total**	**P-Value**	**NO**	**YES**	**Total**	**P-Value**
Age Bracket, n (%)	**≤ 44y**	54 (8.5)	233 (7.2)	287 (7.4)	<0.001	170 (6.4)	117 (9.4)	287 (7.4)	<0.001	181 (7.9)	106 (6.7)	287 (7.4)	0.073
	45-59 y	152 (23.9)	885 (27.2)	1037 (26.7)		697 (26.4)	340 (27.4)	1037 (26.7)		587 (25.5)	450 (28.5)	1037 (26.7)	
	60-74 y	251 (39.4)	1440 (44.3)	1691 (43.5)		1141 (43.2)	550 (44.3)	1691 (43.5)		999 (43.4)	692 (43.8)	1691 (43.5)	
	≥75 y	180 (28.3)	690 (21.2)	870 (22.4)		635 (24.0)	235 (18.9)	870 (22.4)		537 (23.3)	333 (21.1)	870 (22.4)	
Gender, n (%)	**Female**	330 (51.8)	1500 (46.2)	1830 (47.1)	0.011	1235 (46.7)	595 (47.9)	1830 (47.1)	0.514	1116 (48.4)	714 (45.2)	1830 (47.1)	0.048
	Male	307 (48.2)	1748 (53.8)	2055 (52.9)		1408 (53.3)	647 (52.1)	2055 (52.9)		1188 (51.6)	867 (54.8)	2055 (52.9)	
Ethnicity, n (%)	**Asian**	53 (8.3)	415 (12.8)	468 (12.0)	0.031	347 (13.1)	121 (9.7)	468 (12.0)	0.040	273 (11.8)	195 (12.3)	468 (12.0)	0.288
	European	310 (48.7)	1592 (49.0)	1902 (48.9)		1272 (48.1)	630 (50.7)	1902 (49.0)		1147 (49.8)	755 (47.8)	1902 (49.0)	
	MELAA	4 (0.6)	28 (0.9)	32 (0.8)		24 (0.9)	8 (0.6)	32 (0.8)		25 (1.1)	7 (0.4)	32 (0.8)	
	Māori	221 (34.7)	991 (30.5)	1212 (31.2)		810 (30.6)	402 (32.4)	1212 (31.2)		703 (30.5)	509 (32.2)	1212 (31.2)	
	Other	2 (0.3)	12 (0.4)	14 (0.4)		8 (0.3)	6 (0.5)	14 (0.4)		8 (0.3)	6 (0.4)	14 (0.4)	
	Pacific	47 (7.4)	206 (6.3)	253 (6.5)		180 (6.8)	73 (5.9)	253 (6.5)		145 (6.3)	108 (6.8)	253 (6.5)	
PHO, n (%)	**Hauraki**	305 (47.9)	1594 (49.1)	1899 (48.8)	0.611	1326 (50.2)	573 (46.1)	1899 (48.9)	0.021	1106 (48.0)	793 (50.2)	1899 (48.9)	0.198
	Pinnacle	332 (52.1)	1654 (50.9)	1989 (51.2)		1317 (49.8)	669 (53.9)	1986 (51.1)		1198 (52.0)	788 (49.8)	1986 (51.1)	
Total		637	3248	3885		2643	1242	3885		2304	1581	3885	

Measurement of medication adherence (MPR)

Metformin had an average MPR of 0.91 and 82.4% of patients on metformin had adequate adherence (MPR ≥ 0.8). Similarly, the mean MPR for sulfonylureas was 0.90, and 80.5% of patient had adequate adherence. These data suggest that both medications are well complied with by patients, though up to 1 in 5 patients may not have full coverage across the year. This study has not explored the reasons behind this, but other studies suggest that this may be due to the cost of getting prescriptions written and/or dispensed (ie access to healthcare issues) and lifestyle issues (remembering and/or actively choosing to take their medication as prescribed).

To explore MPR further, we completed a series of logistic regressions:

<u>For metformin:</u>

- Māori (OR 0.57, 95% CI: 0.46-0.72, P < 0.001). and Pacific Peoples (OR 0.67, CI: 0.46-0.98, P = 0.04) were less likely to have adequate adherence compared to Europeans. There were no other significant differences by ethnicity.
- Patients aged ≤ 44y (OR 0.45, 95% CI: 0.33-0.63, P < 0.001) and 45-59y (OR 0.60, 95% CI: 0.49-0.75, p < 0.001) were less likely to have adequate adherence compared to those aged 60-74y). Patients aged ≥ 75y were more likely to have adequate adherence compared to those aged 60-74y (OR 1.37, 95% CI: 1.03-1.83, P = 0.03).
- Patients on a combination regimen of metformin, insulin, and sulfonylureas were more likely to have adequate adherence compared to those only on metformin alone (OR 1.80, 95% CI: 1.26-2.55, P = 0.001). There were no other significant differences by regimen.
- There were no significant differences by PHO or gender.

<u>For sulfonylureas:</u>

- Māori (OR 0.47, 95% CI: 0.34-0.65, P < 0.001) and Pacific Peoples (OR 0.47, 95% CI: 0.28-0.77, P = 0.003) were less likely to have adequate adherence compared to Europeans. There were no other significant differences by ethnicity.
- Patients aged ≤ 44y (OR 0.56, 95% CI: 0.34-0.92, P = 0.02) and 45-59y (OR 0.53, 95% CI: 0.40-0.72, P < 0.001) were less likely to have adequate adherence compared to those aged 60-74y. There were no other significant differences by age.
- Patients on a combination regimen of metformin, insulin, sulfonylureas, and pioglitazone were less likely to have adequate adherence compared to those on metformin and sulfonylureas (OR 0.27, 95% CI: 0.09-0.82, P = 0.02).
- There were no significant differences by PHO or gender.

<u>For pioglitazone</u>: there were no significant differences found in the logistic regression.

Project 2: Association of medication use with HbA1c levels

Using the cohort of patients from Study 1 we then looked at how MPR correlated with HbA1c levels. The mean HbA1c for all patients on diabetes medication was 64.6 mmol/mol. Mean HbA1c levels were then 73.6, 63.6, 67.9 and 67.3 mmol/mol for users of insulin, metformin, sulfonylureas and pioglitazone, respectively..

Metformin Usage Linear Regression Results (n = 3248)

- Asians had a lower mean HbA1c than Europeans (difference 1.58 mmol/mol, 95% CI: 0.10-3.06, P = 0.04) whilst Māori (difference 3.72 mmol/mol, 95% CI: 2.58-4.86, P < 0.001) and Pacific (difference 4.01 mmol/mol, 95% CI: 2.04-5.98, P < 0.001) had a higher mean HbA1c than Europeans.
- Patients aged ≤ 44 (difference 7.36 mmol/mol, 95% CI: 5.52-9.20, P < 0.001) and 45-59y difference 4.83 mmol/mol, 95% CI: 3.72-5.93, P < 0.001) had a higher mean HbA1c than patients aged 60-74y. Patients aged ≥75y had a lower mean HbA1c than patients aged 60-74y (difference 2.51 mmol/mol, 95% CI: 1.30-3.72, P < 0.001).
- Patients on metformin and insulin had a higher mean HbA1c than patients just on metformin alone (difference 17.73 mmol/mol, 95% CI: 16.38-19.09, P < 0.001). Patients on metformin, insulin, and pioglitazone had a higher mean HbA1c than patients just on metformin (difference 12.29 mmol/mol, 95% CI: 2.61-21.98, P = 0.01). Patients on metformin, insulin, and sulfonylureas, had a higher mean HbA1c than patients just on metformin (difference 19.23 mmol/mol, 95% CI: 17.69-20.77, P < 0.001).
- **Patients with an MPR ≥ 0.8 had a lower mean HbA1c than patients who had MPR < 0.8 (difference 4.50 mmol/mol, 95% CI: 3.30-5.70, P < 0.001).**

Sulfonylureas Usage Linear Regression Results (n = 1581)

- Asians had a lower HbA1c than Europeans (difference 2.37 mmol/mol, 95% CI: 0.07-4.67, P = 0.04)m whilst Māori had a higher HbA1c than Europeans (difference 3.45 mmol/mol, 95% CI: 1.71-5.19, P < 0.001).
- Patients aged ≤44y (difference 9.30 mmol/mol, 95% CI: 6.42-12.19, P < 0.001) and 45-59y (difference 5.17 mmol/mol, 95% CI: 3.51-6.83, P < 0.001) had a higher HbA1c than patients aged 60-74y. Patients aged≥75y had a lower HbA1c than patients aged 60-74 (difference 4.19 mmol/mol, 95% CI: 2.32-6.07, P < 0.001).
- Patients on insulin and sulfonylureas had a higher HbA1c than patients on metformin and sulfonylureas (difference 5.76 mmol/mol, 95% CI: 2.60-8.93, P < 0.001). Patients on metformin, insulin, and sulfonylureas had a higher HbA1c than patients on metformin and sulfonylureas (difference 8.75 mmol/mol, 95% CI: 7.04-10.46, P < 0.001).
- Patients on sulfonylureas alone, on average, had a lower HbA1c than patients on metformin and sulfonylureas (difference 4.46, 95% CI: 2.18-6.75), P < 0.001).
- **Patients with an MPR≥0.8, on average, had a lower HbA1c than patients who had MPR < 0.8 (difference 3.79 mmol/mol, 95% CI: 2.03-5.54, P < 0.001).**

Pioglitazone Linear Regression Results (n = 69)

- Pacific Peoples, had a higher mean HbA1c than Europeans (difference 21.73 mmol/mol, 95% CI: 5.82-37.64, P = 0.008).

- Patients on metformin, insulin, sulfonylureas, and pioglitazone had a higher mean HbA1c than patients on metformin, sulfonylureas, and pioglitazone (difference 16.11 mmol/mol, 95% CI: 5.68-26.54, P = 0.003).
- Female patients, on average, had a higher mean HbA1c than male patients (difference 8.37 mmol/mol, 95% CI: 0.52-16.22, P = 0.04).
- **There was no significant difference in HbA1c in patients with MPR≥0.8 and MPR < 0.8.**

In conclusion: Māori and Pacific patients had worse glycaemic control than European T2D patients, which likely correlates to the lower MPR in these groups. As expected, patients on combination therapy had higher HbA1c levels as did those with lower MPR values. This indicates the need to ensure that patients are compliant with medication, and that they are receiving optimal therapies to reduce HbA1c to as close to target as possible.

Project 3: Evaluating initiation of Vildagliptin therapy in patients in primary care

Because of the recent interest in the Special authority criteria required for patients with T2D to access the new SLGT2i and GL1RA medications, we thought it was timely to explore whether there was inequity in access to other 'new' medications where special authority applications were not required. Thus, we investigated the initiation of vildagliptin, which became available open access in October 2018. This work is currently under review with the NZ Medical Journal (and was presented to GP21: Conference for General Practice in August 2021), but a summary is provided below:

Data was collected for medication use in the 12 months prior to vildagliptin approval in Oct 2018, and then for the 14-month post-funding period. The additional two months was added to allow for any initial delays in GP awareness of the new guidelines. Patients were included in this cohort if they were receiving regular glucose lowering therapy prior to the availability of vildagliptin, but were excluded if they had been dispensed unfunded vildagliptin prior to approval. The total sample size was n=3971.

Results

A total of 724 of 3971 (18.2%) of patients initiated Vildagliptin therapy in the 14 months following approval, and the mean time to first prescription was 192.1 ± 112.4 days. The mean HbA1c of those who commenced vildagliptin therapy was 72.5 ± 18.2 mmol/mol compared to 62.6 ± 17.6 mmol/mol in those who did not initiate therapy. Those initiating vildagliptin were more likely to be younger, Asian, Pacific and/or already on combination therapy. Māori patients were significantly less likely to commence vildagliptin therapy (P < 0.01).

In logistic regression, adjusting for age, gender, medication regimen, VLCA status and HbA1c levels, Asian patients were more likely and Māori less likely to receive vildagliptin than Europeans (P < 0.001; Table 2). Younger patients and those with an HbA1c of > 64 mmol/mol were also more likely to initiate therapy.

Table 1 – Odds ratio (with 95% confidence intervals)[1] of patients initiating Vildagliptin therapy

	OR	P value	95% Confidence Interval	
			[0.025	0.975]
Ethnicity (vs. European)				
Asian	1.34	0.039	1.02	1.78
Māori	0.67	0.001	0.53	0.84
Pacific Peoples	1.25	0.212	0.88	1.78
Other	1.74	0.113	0.88	3.45
Age (vs. 60-74 years)				
≤ 44	1.51	0.012	1.09	2.10
45-59	1.41	0.001	1.14	1.74
≥ 75	0.69	0.007	0.52	0.90
Medication regimen (vs. Metformin only)				
Insulin	0.64	0.043	0.425	0.986
Metformin + Insulin	0.88	0.418	0.63	1.20
Metformin + Insulin + Sulfonylureas	1.01	0.953	0.72	1.41
Metformin + Sulfonylureas	1.68	< 0.001	1.32	2.14
Others	1.34	0.075	0.97	1.85
HbA1c (vs. > 64 mmol/mol)				
< 53 mmol/mol	0.22	< 0.001	0.16	0.29
53 – 64 mmol/mol	0.43	< 0.001	0.34	0.54
VLCA (vs. non-VLCA)	0.95	0.627	0.74	1.15
Female (vs. Male)	1.13	0.182	0.94	1.37

[1] Derived from a binomial multivariate logistic regression model with all variables included.

The mean overall time to first vildagliptin dispensing was 192.1 ± 112.4 days, and nine of the 31 general practices (29%) had a mean time to vildagliptin use of less than 192.1 days. Vildagliptin uptake varied significantly across the 31 different general practices, ranging from 0.0 - 82.4% (Figure 1). Only nine GP practices had a mean time to vildagliptin initiation that was lower than the overall average of 192.1 days, whilst four practices did not commence vildagliptin therapy in any of their T2D patients during this time. This suggests that GP education may be needed to ensure appropriate and early adoption of new diabetes medications.

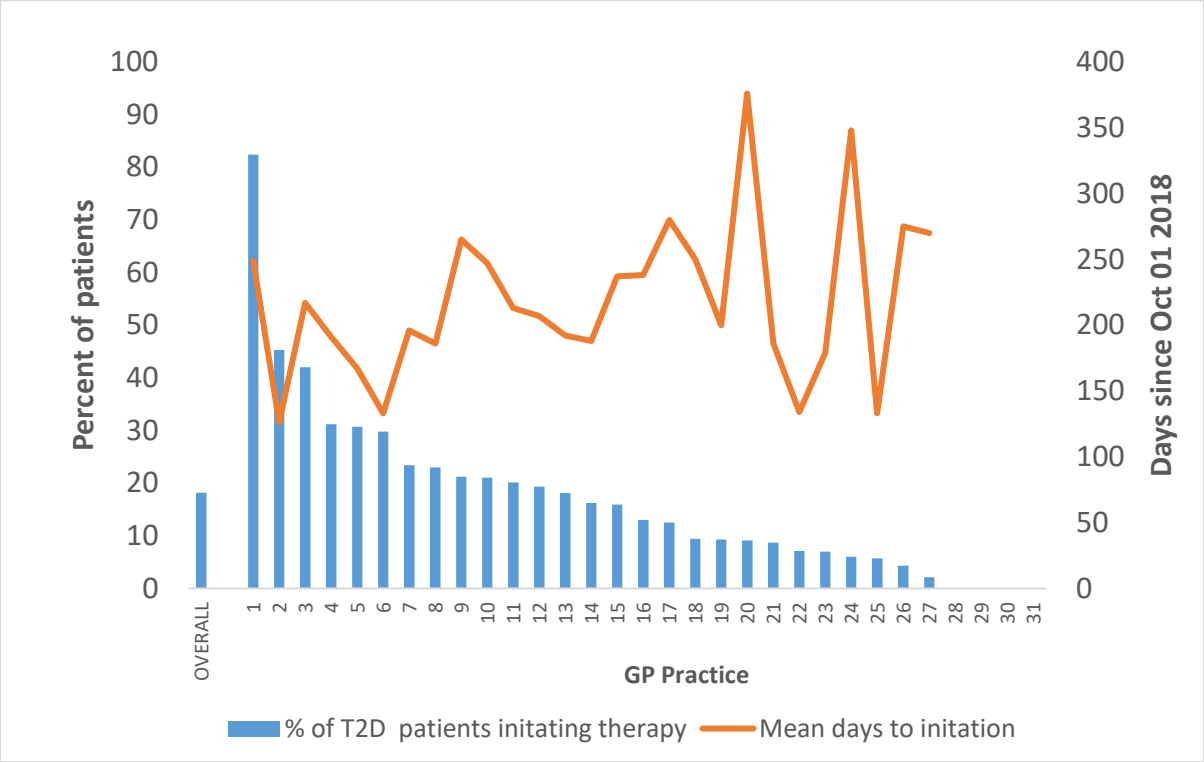


Figure 1: Proportion of type 2 diabetes patients within each practice initiating vildagliptin therapy (Oct 2018 – Dec 2019; blue bars) and mean time to initiation (orange line). Note that practices 28-31 had zero patients commencing vildagliptin therapy.

The cumulative uptake of vildagliptin by VLCA status, ethnicity and HbA1c level is shown in Figure 1. No differences in the cumulative uptake were seen by gender.

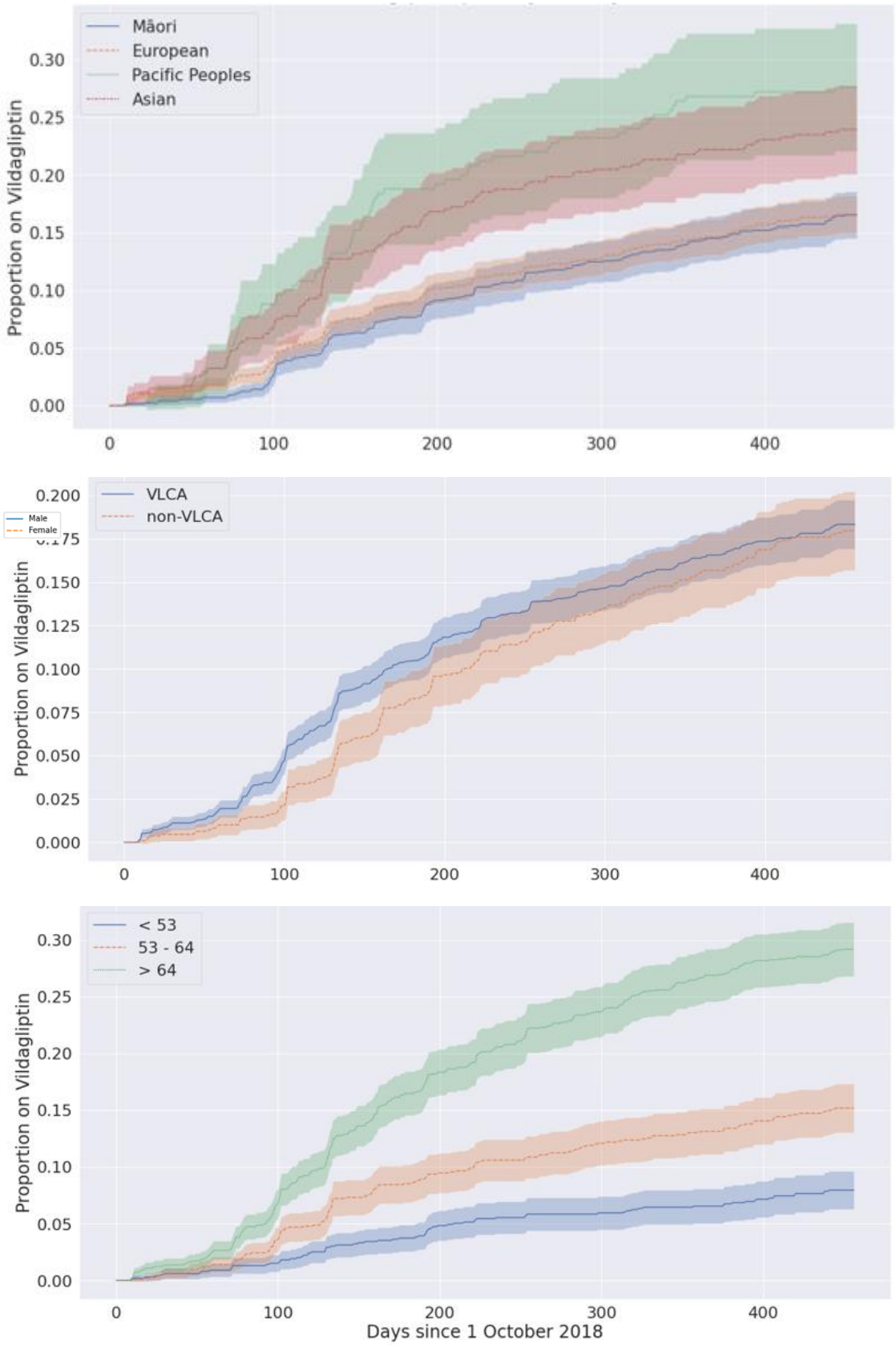


Figure 2: Mean time to first dispensing (with 95% confidence intervals) of vildagliptin following PHARMAC open access funding approval in October 2018. A) by ethnicity, B) by VLCA Status, C) by HbA1c group (mmol/mol)

Project 4: Evaluating initiation and/or use of Insulin therapy in patients with T2D in primary care

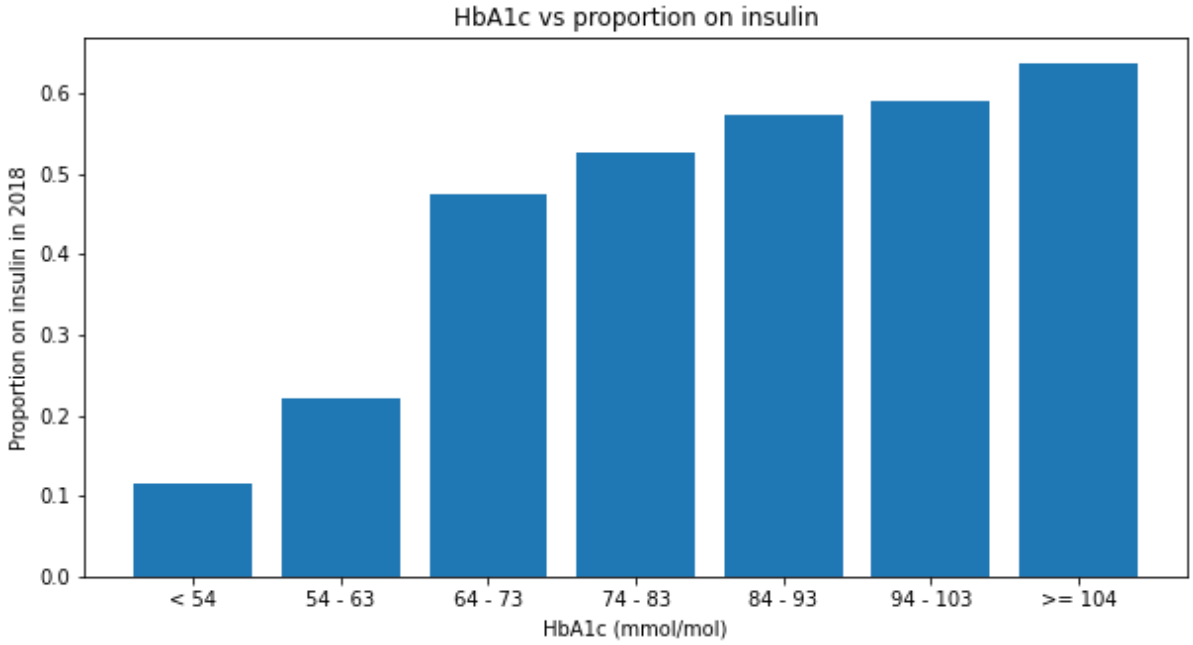
For this study we wanted to evaluate whether there was inequity in the initiation and/or current use of insulin therapy. Although, the HbA1c level at which insulin should be commenced is individualised for each particular patient, for this evaluation we used a level of 64 mmol/mol (based on a previously published guideline) as the trigger point required to initiate therapy. Using the same primary care T2D population as described above, this study included 2532 patients with T2D who were not already using insulin therapy, of which 721 had an HbA1c of ≥ 64 mmol/mol. Medication data use was extracted from the PHARMS database using master NHI.

Results

Of the 721 patients with a 2018 HbA1c ≥ 64 mmol/mol, 644 did not initiate insulin during 2018 whilst 77 did.

Logistic regression results showed that this differ by ethnicity, age or HbA1c levels, though patients on metformin + sulfonylureas were more likely to initiate insulin compared to patients on metformin alone (OR 4.34, 95% CI: 2.07-9.12, P < 0.001)

HbA1c vs proportion of patients currently using insulin



Next, we aimed to characterise the T2D patients who had an elevated HbA1c but had not initiated insulin therapy.

Logistic regression results showed that:

- Pacific Peoples were less likely to be on insulin than Europeans (OR 0.67, 95% CI: 0.45-1.00, P = 0.05)
- Patients aged ≤ 44y (OR 0.65, 95% CI: 0.46-0.91, P = 0.01) and 45-59y (OR 0.62, 95% CI: 0.49-0.78, P < 0.001) were less likely to be on insulin than those aged 60-74y
- Compared to HbA1c 64-74 mmol/mol, patients with HbA1c 75-99 mmol/mol (OR 1.56, 95% CI: 1.25-1.94, P < 0.001) and ≥100 mmol/mol (OR 2.64, 95% CI: 1.84-3.80, P < 0.001) were more likely to be on insulin
- Patients in the Hauraki cohort were less likely to be on insulin compared to patients in the Pinnacle cohort (OR 0.61, 95% CI: 0.49-0.76, P < 0.001). This may be a reflection of the VLCA status of these GP practices.

Whereas patients being prescribed insulin in general tended to be younger and more likely to be Māori, patients prescribed insulin with a high HbA1c tended to be older and less likely to be Māori (although the ethnic effect is highly linked with reduced insulin dispensing in the Hauraki cohort).

OVERALL SUMMARY: The above studies report on the characteristics of diabetes use by T2D patients in primary care, and indicate that there are differences in use and initiation of new therapies by ethnicity and age. However, we do note that we have been unable to source prescription data, hence we have reported only on adherence using PHARMS dispensing data only.

We thank the College of GPs for funding this study. As well as the key publications and conference outputs, this work has also led to more intangible benefits. These include the ability to establish a primary care research team comprised of GPs, specialists and researchers, and to support primary care / PHOs to be involved in the process, including feedback of data for reflection and internal analysis. We were also able to expose a medical summer student to primary care data, which aligns with the College goal of exposing more medical students to general practice.

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