Pharmacologic therapy among patients with type 2 diabetes mellitus admitted to the cardiology service

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ABSTRACT

AIM: To review the management of diabetes control in patients with type 2 diabetes admitted to the cardiology service at Auckland City Hospital for over 48 hours; to assess how many would potentially benefit from introduction of empagliflozin under current Pharmac guidelines.

METHODS: A retrospective audit of all admissions into cardiology between 1 November 2020 and 31 January 2021 prior to the availability of empagliflozin. Data collected included diagnosis and presence of type 2 diabetes, HbA_{1c} and diabetes medications.

RESULTS: A total of 449 patients were admitted, of whom 98 had type 2 diabetes. The median age was 64 years old (IQR 56–76) and 66% of patients were male. Pacific peoples were over-represented in this study population. Fifty percent had an HbA_{1c}>60mnmol/mol and diabetes medication was changed in 50% of these. Overall, 50% of patients would be eligible for empagliflozin under current criteria.

CONCLUSIONS: High proportions of patients have poor glycaemic control and are not up-titrated, suggesting a missed opportunity for medication optimisation. Pacific peoples are over-represented in this group, suggesting that they are at high risk of diabetes and cardiovascular admissions. Empagliflozin provides a targeted way to address renal and cardiovascular outcomes.

Introduction

Type 2 diabetes mellitus (T2DM) is an important risk factor for cardiovascular disease. It confers a two- to four-fold increase in cardiovascular risk[1–3] and is associated with poor outcome. Intensive glycaemic control with agents such as sulphonylureas and insulin have little effect on cardiovascular outcomes and are associated with increased risk of hypoglycaemia.[4] Until February 2021, second-line agents in New Zealand were predominantly sulphonylureas and insulin. These drugs are associated with increased mortality,[5] so are not usually introduced or up-titrated during an acute cardiovascular admission unless HbA_{1c} levels are above 60mmol/mol. Vildagliptin was publicly funded in October 2018 but has limited effects on glycaemic control and offers no cardiovascular benefit.[5]

The advent of sodium-glucose co-transporter 2 (SGLT-2) inhibitors has changed the landscape in the management of T2DM. These drugs reduce all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction and progression of kidney disease without the risk of hypoglycaemia.[6–8] More recent studies indicate that these medications also have similar effects in those with heart failure or chronic kidney disease without diabetes.[8–9] These data strongly suggest these medications should be considered cardiovascular and renal therapy rather than purely agents to improve glycaemic control. A consensus guideline by the American Diabetes Association and the European Association for the Study of Diabetes recommends SGLT-2 inhibitors as second-line agents after metformin for the management of hyperglycaemia in patients with T2DM.[10]

Empagliflozin, an SGLT-2 inhibitor, was publicly funded in New Zealand on special authority from 1 February 2021 for those with T2DM who have an HbA_{1c}≥53mmol/L on at least one blood glucose lowering agent. To target those with T2DM who are most likely to benefit from these medications, Pharmac require certain enrichment criteria be met to qualify for subsidisation. For instance, prerequisites include established renal or cardiovascular complications of T2DM or an increased risk of future cardiovascular disease. The special authority criteria, for the first time, included ethnic groups at higher risk of complications such as Māori and Pacific people (Figure 1).[11]

The aims of this retrospective audit of patients admitted to an inpatient cardiology service are to: measure the prevalence of T2DM; describe their glycaemic control; assess changes to glycaemic treatment during the index hospitalisation; and

Figure 1: Criteria for subsidy of empagliflozin by special authority. Obtained from the New Zealand Formulary website.[11]

Initial Application

Applications from any relevant practitioner. Approvals valid without further renewal unless notified.

Pre-requisites

Patient has type 2 diabetes

and

Patient is Māori or any Pacific ethnicity **or**

Patient has pre-existing cardiovascular or risk equivalent (see note a) **or**

Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator **or**

Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult **or**

Patient has diabetic kidney disease (see note b) **

and

Target HbA_{1c} (of 53mmol/mol or less) has not been achieved despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin or insulin) for at least 3 months

determine the proportion that are eligible for empagliflozin.

Methods

All patients admitted to the cardiology service at Auckland City Hospital during the 3-month period between 1 November 2020 and 31 January 2021 are included in this retrospective study. Patients were identified by the Health Information and Technology Service at Auckland District Health Board. Any patient readmitted during this period was included in the analysis only once. The inclusion criteria were a diagnosis of T2DM and admission under the cardiology service for more than 48 hours. The diagnosis of T2DM was defined by a historical $HbA_{1c} \geq 50$mmol/mol[8] and documentation of physician diagnosis in the medical record. When a prior HbA_{1c} measurement was unavailable, a clinical diagnosis was deemed sufficient.

Chronic kidney disease was defined according to the position statement from Kidney Disease: Improving Global Outcomes (KDIGO).[12]

Stage 1 (>90mL/min/1.73m2), Stage 2 (60–89mL/min/1.73m2), Stage 3A (45–59mL/min/1.73m2), Stage 3B (30–44mL/min/1.73m2), Stage 4 (15–29mL/min/1.73m2), Stage 5 (<15mL/min/1.73m2).

Albuminuria was classified according to the urinary albumin:creatinine ratio. It was defined as minimal <3mg/g), mild (3 to 30mg/g), moderate (30 to 300mg/g) and severe (>300mg/g).[12] Optimisation of medication was defined as change in glycaemic medication at discharge. This was then stratified by patients with an HbA_{1c}>60mmol/mol, or an HbA_{1c}<60mmol/mol.

Two authors (EL and TS) obtained data through electronic medical records and clarified any discrepancies, if there were any, within the data. Information collected was stored on Excel and statistical analysis was done on this program. Data collected included baseline demographics, anthropometric measurement, microvascular complications of diabetes, discharge diagnosis, cardiac and glycaemic therapy on admission and discharge and baseline admission laboratory results.

The cardiovascular comorbidities listed were defined as patients with a previous or current clinical diagnosis based on their medical records. When left ventricular ejection fraction was described as "normal", "mildly impaired", "moderately impaired" or "severely impaired" without a numeric fraction, these were converted to 55%, 45%, 35% and 30% respectively for the purpose of statistical analysis. Likewise, an NT-proBNP of <6pmol/L was recorded as 3pmol/L. Determination of eligibility for subsidisation of empagliflozin was based on published Pharmac criteria[11] and an estimated glomerular filtration rate (eGFR) >30mL/min.

Statistical analysis

Absolute numbers are presented as N. For continuous variables, both the mean ± standard deviation and median with the interquartile range (IQR) have been presented in the tables.

Results

Of 1,290 patients admitted to the cardiology service at Auckland City Hospital between 1 November 2020 and 31 January 2021, 449 patients were in hospital for >48 hours and 98 (22%) patients had T2DM (Figure 2). The median length of stay was 102 (IQR 74–181) hours, or 4 days. The most common reason for hospitalisation was coronary heart disease (41%) followed by heart failure (22%).

The baseline demographics are presented in Table 1. The median age was 64 (IQR 56–76) years and 66% of patients were male. The ethnicities in this study do not reflect the demographics of Auckland, with Pacific people over-represented at 30% (compared to 11% in the community).[13] European and Asian people were under-represented at 30% vs 47% and 24% vs 34% respectively.[14]

The median HbA_{1c} was 60mmol/mol (IQR 52–71). In this cohort, many had cardiovascular comorbidities with approximately 40% previously diagnosed with coronary heart disease and 22% with heart failure. Eighty-seven percent had chronic kidney disease Stage ≥2 and 61% had albuminuria (Table 2). Diabetic retinopathy was documented in 35% of patients, and 19% had established peripheral neuropathy.

Overall, 37% of patients had their glycaemic medications changed during their admission (Table 3). Just over half of all patients had no change to their glycaemic therapy and 11% of patients were discharged with no glycaemic treatment. In patients with an HbA_{1c}≥60 mmol/mol, 50% had their glycaemic medications changed, 6% were discharged on no treatment and 44% had no change.

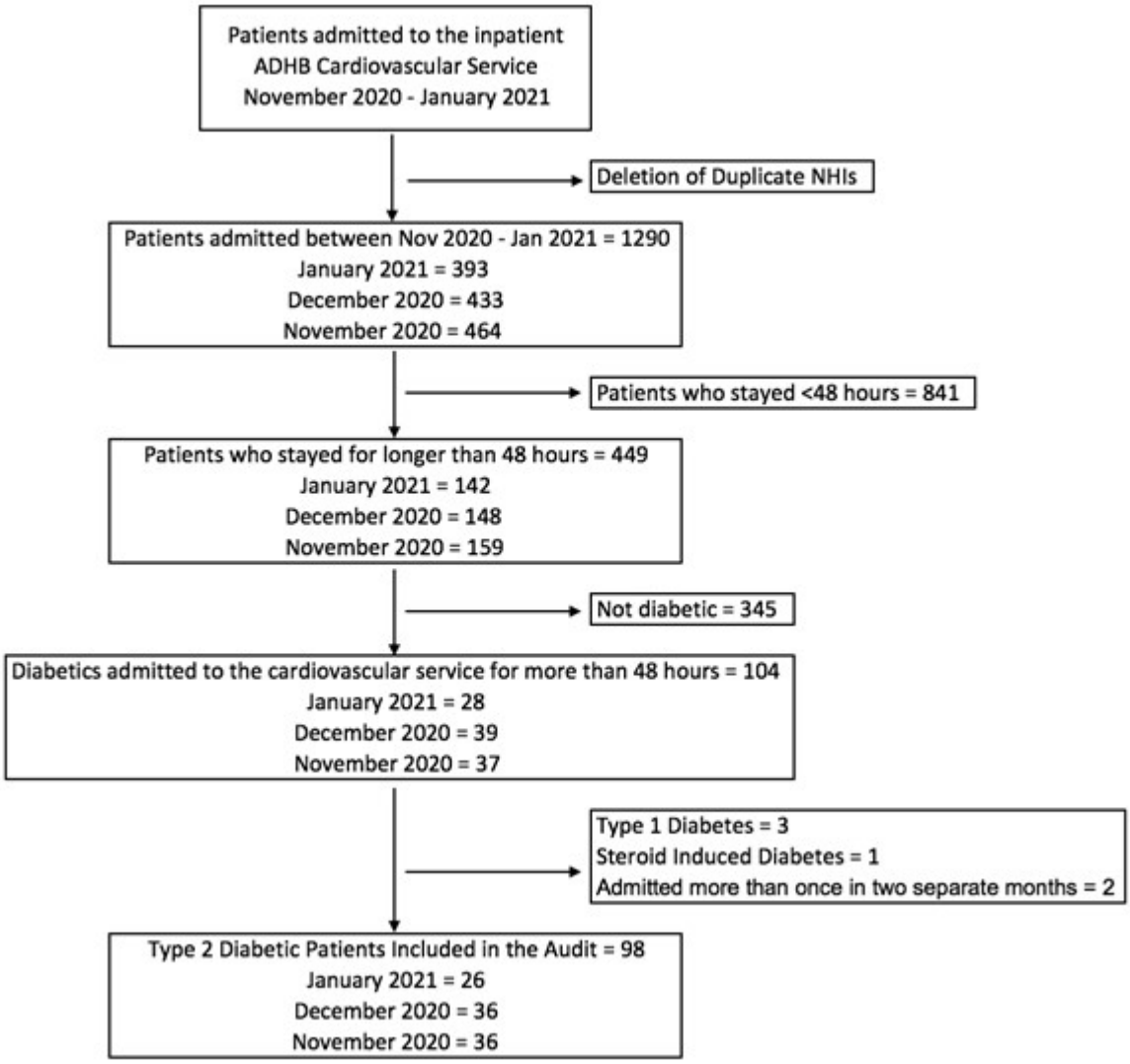
Of the 98 patients included in this study, 50% were eligible for subsidisation of empagliflozin using the current Pharmac special authority criteria (Table 4). Thirty-four patients (34%) did not meet the special authority criteria. Empagliflozin was contraindicated in 13% as their eGFR was less than 30mL/min. In comparison, only 34% of this cohort would meet the eligibility criteria for either of the two main randomised controlled trials that evaluated empagliflozin including EMPA-REG OUTCOME[7] and/or EMPEROR-REDUCED[9] (Table 4).

Common reasons for not meeting eligibility criteria for either study included: body mass index >45kg/m^2, eGFR<30mL/min/1.73m^2, HbA_{1c} less than 53mmol/mol or more than 85mmol/mol or if there were changes to their glycaemic medications within 12 weeks prior to admission. Five patients did not meet inclusion criteria due to their diagnosis being made within 3 months.

Discussion

In this contemporary single-centre retrospective study, we found that one in five patients under the cardiology service had T2DM. The prevalence of T2DM among cardiology inpatients is comparable to the rates seen nationally as per

Figure 2: Study flowchart.



the Acute Coronary Syndrome Quality Improvement (ANZACS-QI) registry data,[15] but perhaps lower than what is seen internationally where the prevalence of T2DM ranges from 30% to 40%.[16,17]

Overall, these patients had poor glycaemic control, with half of them having an HbA_{1c} of more than 60mmol/mol. Only half of those with poorer glycaemic control had any alteration of their glycaemic therapy during a hospitalisation under a cardiology service and 50% of this group met current Pharmac special authority criteria for subsidisation of empagliflozin. It is not clear why changes to glycaemic therapy are made infrequently in these inpatients. The two most likely reasons are a reluctance to change medications during a time of acute illness or pre-procedural fasting and a lack of prescribing confidence in relation to glycaemic pharmacotherapy. This may be exacerbated by the perceived risk of inducing hypoglycaemia with tight control on sulphonylureas and insulin, which is shown to have poor outcomes.

There are several ways in which the management of these patients could be improved during their cardiology hospitalisation. For instance, a diabetes screening tool pathway could be employed to identify more patients with poor glycaemic control. These patients are likely to benefit from the services of dedicated Clinical Nurse Specialists with specific training in both cardiology and diabetes. Alternatively, enabling cardiologists to alter medications themselves through further

Table 1: Baseline characteristics.

	Mean ± SD	Median (IQR)	N=98 (%)
Age [years]	65±13	64 (56–76)	
Male			65 (66)
Ethnicity			
European			29 (30)
Māori			15 (15)
Asian			24 (24)
Pasifika			29 (30)
Middle Eastern			1 (1.0)
Length of stay [hours]	153±131	102 (74–181)	
Presentation			
ST-elevation myocardial infarction			12 (12)
Non-ST-elevation myocardial infarction			16 (16)
Unstable angina			3 (3.1)
Heart failure			22 (22)
Arrhythmia			18 (18)
Aortic valve intervention			3 (3.1)
Non-cardiac chest pain			3 (3.1)
Other cardiac			6 (6.1)
Other non-cardiac			6 (6.1)
Body mass index [kg/m^2]	32±8.4	30 (25–37)	
Cardiovascular comorbidities			
Hypertension			77 (79)
Heart failure			48 (49)
Atrial arrhythmias			30 (31)
Coronary heart disease			68 (69)
Dyslipidaemia			61 (62)
Stroke			13 (13)
Peripheral vascular disease			5 (5.1)
Smoking status			
Never smoked			45 (46)

Table 1 continued: Baseline characteristics.

Ex-smoker			40 (41)
Current smoker			13 (13)
Cardiac medications			
Statins and/or ezetimibe			76 (78)
Alpha-blockers			11 (11)
Calcium channel blockers			25 (26)
ACEi or ARB			80 (82)
Beta-blockers			71 (72)
Diuretics			52 (53)
Left ventricular ejection fraction [%]	45±16	46 (33–58)	
NT-proBNP [pmol/L]	412±593	151 (42–551)	

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; IQR = interquartile range.

education would improve patients' care. Either of these options may help to overcome potential lack of prescribing confidence and break down siloed care. The significance of optimal management of T2DM in those with cardiovascular disease could be reflected and communicated more carefully on discharge summaries. Finally, among those admitted with acute coronary syndromes, HbA_{1c} could be made a mandatory field for data entry on the ANZACS-QI registry.[18] This would allow a more comprehensive study of glycaemic control in this important subset of patients admitted under cardiology services throughout the nation. Additionally, the inclusion and reporting of data relating to agents that improve cardiovascular outcomes, such as SGLT2 inhibitors and glucagon-like peptide 1 (GLP-1) agonists, would aid in the appropriate uptake of these medications.

Interestingly, half of those included in this study met the Pharmac special authority criteria for subsidisation of empagliflozin, while only one in three would have been eligible for enrolment in the two pivotal randomised controlled trials of empagliflozin. For the first time the Pharmac special authority criteria for subsidisation of a medication included ethnicities (Māori and Pacific people) at high risk of poor outcomes. The prevalence of T2DM is two to three times higher in these ethnic groups compared to others.[19] In our cohort, Pacific people were overrepresented relative to the local population. Of those who met the special authority criteria, 47% were Māori or Pacific people. According to the current Pharmac criteria, those with an eGFR less than 30mL/min/1.73m^2 are ineligible for empagliflozin. However, it is known that empagliflozin can be safely used in those with chronic kidney disease who have an eGFR more than 20mL/min/1.73m^2.[9] A more recent analysis demonstrated the value of empagliflozin in improving renal and cardiovascular outcomes across the spectrum of chronic kidney disease.[20] Furthermore, it slows progression of kidney disease and reduces rates of renal events.[21]

Limitations

The sample size of this study is small and are all from a single centre. They may be non-representative of all patients admitted under a cardiology service throughout the country.

As this is a retrospective study, there were missing data in some variables. The short study timeframe of 3 months and the inclusion of a holiday period may introduce a temporal bias.

Table 2: Baseline diabetes characteristics.

	Mean (SD)	Median (IQR)	N=98 (%)
HbA_{1c} (mmol/mol)	64±18	59.5 (52–71)	
<60			48 (50)
≥60			48 (50)
Blood pressure			
SBP ≥140mmHg or DBP ≥90mmHg			25 (26)
SBP<140mmHg or DBP <90mmHg			73 (74)
eGFR [mL/min/1.73m^2]			
≥90			13 (13)
60 to <90			41 (42)
30 to <60			31 (32)
<30			13 (13)
Chronic kidney disease stage			
1			13 (13)
2			41 (42)
3A			20 (20)
3B			11 (11)
4			7 (7.1)
5			6 (6.1)
Urine albumin:creatinine ratio (mg/g)			
<3			34 (35)
≥3 to <30			43 (44)
≥30 to 300			11 (11)
>300			6 (6.1)
Nil			4 (4.1)
Glycaemic medications on admission			
Metformin			49 (50)
Vildagliptin			5 (5.0)
Vildagliptin/metformin combination			16 (16)
Sulphonylurea			18 (18)
Insulin			34 (35)
None			16 (16)

Abbreviations: DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NTproBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure.

Table 3: Changes to glycaemic medications during admission.

All patients (n=98)	
Changed	36 (37%)
No change	51 (52%)
No treatment at discharge	11 (11%)
HbA_{1c}>60 mmol/mol (n=48)	
Changed	24 (50%)
No change	21 (44%)
No treatment at discharge	3 (6.0%)
HbA_{1c}≤60 mmol/mol (n=48)	
Changed	12 (25%)
No change	8 (17%)
No treatment at discharge	28 (58%)

NB: Two patients had type 2 diabetes as part of their medical history, however, their primary residence was not Auckland, so no HbA_{1c} was recorded on their electronic medical records, thus they were not included in the sub-group analysis of HbA_{1c} control.

Table 4: Eligibility for subsidisation of SGLT-2 trials.

Eligible for subsidisation of empagliflozin under special authority	
Yes	49 (50%)
No due to <3 months glycaemic therapy prior to admission	11 (11%)
No due to HbA_{1c}≤53mmol/mol	23 (23%)
Insufficient information	2 (2.0%)
Excluded as eGFR<30 mL/min/1.73 m2	13 (13%)
Eligible for inclusion in EMPA-REG OUTCOME and/or EMPEROR-Reduced	
Yes	34 (35%)
No	64 (65%)

Abbreviations: eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; EMPEROR-Reduced = Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure.

Conclusion

In this 3-month retrospective snapshot study on this single centre, we found a high prevalence of T2DM among patients admitted under the cardiology service. These patients generally had poor control. Most did not have any change to their glycaemic therapy. Patients with established cardiac disease constitute a high-risk population that warrant opportunistic optimisation of their diabetes therapy during their hospitalisation. With the recent subsidisation of SGLT2 inhibitors and GLP-1 agonists, glycaemic agents that improve cardiovascular outcomes, cardiology services throughout the country should be comfortable with the initiation and titration of these medications. Moreover, each hospitalisation should be viewed as an opportunity to initiate these medications where appropriate.

COMPETING INTERESTS
None to declare.

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