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# Evaluation of SGLT-2 inhibitor treatment in type 2 diabetes patients with very high cardiovascular risk

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ABSTRACT

*Aims:* To evaluate whether the prescription of SGLT2-inhibitors in primary care patients with type 2 diabetes (T2DM) and a very high risk was according to the newest updated Dutch general practitioners' practice guidelines on T2DM.

*Methods:* This observational study with routine care data was conducted in a primary care setting in the Netherlands. The very high-risk population size was identified and analyzed via descriptive statistics. In this high-risk group the percentage of patients treated with SGLT2-inhibitors was assessed.

*Results:* Of the 1492 T2DM patients managed in primary care, 475 (31.8%) were classified as very high-risk based on (a history of) ischemic cardiovascular disease, chronic kidney disease, and/or heart failure. Of the very high-risk patients, 49 (10.3%) received SGLT2-inhibitors conform the guidelines. Of the remaining 426 high-risk patients 334 (70.3%) had no contraindication (eGFR <30 ml/min/1.73 $m^2$ or HbA1c <53 mmol/mol) for initiating SGLT2-i prescription according to the guidelines. None of these patients received an GLP-1 agonist as alternative.

*Conclusions:* The vast majority of very high-risk type 2 diabetes patients were not prescribed SGLT2-I. There is substantial room for improvement in the management of these critical T2DM patients because most of them had no contraindications for initiating SGLT2-I prescription.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is currently one of the most prevalent chronic conditions in the Netherlands. In 2018, T2DM affected about 6.5% of the Dutch population at a cost of 8173 million euro's, which amounts up to 9.4% of the annual Dutch healthcare budget [1]. Diabetes mellitus is associated with a 2–4 times higher risk in cardiovascular disease, is one of the leading causes of chronic kidney disease (CKD) and is associated with a 9–58% increased risk of heart failure (HF), adding up to a 75% increase in all-cause mortality rate [2–5]. Given the prevalence of cardiovascular and renal complications, the paramount aim in T2DM treatment is the prevention of these cardiovascular and renal complications. Risk reduction is achieved mainly via cardiovascular risk reduction, subsequently improving overall quality of life through the management and risk mediation of diabetes-associated complications.

The Dutch college of general practitioners (NHG) published revised T2DM guidelines in November 2021 that introduced a new treatment algorithm specifically aimed at T2DM patients with a very high cardiovascular risk. This new treatment algorithm recommends the use of Sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) as first choice treatment in such T2DM patients. With SGLT-I, mortality is reduced by 15%, and ischemic cardiovascular events prevented in 12%. But in addition, it slows chronic renal disease progression (−30%), and prevents hospitalization for heart failure (−29%) in patients with T2DM with a very high cardiovascular risk [6].

In the updated 2021 T2DM NHG guidelines the very high-risk population was defined as (i) prior cardiovascular events, i.e. acute coronary syndrome (ACS) including myocardial infarction (MI), stable angina pectoris (AP), transient ischemia attack (TIA), ischemic stroke, abdominal aortic aneurysm (AAA), intermittent claudication caused by symptomatic iliofemoral atherosclerosis or ischemia, other atherosclerosis, advanced chronic kidney disease, and/or heart failure with a reduced ejection fraction (LVEF <40%) (HFrEF) [7]. The GLs consider frailty, a

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life expectancy < five years, an eGFR < 30 ml/min/1.73 $m^2$ and/or hemoglobin-a1c (HbA1c) < 53 mmol/mol as contra-indication for initiating SGLT2-I prescription in very high-risk T2DM patients.

The aim of this study is to evaluate the prescription of SGLT2-Is in primary care high-risk T2DM patients according to the newly revised Dutch 2021 T2DM guidelines.

## 2. Methods

### 2.1. Study design and setting

This observational study was conducted at the Leidsche Rijn Julius Health Centers, in Utrecht, the Netherlands. Five primary care clinics (30 GPs, 13 practice nurses) provide care to a population of 48,795 people.

T2DM patients were identified via the International Classification of Primary Care (ICPC) code which is used to classify and categorize patient episodes in the primary care electronic health record (EHR)[8]. The T2DM ICPC code (T90.02) was used to filter the total population to the population of interest. Data of participants managed in the primary care integrated care program for type 2 diabetes were analysed.

### 2.2. Data collection

Patient characteristics (age, gender, body mass index (BMI), diabetes duration, systolic and diastolic blood pressure, smoking status, frailty, physical activity, alcohol use, estimated glomerular filtration rate (eGFR), urine albumin/creatinine ratio (ACR), hemoglobin A1C (HbA1c) were collected from the EHR. Data was retrospectively collected over a timeframe of 12 months from May 2021 to May 2022.

Frailty was assessed and calculated via the UPRIM frailty index, a frailty indicator based on age (60 +), consultation gap > 3 years, polypharmacy > 5 medications and multimorbidity, where a score of > 0.2 indicates patient frailty and was set as the cut off point [9].

Patient physical activity was scored according to the Dutch activity guidelines of 2017 recommending on average daily 2.5 h of moderate intensive exercise, in combination with muscle and bone strengthening exercises twice a week [10]. Patient were dichotomized (yes/no) reaching these physical activity goals.

Patients were classified as very-high risk according to the ICPC codes recorded in the EHR: ischemic cardiac diseases: Acute coronary syndrome/ myocardial infarction (ICPC: K75), angina pectoris (AP-ICPC: K74), TIA (ICPC: K89), Ischemic stroke (ICPC: K90.03), Abdominal Aortic Aneurysm (ICPC: K99.01), Intermittent claudication with symptomatic iliofemoral atherosclerosis or ischemia (ICPC: K92.01), atherosclerosis(ICPC: K91). Patients suffering from heart failure (ICPC: K77) were considered at very high-risk in case of a reduced left ventricular ejection fraction (LVEF<40%) (HFrEF).

Patients who suffered from chronic kidney disease were classified very high-risk based on eGFR an ACR. Very high-risk status was given to patients with either eGFR > 60 ml/min/1.73 $m^2$ and ACR> 30 or eGFR > 45–59 ml/min/1.73 $m^2$ and ACR> 3 or eGFR > 10–44 ml/min/1.73 $m^2$.

#### 2.2.1. Ethical approval

The Medical Research Ethic Committee (MREC) of the University Medical Centre Utrecht confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study and therefore an official approval of this study by the MREC UMC Utrecht is not required under the WMO.

### 2.3. Medication

Data on medication use was extracted via the anatomical therapeutic chemical classification code (ATC code)[11]: SGLT2-inhibitors (ATC: A10BK), GLP-1 agonists(ATC: A10BJ), Metformin (ATC: A10BA02), SU derivates (ATC:A10BB), DPP4-inhibitors (ATC: A10BH), Insulin (ATC: A10A), Diuretics (ATC; CO3), Calcium antagonists (ATC:C08), ACE/angiotensin inhibitors (ATC:C09) Beta blockers (ATC:C07) and statins (ATC: C10A).

Life expectancy was not used as exclusion criterium for SGLT2-I in this study because this variable is difficult to assess and not systematically noted in the EHR.

### 2.4. Data analyses

To quantitatively describe extracted patient data, percentages, mean with standard deviation (SD), medians with interquartile range (IQR) and quantitative data were calculated. SPSS statistics (version 28.0.1.0) and Microsoft Excel (version 16.59) were used for database construction, calculations, and statistical analysis.

## 3. Results

### 3.1. Characteristics of the study population

A total of 1629 T2DM patients were identified, with 1.525 (93.6%) of them treated in primary care (1.492 (91.6% of all T2DM) in the primary care integrated care program). See Fig. 1. For the latter group, patient characteristics were calculated (Table 1). Mean age was 63.0 (SD 12.9) years, and 54.6% were male. The median diabetes duration was 9.5 (IQR 8.6) years, the median BMI 28.7 (IQR =7) kg/$m^2$. 13.8% were active smokers, 32.7% quit smoking, 50.7% had never smoked. 27.6% consumed alcohol on a regular basis. Mean systolic blood pressure (SBP) was 136 (SD 15.6) mmHg and diastolic blood pressure was 82 (SD 10.3) mmHg. In total, 40.1% was frail and 42.6% met the physical activity standards. Median HbA1c was 54 (IQR 15) mmol/mol, median eGFR 86 (IQR 30) ml/min/1.73 $m^2$, median ACR 0.8 (IQR 1.8) mg/g and median LDL cholesterol was 2.2 mmol/l (IQR 1.3).

### 3.2. High-risk identification

In total, 475 patients (31.8%), were classified as very high-risk, and 316 (66.5%) of them were frail.

Among the 385 patients that had either one or multiple episodes of iCVD (25.8%), 162 patients met the eGFR and ACR criteria for CKD (31.8%) and 9 HFrEF (LVEF <40%) were identified (Table 2). Subgroup analysis was performed to identify patients with multiple comorbidities. A total of 71 patients were found to have both iCVD and CKD, three patients had iCVD in combination with HFrEF (LVEF <40%), one patient had CDK as well as HFrEF and three patients were identified to have a combination of all three comorbidities (Table 2). All subgroups were analyzed to establish distribution of frailty and SGLT2-I's use among patients (Fig. 2). In total 308 patients only had iCVD and among them 192 (62%) was frail and 28 (9%) used SGLT2-I. Of the 87 patients with only CKD almost 70% was frail and 11.5% (n = 10) used SGLT2-I. Relatively few patients (n = 2) had HFrEF only, and one of them used SGLT2-I (50%). The iCVD|CKD group was the biggest combined group consisting of 71 patients, including 59 (83%) frail patients and 8 (11%) SGLT2-I users.

### 3.3. Treatment limitations for very high-risk patients

The new T2DM guideline advises to start treatment if the very-high risk patient is not frail, has an eGFR> 10 ml/min/1.73 $m^2$and a life expectancy of more than five years. Moreover treatment with SGLT2-I's is not recommended when eGFR is below 30 ml/min/173 $m^2$ and when HbA1c is < 53 mmol/mol. If the eGFR lies between 10 and 30 ml/min/1.73 $m^2$, GLP-1 agonist substitution for SGLT2-I's is advised. To accurately assess guideline adherence the high risk T2DM was filtered for frail patients (UPRIM frailty index >0.2) and eGFR. In 475 very high-risk patients, 316 patients were considered frail and one individual had a

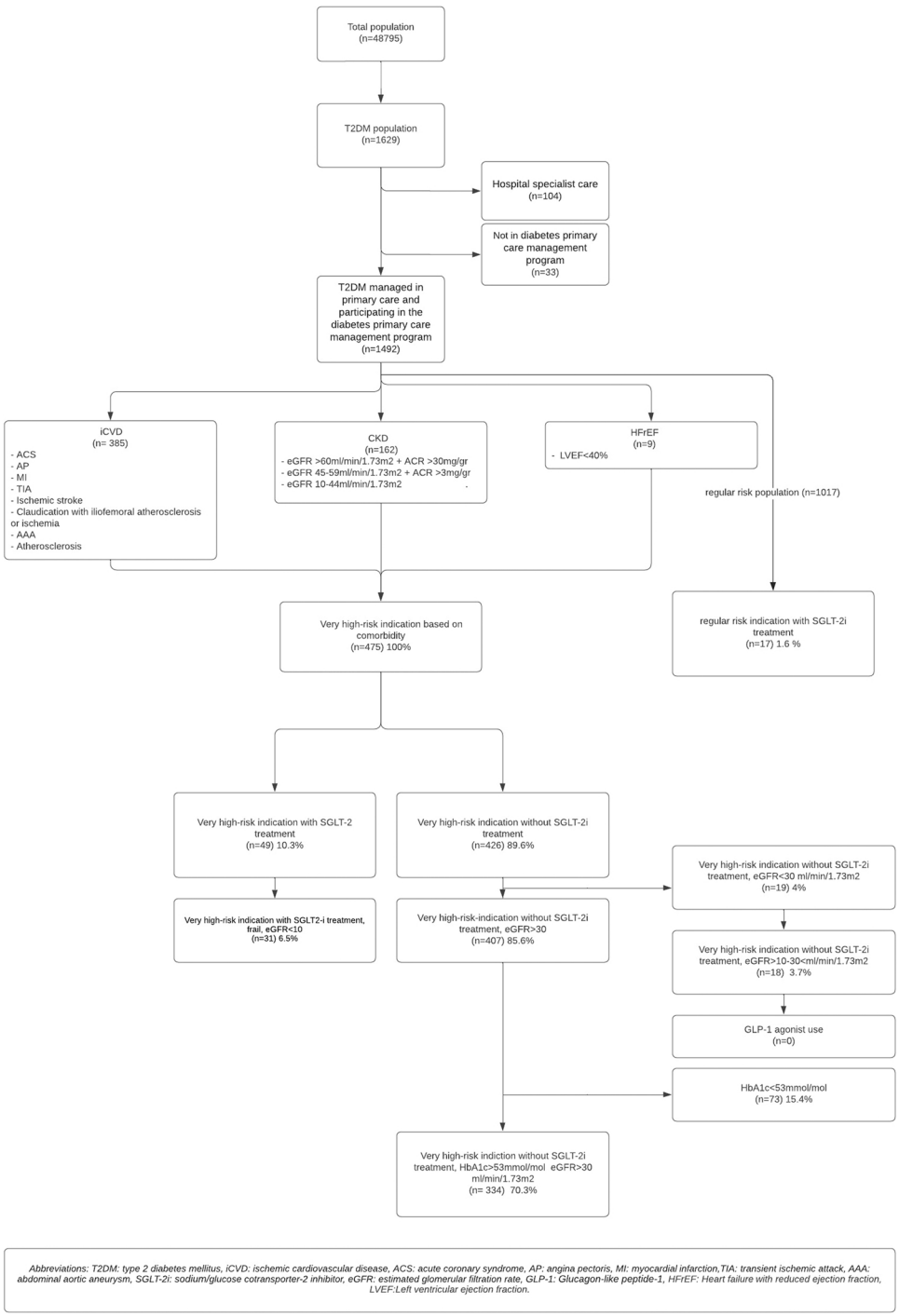


**Fig. 1.** Schematic presentation of the study population and subgroup differentiation. Abbreviations: T2DM: type 2 diabetes mellitus, iCVD: ischemic cardiovascular disease, ACS: acute coronary syndrome, AP: angina pectoris, MI: myocardial infarction,TIA: transient ischemic attack, AAA: abdominal aortic aneurysm, SGLT-2i: sodium/glucose cotransporter-2 inhibitor, eGFR: estimated glomerular filtration rate, GLP-1: Glucagon-like peptide-1, HFrEF: Heart failure with reduced ejection fraction, LVEF:Left ventricular ejection fraction.

eGFR below 10 ml/min/1.73 $m^2$, leaving 158 non-frail with an eGFR > 10 ml/min/1.73 $m^2$ (Table 2).

### 3.4. Medication use

In total, 66 patients used SGLT2-I of whom 49 (10.3%) could be classified as very high-risk (Table 3, Fig. 1). Of the 426 patients with very high risk and without SGLT2-I, 334 (70.3%) had no contraindication for initiation of SGLT2-I (eGFR <30 ml/min/1.73 $m^2$ and/or Hb1Ac <53 mmol/mol). See Fig. 2.

In total 19 patients had an eGFR <below 30 ml/min/1.73 $m^2$, with one of them an eGFR< 10 ml/min/1.73 $m^2$. None of the 18 very high-risk T2DM patients eligible for GLP-1 agonist treatment did receive this as an SGLT2-I alternative.

All 475 very high-risk T2DM patients was also studied for alternative cardiovascular risk mediating medication, e.g. diuretabletics, calcium antagonists, angiotensin inhibitors, beta blockers and statins (see Table 3).

## 4. Discussion

### 4.1. Summary and conclusions

We wanted to evaluate the current state of treatment and T2DM National GP guideline adherence of those with a cardiovascular very high-risk, notably the SGLT2-i uptake. Of the patients with T2DM and

**Table 1**
Patient characteristics of the study population (n = 1.492).

| | n = 1.492 |
|---|---|
| Age (years, mean, SD) | 63 (12.9) |
| Gender (men %) | 54.6 |
| Diabetes duration (years, median, IQR) | 9.5 (8.6) |
| BMI (Kg/m$^2$, median, IQR) | 28.7 (7) |
| Smoking | |
| Active smoker (%) | 13.8 |
| Ex- smoker (%) | 32.7 |
| Never smoked (%) | 50.7 |
| Alcohol (Yes %) | 27.6 |
| SBP mmHG (mean, SD) | 136.1 (15.6) |
| DBP mmHG (mean,SD) | 82.1 (10.3) |
| Frailty* * (Yes, %) | 40.1 |
| Activity* ** (Yes, %) | 42.6 |
| HbA1c (mmol/mol, median, IQR) | 54 [15] |
| eGFR (ml/min/1.73 m$^2$, median, IQR) | 86 [30] |
| ACR (mg/g, median, IQR) | 0.8 (1.8) |
| LDL-Cholesterol (mmol/l, median, IQR) | 2.2 (1.3) |

Abbreviations: SD: Standard deviation, IQR: interquartile range, BMI: Body mass index, SBP: systolic blood pressure, DBP: Diastolic blood pressure, HbA1c: Hemoglobin A1c, eGFR: Estimated glomerular filtration rate, ACR: albumine creatinine ratio LDL: Low density lipoprotein
* * Frailty conform to UPRIM frailty index > 0.2
* **Sufficient physical activity according to Dutch activity guidelines 2017

**Table 2**
High risk population.

| | Total (n = 1.492) |
|---|---|
| **Ischemic cardiovascular disease (iCVD)*** | 385 (25.8%) |
| Angina pectoris (SAP, UAP) | 112 |
| Myocardial infarction | 129 |
| Transient ischemic attack | 43 |
| Ischemic stroke | 68 |
| Abdominal aortic aneurysm | 19 |
| Intermittent claudication | 40 |
| Atherosclerosis | 11 |
| **Chronic kidney disease (CKD)** | 162 (31.8%) |
| eGFR > 60 ml/min/1.73 m$^2$, ACR > 30 mg/g | 38 |
| eGFR 45–59 ml/min/1.73 m$^2$, ACR > 3 mg/g | 43 |
| eGFR 10–44 ml/min/1.73 m$^2$ | 81 |
| **Heart failure (HFrEF)** | 60 (4.0%) |
| LVEF < 40% | 9 |
| LVEF > 40% | 34 |
| LVEF unknown | 17 |
| **Total risk population** | 475 (31.8%) |
| iCVD | 385 |
| CKD | 162 |
| HFrEF < 40% | 9 |
| iCVD and CKD | 71 |
| iCVD and HFrEF< 40% | 3 |
| CKD and HFrEF< 40% | 1 |
| CKD and HFrEF< 40% and iCVD | 3 |
| UPRIM Frailty > 0.2 | 316 |
| eGFR< 10 ml/min/1.73 m$^2$ | 1 |

Abbreviations: SAP: Stable angina pectoris, UAP: unstable angina pectoris, ICPC: International Classification of Primary Care. eGFR: estimated glomerular filtration rate, ACR: Albumine creatinine ratio, HFrEF: heart failure with restricted left ventricle ejection fraction, LVEF: Left ventricle ejection fraction.
*iCVD total is less than cumulative episodes due to patients with multiple ischeamic cardiovascular comorbidities

managed in a primary care management program, 31.8% had a very high risk of whom 10.3% was treated with SGLT2-Is as recommended in the most recent updated Dutch GP guidelines. Importantly, of the very high-risk T2DM patients some had contra-indications according to the guidelines for initiating SGLT2-I, namely eGFR< 30 ml/min/1.73 m$^2$or an HbA1c < 53 mmol/mol), but the vast majority (70.3%) did not have these contra-indications, but nevertheless did not receive SGLT2-I treatment irrespective of having a good indication. Neither was

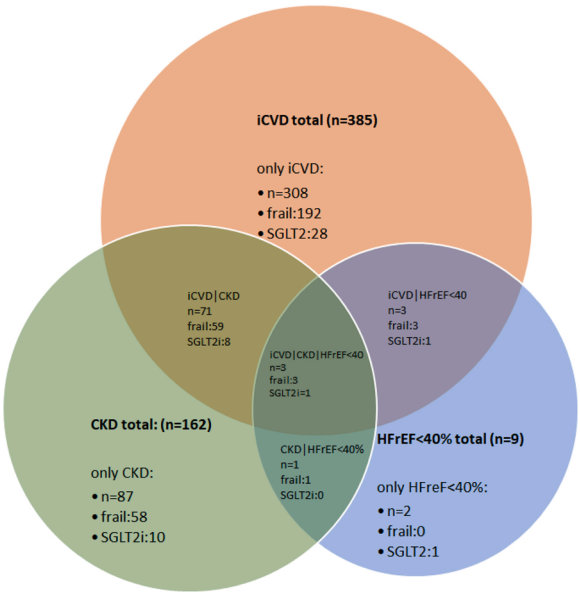


**Fig. 2.** Very high risk population, frailty and treatment with SGLT2-inhibitor. Abbrevations: iCVD – ischemic cardiovascular disease; CKD – chronic kidney disease; HFrEF – heart failure with restricted ejection fraction.

**Table 3**
Medication.

| | Total patients n = 1492 (100%) | High-risk patients n = 475 (100%) |
|---|---|---|
| SGLT2 inhibitor | 66(4.4%) | 49(10.3%) |
| GLP1-agonist | 84(5.6%) | 30(6.3%) |
| Metformin | 1112(74.5%) | 359(75.6%) |
| SU-Derivative | 581(38.9%) | 179(37.7%) |
| DPP4 | 152(10.2%) | 49(10.3%) |
| Insulin | 284(19%) | 128(26.9%) |
| Diuretics | 438(29.4%) | 216(45.5%) |
| Calcium antagonist | 370(24.8%) | 190(40%) |
| ACE/Angiotensin inhibitor | 725(48.6%) | 324(68%) |
| Beta blocker | 424(28.4%) | 245(51.6%) |
| Statins | 960(64.3%) | 384(80.8%) |

substitution with GLP1-agonists considered in very high-risk T2DM patients with an eGFR 10–30 ml/min/1.73 m$^2$ as is recommended in the updated Dutch GP T2DM guidelines.

These results illustrate that cardiovascular risk prevention with SGLT2-I in very high-risk T2DM patients is low. The COVID-19 pandemic has hampered regularly planned control visits to the surgery in this period and this could have negatively affected the results. We collected data in May 2022, only six months after publication of the updated Dutch GP guidelines for T2DM patients. Thus, GPs and practice nurses had likely insufficient time to initiate SGLT2-I. Finally, polypharmacy and the shared decision process could have hampered initiation of SGLT2-I. Nevertheless, there is sufficient room for improvement for lower the cardiovascular risk in very high-risk T2DM patients by starting SGLT2-I given that 70.3% did not receive these drugs while they had no contra-indications.

### *4.2. Strengths and limitations*

#### *4.2.1. A strength of this observational study is the large number of participants*

A limitation is that GPs in every day practice do not use a frailty index. We therefore could not consider frailty as a contraindication. Neither did we consider a life expectancy < five years as contraindication because we could not extract this item from the routine care data.

Therefore, we could have overestimated the number of eligible patients for SGLT2-I. Other contraindications for SGLT2-I we could also not assess; alcoholism, malnutrition, ketogenic diets, active foot ulcus or recurrent genital fungal infections. On the other side, SGLT2-I treatment is also prescribed with good results to non-diabetic patients and therefore it is debatable whether an HbA1c $< 53$ mmol/mol should be considered as a contra-indication for prescribing SGLT2-I. Also reduction in dosage of other oral anti-diabetes could be considered in that situation. Inherent to routine care data, there can be misclassification and under-registration of comorbidities, and missing data on certain measurents. E.g. the left ventricular ejection fraction (LVEF) was not registered in 28.3% of the patients labelled with heart failure. Furthermore, we could not consider unrecognized heart failure. Selective screening of T2DM patients aged over 60 years showed that this is a very common problem, notably heart failure with preserved ejection fraction (HFpEF). [12].

#### *4.2.2. Practical implications and recommendations*

This study indicates that there is potential for improvement of the treatment with SGLT2-I's in the T2DM population with a very high-risk. The available dataset could be used to identify specific very high-risk individuals without current SGLT2-I treatment and mark their files in the EHR in such a way that it alerts the physician via pop up messages. This would insure physicians to reevaluate treatment during the next visit, would possibly elevate the SGLT2-I use and improve overall secondary preventative care. It would be interesting to revisit and restudy this patient population one year after the pop-up message implementation to assess the progress made.

Future optimalisation though a learning healthcare system would also be recommended. The EMR is able to do calculations based on patient information and is therefore able to calculate and add a very high-risk classification column to its quarterly T2DM care rapport, making very high-risk indication and treatment evaluation readily available. A requirement for such a system to function properly is the correct ICPC classification and improvement in data registration such as ejection fraction in HF patients.

Due to the current formulation of the Dutch GP guidelines on T2DM, patients who have a HbA1c value below the target goal of 53 mmol/mol, e.g. with SU derivative or insulin treatment, might not receive SGLT2-I treatment and therefore potentially lose out on its positive preventative effect on cardiovascular health. Addition of SGLT2 inhibitors in these patients should be considered to further improve cardiovascular prevention as both SU derivative's and insulin have an adverse effect on cardiovascular risk compared to SGLT2-I's and GLP-1 receptor agonists [13].

## 5. Conclusion

The vast majority of very high-risk type 2 diabetes patients were not prescribed SGLT2-I. There is substantial room for improvement in the management of these critical T2DM patients because most of them had no contraindications for initiating SGLT2-I prescription.

## Ethical approval

The Medical Research Ethic Committee (MREC) of the University Medical Centre Utrecht confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study and therefore an official approval of this study by the MREC UMC Utrecht is not required under the WMO.

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## Author agreement

all authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

## Declaration of interest

All authors declare that there's no financial/personal interest or belief that could affect their objectivity.

## References

[1] R.J. Geurten, A.M.J. Elissen, H.J.G. Bilo, J.N. Struijs, C. Van Tilburg, D. Ruwaard, Identifying and delineating the type 2 diabetes population in the Netherlands using an all-payer claims database: characteristics, healthcare utilisation and expenditures, BMJ Open 11 (12) (2021) 1–10.
[2] E. Dal Canto, A. Ceriello, L. Rydén, M. Ferrini, T.B. Hansen, O. Schnell, et al., Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications, Eur. J. Prev. Cardiol. 26 (2_suppl) (2019) 25–32.
[3] E. Nordheim, T.G. Jenssen, Chronic kidney disease in patients with diabetes mellitus, Endocr. Connect 10 (5) (2021) R151–R159.
[4] A. Ceriello, D. Catrinoiu, C. Chandramouli, F. Cosentino, A.C. Dombrowsky, B. Itzhak, et al., Heart failure in type 2 diabetes: current perspectives on screening, diagnosis and management, Cardiovasc Diabetol. [Internet] 20 (1) (2021) 1–19, https://doi.org/10.1186/s12933-021-01408-1.
[5] X. Cai, X. Liu, L. Sun, Y. He, S. Zheng, Y. Zhang, et al., Prediabetes and the risk of heart failure: a meta-analysis, Diabetes, Obes. Metab. 23 (8) (2021) 1746–1753.
[6] S.C. Palmer, B. Tendal, R.A. Mustafa, P.O. Vandvik, S. Li, Q. Hao, et al., Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials, BMJ 372 (2021) 1–14.
[7] Barents E.S.E., Bilo H.J.G., Bouma M., Dankers M., De Rooij A., Hart H.E., Houweling H.S., IJzerman R.G., Janssen P.G.H., Kerssen A., Oud M., Palmen J., Van den Brink-Muinen A., Van den Donk M., Verburg-Oorthuizen A.F.E., Wiersma T. NHG-Standaard Diabetes mellitus type 2 (M01). NHG-Standaard. 2021;2 (november).
[8] I.M. Hofmans-Okkes, H. Lamberts, The International Classification of Primary Care (ICPC): new applications in research and computer-based patient records in family practice, Fam. Pr. 13 (3) (1996) 294–302.
[9] I. Drubbel, N.J. De Wit, N. Bleijenberg, R.J.C. Eijkemans, M.J. Schuurmans, M. E. Numans, Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data, J. Gerontol. - Ser. A Biol. Sci. Med Sci. 68 (3) (2013) 301–308.
[10] M. Duijvestijn, S.W. van den Berg, G.C.W. Wendel-vos, Adhering to the 2017 dutch physical activity guidelines: a trend over time 2001–2018, Int J. Environ. Res Public Health 17 (3) (2020).
[11] G.C. Miller, H. Britt, A new drug classification for computer systems: the ATC extension code, Int J. Biomed. Comput. 40 (2) (1995) 121–124.
[12] L.J.M. Boonman-De Winter, F.H. Rutten, M.J.M. Cramer, M.J. Landman, A. H. Liem, G.E.H.M. Rutten, et al., High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes, Diabetologia 55 (8) (2012) 2154–2162.
[13] M.J. O'Brien, S.L. Karam, A. Wallia, R.H. Kang, A.J. Cooper, N. Lancki, et al., Association of second-line antidiabetic medications with cardiovascular events among insured adults with type 2 diabetes, JAMA Netw. Open 1 (8) (2018) 1–15.