

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Associations between cardiovascular disease and type 2 diabetes
mellitus in the Hungarian population

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UNIVERSITY OF DEBRECEN
KÁLMÁN LAKI DOCTORAL SCHOOL

DEBRECEN, 2025

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The **PhD Defense** takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on **October 17th, 2025, at 13:00.**

1. Introduction

Cardiovascular disease (CVD) continues to be the world's leading cause of morbidity and mortality, while type 2 diabetes mellitus (T2DM) is one of the most prevalent non-communicable diseases, and its prevalence is predicted to rise. According to the Global Burden of Disease Study 2019, CVD remain the leading cause of death worldwide, accounting for approximately 17.9 million deaths annually, while the global prevalence of T2DM has risen drastically, contributing to over 1.5 million deaths and substantial disability-adjusted life years (DALYs) in 2019. These estimates enable consistent comparisons across regions and causes and underscore the growing burden of T2DM and CVD both globally and in Central and Eastern Europe, including Hungary.

These illnesses frequently co-occur in the same person due to their comparable etiology, pathophysiology, and risk factors. Micro and macrovascular complications of T2DM lead to atherosclerotic cardiovascular diseases (ASCVD), including cerebral stroke, acute myocardial infarction, and coronary heart disease. These CVDs are the leading cause of death in people with DM. In addition to worsening clinical outcomes, the co-occurrence of T2DM and CVD highlights the urgent need for targeted studies to identify patterns, risk factors, and potential mitigators of CVD among populations with T2DM. The intersection of these two health issues necessitates immediate attention, as the prevalence of T2DM is continuously rising globally.

Insulin resistance (IR) and increasing β -cell dysfunction are hallmarks of T2DM, a chronic metabolic disease that results in persistent hyperglycemia. Crucial to the pathophysiology of CVD, this hyperglycemic environment accelerates atherosclerosis, encourages endothelial dysfunction, and stimulates pro-inflammatory states. This risk is further increased by a grouping of cardiovascular risk factors, which are frequently seen in people with T2DM, including obesity, dyslipidemia, and hypertension. As a result, people with T2DM have a far higher risk of cardiovascular events, such as myocardial infarction, stroke, and heart failure (HF), than people without T2DM.

As certain genetic, behavioral, and socioeconomic factors that affect the onset and course of both T2DM and CVD, the healthcare system in Hungary offers a unique setting for examining this association. Disease prevalence and outcomes may be influenced differently in Hungary than in other populations due to historical and current trends in dietary practices, physical activity, and access to healthcare. Furthermore, thorough assessments of epidemiological trends and clinical outcomes are made easier by Hungary's integration of national registries and electronic health information.

There is still a lack of region-specific assessments in Hungary, despite the abundance of worldwide data connecting T2DM with CVD. This disparity emphasizes how crucial it is to do local research to customize therapeutic and preventative approaches to the requirements of the Hungarian population. Furthermore, knowing how comorbidities, glycemic control, illness duration, and demographic factors affect the risk of CVD in Hungarian patients with T2DM might help direct individualized medical interventions and public health campaigns.

This thesis aims to assess the prevalence, trends, and risk factors of CVD in patients with T2DM in Hungary.

This study aims to add to the expanding body of information on the bidirectional association between T2DM and CVD by conducting a thorough examination of clinical and epidemiological data. These findings may support the development of targeted interventions such as routine cardiovascular risk stratification using laboratory markers, earlier screening in high-risk subgroups, and tailored treatment approaches that include the timely initiation of cardioprotective medications, thereby contributing to improved health outcomes in patients with T2DM.

2. Aims and objectives

In this study, we aimed to examine the burden and risk factors of CVD among patients with T2DM in Hungary, and to explore potential clinical and pharmacological strategies for improving cardiovascular outcomes in this high-risk population.

The objectives include:

1. To estimate the prevalence and trends of CVD among individuals with T2DM using nationally representative survey data and identify key risk factors for CVD in individuals with T2DM.
2. To evaluate the association between clinical laboratory parameters and CVD risk in patients with T2DM using hospital-based data.
3. To evaluate the effect of sodium-glucose co-transporter 2 inhibitors (SGLT2i) on cardiovascular outcomes in patients with T2DM based on real-world hospital data.

Study hypothesis:

1. We hypothesized that certain demographic, socioeconomic and lifestyle factors are significantly associated with increased risk of CVD among individuals with T2DM in the Hungarian population.
2. As a result of the interrelated pathological mechanisms between T2DM and CVD, it is hypothesized that CVD in patients with T2DM can be evaluated by certain clinical laboratory tests including lipid profiles, kidney function tests and blood sugar control parameters.
3. The use of SGLT2i is associated with a lower risk of cardiovascular events in patients with T2DM compared to those not receiving SGLT2i therapy.

3. Methods

Following the aims and objectives outlined in this thesis, three distinct studies were conducted. Each study utilized unique research materials and methods, which are detailed individually below.

3.1 Study 1: Cardiovascular disease and risk factors in adults with diabetes mellitus in Hungary: A population-based study

3.1.1 Study design

We used pooled data derived from three waves of the European Health Interview Survey (EHIS). The study was conducted every 5 years among the member states of the European Union to evaluate the health status of the population, the risk factors affecting it, the quality and scope of healthcare services, and the level of people's satisfaction with them. Data were collected in 2009, 2014, and 2019 the survey used pre-tested and standardized questionnaires, and the research methodologies and data collection process were supervised by Eurostat. Three waves of EHIS were conducted using stratified, multistage probability sampling. After applying the provided sampling weights, the dataset is considered nationally representative of the Hungarian adult population with respect to age, sex, and geographic distribution.

The Hungarian three waves of EHIS data included sample sizes of 5,051 people in 2009, 5,826 in 2014, and 5,603 in 2019. For this study, we focused on participants with diabetes mellitus (DM), resulting in a final sample size of 421 in 2009, 470 in 2014, and 545 in 2019. The study sample consisted of people aged 18 or older and up from Hungary (see Figure 1).

3.1.2 Variables

To define the study's sample, the two-stage exclusion technique was used to exclude data from people who did not indicate a history of DM. First, individuals under the age of 18 and those who indicated no history of DM within the previous year were eliminated. Next, respondents who stated that they had not received a physician's diagnosis of DM were excluded to improve the accuracy of prevalence estimates. The survey does not indicate the type of DM, hence all types of DM are considered in the study.

The prevalence of CVD was estimated using two criteria: respondents must have had at least one of the CVD including AMI, stroke, or CAD in the previous year and these illnesses must have been identified by a physician in accordance with guidelines.

The analysis included demographic information and lifestyle characteristics, including gender (self-identified), age (categorized as <65 or ≥65 years), educational attainment

(elementary, secondary, university), perceived income (categorized as low, lower middle, middle, upper middle, and high income), and body mass index (BMI) (categorized as normal ($BMI < 25$), overweight ($25 \leq BMI < 30$), and obese ($BMI \geq 30$). Lifestyle factors included smoking status (current smoker versus non-smoker, including former smokers). Depression was considered a comorbidity, while self-reported hypertension and high blood cholesterol were identified as cardiometabolic risk factors.

3.1.3 Statistical analysis

Pearson's Chi-square test was performed to investigate the relationships between study variables. The pooled sample was subjected to multiple logistic regression analysis to determine the relationship between putative risk variables and CVD in patients with DM. Binary logistic regression was chosen as the outcome variable was binary, and variables were included in the model based on their statistical significance in bivariate analyses ($p < 0.05$) and clinical relevance supported by existing literature. Sampling weights were adjusted to the sample using Stata's 'svy' command to improve its representativeness relative to the population. The logistic regression results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were carried out using the STATA IC program, version 17.0.

3.1.4 Ethics Statement

All human studies received ethical approval from the Ethics Committee of the University of Debrecen (approval number 5609-2020) and were carried out in compliance with relevant local laws and institutional guidelines. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

3.2 Study 2: Evaluation of CVD risk in patients with T2DM using clinical laboratory markers

3.2.1 Study Design and Data

This study utilized a longitudinal design based on data from the Clinical Center of the University Hospital of Debrecen, Hungary, covering a five-year follow-up period from 2016 to 2020. The dataset consists of records from 5,593 individuals diagnosed with T2DM in accordance with clinical guidelines, including fasting plasma glucose levels, oral glucose tolerance test results, and HbA1c measurements as of 2016. None of the participants had a prior diagnosis of AMI or stroke at baseline. The dataset also contains annual demographic and laboratory data to track changes in clinical and health-related parameters throughout the study period, as well as documentation of additional diagnoses recorded between 2017 and 2020.

The primary endpoint of the study is the incidence of AMI (I21, I22) or stroke (I61, I63, I64), identified by filtering the relevant International Classification of Diseases, 10th Revision (ICD-10) codes. Over the four years from 2017 to 2020, a total of 347 new cases of AMI and stroke were reported in the sample, with diagnoses confirmed according to clinical guidelines. Patients who were deceased or lost to follow-up were excluded from the analysis due to limited data on the causes of death, which could potentially distort the interpretation of cardiovascular risk factors and impact the reliability of the findings.

Finally, the dataset was reshaped into a longitudinal format for Cox proportional hazards regression analysis, incorporating annual laboratory test results and unique patient identifiers from 2016 to 2020.

3.2.2 Variables

In addition to the previously mentioned variables, several others were derived from the available data. Laboratory parameters—including total cholesterol, HDL, LDL, blood glucose, HbA1c, serum albumin, uric acid, creatinine, estimated glomerular filtration rate (eGFR), and C-reactive protein—were analyzed in comparison with reference ranges provided by the Clinical Center of Laboratory Medicine at the University of Debrecen. Clinical thresholds for laboratory markers were defined according to the ADA guidelines. Each parameter was categorized as elevated, decreased, or within the normal reference range based on these international standards.. If a laboratory test was performed more than once in a given year, the median value was used. The TyG index was computed using the formula $\text{Ln} [\text{fasting triglycerides (mg/dL)} \times \text{fasting plasma glucose (mg/dL)}/2]$. As triglyceride and fasting plasma glucose provided in mmol/L in the data, following formula used for the conversion.

$$\text{TyG index} = \ln \left(\frac{(\text{Triglycerides in mmol/L} \times 88.57) \times (\text{Glucose in mmol/L} \times 18)}{2} \right)$$

In addition, a new variable called “Adequate care” was created, which was based on the frequency of HbA1c testing throughout the year. According to the American Diabetes Association (ADA) guidelines, which recommend measuring HbA1c twice annually, diabetes management was classified as adequate if HbA1c was measured exactly twice a year. If the testing occurred less than twice or more than twice a year, it was considered inadequate care.

3.2.3 Statistical Analysis

To investigate potential differences in age and laboratory parameters from 2016 between T2DM patients who experienced stroke or AMI between 2017 and 2020 and those who did not, the Wilcoxon Rank Sum Test was applied. This analysis followed the assessment

of variable normality using the Shapiro-Wilk test and visual inspection of histograms, with results reported as medians and interquartile ranges. Laboratory values were also categorized based on standard reference ranges and Pearson's Chi-square test was employed to examine associations between these categorized results and the incidence of cardiovascular events.

Cox proportional hazards regression was chosen for the multivariate analysis, as the outcome involved time-to-event data, allowing for the assessment of the time until primary outcome events occurred. Variables were included in the model based on their significance in univariate analyses ($p < 0.05$), clinical relevance, and consistency with findings from previous research. For the purposes of Cox proportional hazards regression, survival time was defined as the period from the beginning of follow-up to the first occurrence of a cardiovascular event, as previously described. Data preparation for survival analysis was carried out in Stata using the "stset" command, specifying the start time and CVD events occurring within the four-year follow-up period. The panel structure of the dataset was established with the "xtset" command, using individual subject identifiers and the time variable. The Cox regression analysis was conducted with the "xtstreg" command, applying a Weibull distribution to appropriately model the hazard function over time.

Initially, a model was created using only baseline data, including gender, age group, proper care, and comorbidities. Laboratory parameters were subsequently added to the model based on associations identified through the Chi-square test. The results from the Cox regression analysis were presented as hazard ratios (HRs) with 95% CIs. All statistical analyses were conducted using STATA IC version 17.0.

4.2.4 Ethics Statement

The study complied with all applicable local laws and institutional regulations. Ethical approval was obtained from the Ethics Committee of the University of Debrecen (approval number 5610-2020).

3.3 Study 3: Study 3: Cardioprotective effect of SGLT-2 inhibitors in patients with T2DM

3.3.1 Study Design and Data

This study followed a longitudinal design, drawing on patient data from the Department of Internal Medicine at the University Hospital of Debrecen, Hungary, spanning the years 2016 to 2020. The dataset included 2,542 individuals diagnosed with T2DM, as defined by clinical criteria, all of whom were free of HF at baseline. Participants were identified in the hospital's database using the ICD-10 code E11, specific to T2DM. Records were excluded if they contained the E10 code (commonly associated with type 1 diabetes), showed evidence of

preexisting HF, involved individuals younger than 45 years, or reflected an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m²—criteria applied to minimize confounding risk factors for HF. The data included yearly updates on demographic variables, laboratory values, and treatment histories, enabling a detailed assessment of patients' clinical trajectories. Clinical thresholds for laboratory markers were defined according to the ADA guidelines. For analysis purposes, data were structured longitudinally, sorted by patient identification and observation year.

3.3.2 Variables

When an appropriate ICD-10 code was found in the diagnostic records, the associated indicator was set to 1 for every patient in the year. The diagnostic codes were taken from the patient registry. Clinical outcomes were described using ICD-10 diagnostic codes for peripheral artery disease, atherosclerosis, stroke, AMI, HF, diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy. For each disease, binary indicator variables were created to indicate whether or not it existed for every patient-year. The incidence of HF was the primary outcome of the study. International, generic, and brand names were used to filter and identify medications from the treatment records of patients with T2DM that belong to the class of SGLT-2 inhibitors that are approved for use in Hungary. The application of SGLT-2 inhibitor medication was then indicated by a binary variable.

3.3.3 Statistical analysis

To assess outcomes based on baseline characteristics, Pearson's chi-squared test was employed. The comparison included categorical variables such as gender, age group, creatinine levels, LDL levels, HbA1c, triglyceride levels, and the presence of comorbidities, including atherosclerosis, stroke, AMI, peripheral artery disease, nephropathy, retinopathy, and neuropathy. To assess the association between the use of SGLT-2 inhibitors and the occurrence of HF, we applied multiple logistic regression models, incorporating time as an adjustment factor. Given the annual structure of the dataset, logistic regression was favored over Cox proportional hazards models, which are more appropriate for continuous time-to-event data. Logistic regression was more suitable for estimating the likelihood of HF within defined yearly intervals. Additionally, due to the relatively small number of HF cases, this approach offered greater stability, did not rely on the proportional hazards assumption, and yielded interpretable odds ratios. Variables were included based on their significance in univariate analyses ($p < 0.05$), clinical relevance, and support from existing literature. Evaluation of model performance using AIC and BIC criteria supported the choice of logistic regression as a more parsimonious and reliable method. To gauge predictive performance, ROC curve analysis was conducted,

assessing both sensitivity and specificity across varying probability cutoffs. A high area under the curve (AUC) indicated strong model discrimination. All statistical computations were carried out using Stata IC version 17.0.

3.3.4 Ethics Statement

Approval for the study involving human subjects was granted by the University of Debrecen's Ethics Committee. All activities adhered to relevant institutional guidelines and local legal requirements. The committee issued official authorization on December 17, 2020, under the reference code 5610-2020.

4. Results

4.1 Study 1: Cardiovascular disease and risk factors in adults with diabetes mellitus in Hungary: A population-based study

Table 1 shows the prevalence of DM and CVD in DM patients in Hungary across the three surveys. According to the data, the prevalence of DM increased significantly from 8.3% in 2009 to 9.7% in 2019 ($p=0.004$), but the prevalence of CVD among DM patients decreased from 33.9% in 2009 to 23.8% in 2014, but increased to 29.4% in 2019, however over all prevalence of CVD in patients with DM showed declining trend ($p<0.001$). Among CVDs, there was a declining tendency in the prevalence of stroke, while AMI ($p=0.003$) and CAD ($p<0.001$) displayed a substantial declining trend.

The findings show that 52.7% of DM patients were female, 49.2% were over 65 years old, and 52.2% had completed primary school education, according to the data. Furthermore, in the whole pooled sample of three waves of the EHIS in Hungary, 45.5% and 36.5% of DM participants were overweight and obese, respectively, and 75% had high blood pressure, 37.8% had increased blood cholesterol, and 8.2% had depression. In addition to a higher proportion of individuals aged ≥ 65 years compared to those without CVD (61.6% vs. 45.0%; $p < 0.001$), people with CVD also had higher rates of depression (14.2% vs. 6.1%; $p < 0.001$), hypertension (84.9% vs. 71.5%; $p < 0.001$), and hypercholesterolemia (50.9% vs. 33.3%; $p < 0.001$).

The amount of alcohol consumed by DM patients with and without CVD differed statistically significantly ($p=0.009$). Additionally, there is evidence suggesting that individuals with CVD were more likely to report lower perceived income ($p = 0.019$) and had a higher likelihood of completing only primary education (65.2% vs. 47.7%; $p < 0.001$). In contrast, the data do not provide strong evidence of differences in BMI or smoking status based on CVD status.

The multivariate model showed that women were 40% less likely than men to have CVD (OR 0.6; 95% CI 0.45 – 0.81). CVD was 2.13 times more common in people 65 and older (OR 2.13; 95% CI 1.58 – 2.87). Prevalence of CVD was substantially linked to hypertension (OR 1.53; 95% CI 1.05 – 2.22) and hypercholesteremia (OR 2.12; 95% CI 1.61 – 2.81) (Table 3). There is strong evidence against the null hypothesis, indicating that depression is associated with a higher risk of CVD among patients with DM (OR 2.62; 95% CI 1.69–4.04, $p < 0.001$). Compared to respondents with primary education, individuals with diabetes who had completed secondary education had 34% lower odds of having CVD (OR 0.66; 95% CI 0.47–0.94), while those with tertiary education had 40% lower odds (OR 0.61; 95% CI 0.38–0.99). A substantial positive association was observed between CVD and lower-middle income (OR 1.79; 95% CI 1.05–3.06) as well as poor income (OR 2.03; 95% CI 1.19–3.46). Compared to 2009, the prevalence of CVD among patients with diabetes decreased in 2014 and 2019, with odds ratios of 0.56 (95% CI 0.40–0.79) and 0.53 (95% CI 0.36–0.77), respectively. The model found no strong evidence against the null hypothesis, suggesting no association between lifestyle characteristics such as alcohol use, smoking status, and BMI and the presence of CVD.

4.2 Study 2: Evaluation of cardiovascular disease risk in patients with T2DM using clinical laboratory markers

Baseline characteristics of the 5,708 participants with T2DM are presented in Table 3. The median age was 66 years (IQR: 60–74), with a near-equal gender distribution (51% female, $n=2,854$). The median duration of T2DM was 12 years (IQR: 7–12). Hypertension was the most prevalent comorbidity at 64% ($n=3,581$), followed by myocardial ischemia (39%, $n=2,203$), neurological diseases (18.7%, $n=1,046$), retinopathy (14%, $n=783$), cancer (12%, $n=670$), nephropathy (1.8%, $n=101$), and blindness (0.29%, $n=16$). Lipid profiles showed a median total cholesterol of 4.6 mmol/L (IQR: 3.8–5.5), HDL of 1.2 mmol/L (IQR: 0.95–1.4), LDL of 2.8 mmol/L (IQR: 1.9–3.4), and triglycerides of 2.4 mmol/L (IQR: 1.9–2.9), respectively. Glycemic control markers included a median blood glucose of 7.9 mmol/L (IQR: 6.4–10.4) and HbA1c of 7.35% (IQR: 6.5–8.4). Renal function was reflected by a median serum creatinine of 80 $\mu\text{mol/L}$ (IQR: 65–102) and eGFR of 77 mL/min/1.73 m^2 (IQR: 55–99), with albumin at 44.5 g/L (IQR: 41–47). Uric acid levels were 325.7 $\mu\text{mol/L}$ (IQR: 268–390), and C-reactive protein, an inflammatory marker, was 4.5 $\mu\text{mol/L}$ (IQR: 2–11.7). The TyG index, an indicator of insulin resistance, had a median value of 9.34 (IQR: 6.83–13.00). These

baseline data indicate a population with critical cardiovascular and metabolic burden, providing a foundation for assessing risk factors and outcomes in T2DM.

Between 2017 and 2020, 6.2% of all new cases of AMI and stroke were recorded among these individuals. Table 5 compares baseline variables in 2016 for patients with T2DM, stratified by the occurrence of CVD events over the subsequent 4 years. Patients who experienced a CVD event were older (median age 68 years, Q1–Q3: 62–76) compared to those who did not (median age 66 years, Q1–Q3: 59–73; $p < 0.001$). Lipid profiles showed significant differences: total cholesterol (4.8 mmol/L, Q1–Q3: 4.0–5.8 vs. 4.6 mmol/L, Q1–Q3: 3.8–5.5; $p = 0.010$), LDL (2.8 mmol/L, Q1–Q3: 2.1–3.8 vs. 2.7 mmol/L, Q1–Q3: 2.0–3.4; $p = 0.034$), and triglycerides (2.1 mmol/L, Q1–Q3: 2.04–2.17 vs. 2.56 mmol/L, Q1–Q3: 2.06–3.06; $p = 0.016$) were higher in the CVD event group, while HDL levels showed no difference ($p = 0.117$). Glycemic control markers, including glucose ($p = 0.381$) and HbA1c ($p = 0.127$), were similar between groups. Renal function markers indicated poorer outcomes in the CVD event group, with higher creatinine (89.5 $\mu\text{mol/L}$, Q1–Q3: 72–113 vs. 79.5 $\mu\text{mol/L}$, Q1–Q3: 65–101; $p < 0.001$) and lower eGFR (68 mL/min/1.73 m², Q1–Q3: 51–88 vs. 78 mL/min/1.73 m², Q1–Q3: 56–99; $p < 0.001$), respectively.

Albumin levels were slightly lower in the CVD event group (43.5 mmol/L, Q1–Q3: 41–46 vs. 44.5 mmol/L, Q1–Q3: 41–47; $p = 0.026$), and uric acid was higher (340 $\mu\text{mol/L}$, Q1–Q3: 266–416 vs. 325 $\mu\text{mol/L}$, Q1–Q3: 268–389; $p = 0.038$). No significant differences were observed in C-reactive protein ($p = 0.658$) or TyG index ($p = 0.07$). These findings suggest that older age, dyslipidemia, elevated uric acid, and impaired renal function at baseline are associated with an increased risk of CVD events in T2DM patients over four years, highlighting these factors as important markers for risk stratification and informing risk-based care.

Based on the results of the chi-square test, male patients ($p = 0.001$) with T2DM and individuals aged over 65 years ($p = 0.001$) were found to have a higher probability of developing AMI or stroke within the following four years. Furthermore, individuals diagnosed with CVD during the subsequent four years had higher total blood cholesterol ($p = 0.01$) and LDL cholesterol levels ($p = 0.001$) in 2016, compared to normal ranges. However, no statistically significant differences were observed in 2016 between individuals with abnormal blood glucose, uric acid, HbA1c, and C-reactive protein levels and those with normal values regarding the likelihood of developing CVDs. Despite this, CVD was notably more prevalent among individuals with impaired kidney function, defined as an eGFR below 90 mL/min/1.73m², compared to those with an eGFR above this threshold ($p = 0.005$). An intriguing finding of this study was the association between serum creatinine levels and CVD

risk. Individuals with serum creatinine levels in 2016 that were either above, or below normal ranges ($p = 0.005$) exhibited a higher likelihood of developing CVD within the next four years.

No significant differences in event rates were observed for gender (females: 131 events vs. males: 216 events, $p=0.41$), age group (<65: 131 events vs. ≥ 65 : 216 events, $p=0.32$), hypertension (yes: 218 vs. no: 129, $p=0.44$), myocardial ischemia (yes: 156 vs. no: 191, $p=0.15$), neuropathy (yes: 60 vs. no: 291, $p=0.09$), cancer (yes: 34 vs. no: 313, $p=0.19$), nephropathy (yes: 6 vs. no: 341, $p=0.76$), blindness (yes: 1 vs. no: 346, $p=0.42$), total cholesterol (<5.0 mmol/L: 116 vs. ≥ 5.0 mmol/L: 103, $p=0.21$), glucose (<6.0 mmol/L: 179 vs. ≥ 6.0 mmol/L: 56, $p=0.25$), HbA1c (<6.5%: 38 vs. $\geq 6.5\%$: 309, $p=0.45$), eGFR (<90 mL/min/1.73 m²: 58 vs. ≥ 90 mL/min/1.73 m²: 189, $p=0.22$), C-reactive protein (≥ 10 mg/dL: 69 vs. <10 mg/dL: 159, $p=0.25$), uric acid ($p=0.49$ across categories), or triglycerides (<1.7 mmol/L: 103 vs. ≥ 1.7 mmol/L: 118, $p=0.07$), respectively. There was strong evidence of associations for retinopathy (yes: 58 vs. no: 289, $p = 0.01$), LDL cholesterol levels (<3.4 mmol/L: 129 vs. ≥ 3.4 mmol/L: 63, $p = 0.03$), creatinine levels ($p = 0.01$ across gender-specific categories), and the adequacy of care (yes: 25 vs. no: 322, $p < 0.001$). These results suggest that retinopathy, elevated LDL, higher creatinine levels, and lack of proper care are associated with reduced survival, while other factors show no significant impact on CVD event rates in this cohort.

According to the first Cox proportional hazards regression model, which included baseline variables such as age group, gender, appropriate care, and comorbidities, there is strong evidence that receiving appropriate care is associated with a reduced risk of CVD. Specifically, the appropriate care was associated with a reduced risk of developing CVD ([HR] = 0.58, 95% CI: 0.41–0.81).

The second Cox proportional hazards regression model, which incorporated laboratory parameters in addition to baseline variables, identified significant associations with CVD risk in patients with T2DM. Patients with elevated triglyceride levels had a 1.56-fold higher risk of developing CVD compared to those with normal levels (HR = 1.56, 95% CI: 1.06–2.29, $p = 0.021$), providing moderate evidence against the null hypothesis of no association. Similarly, an eGFR below 90 mL/min/1.73m² was associated with a 1.6-fold increase in CVD risk (HR = 1.60, 95% CI: 1.04–2.47, $p = 0.034$), suggesting some evidence of elevated risk. The model also indicated a potential protective effect of low serum creatinine levels against CVD, with a hazard ratio of 0.44 (95% CI: 0.21–0.96, $p = 0.039$), providing modest evidence against the null hypothesis. Furthermore, the frequency of annual HbA1c measurements was strongly associated with reduced CVD risk. Patients who measured their HbA1c precisely twice a year

had a 54% lower risk of AMI and stroke compared to those who measured it less than twice or more than twice per year (HR = 0.46, 95% CI: 0.31–0.70, $p < 0.001$), providing strong evidence in support of the association.

4.3 Study 3: Cardioprotective effect of SGLT-2 inhibitors in patients with T2DM

Pearson's chi-squared analysis based on baseline characteristics found no strong evidence of variation in the incidence of HF by gender ($p = 0.099$), age group ($p = 0.723$), LDL levels ($p = 0.642$), or triglyceride levels ($p = 0.383$), respectively. HbA1c $\geq 7\%$, however, was substantially linked to a higher incidence of HF ($p = 0.01$).

Furthermore, individuals diagnosed with CVD during the subsequent four years had higher total blood cholesterol and LDL cholesterol levels in 2016, compared to normal ranges ($p = 0.01$ and $p = 0.001$, respectively). The incidence of HF was notably higher among patients with peripheral artery disease ($p = 0.045$), nephropathy ($p = 0.034$), retinopathy ($p = 0.036$), atherosclerosis ($p = 0.003$), and AMI ($p < 0.001$). There was strong evidence of an association between the use of SGLT-2 inhibitors and a lower incidence of HF ($p < 0.001$; Table 10).

The use of SGLT-2 inhibitors was associated with lower odds of HF incidence, as indicated by the multiple logistic regression model (OR = 0.55, 95% CI: 0.31–0.99, $p = 0.046$), providing modest evidence against the null hypothesis. Additionally, women had lower odds of experiencing HF compared to men (OR = 0.45, 95% CI: 0.28–0.71, $p = 0.001$), representing strong evidence of a sex-related difference. Baseline eGFR also showed a protective association with HF (OR = 0.98, 95% CI: 0.97–0.99, $p = 0.004$), with consistent evidence against the null hypothesis. On the other hand, there was no insufficient evidences to support associations between HF and the length of SGLT-2 inhibitor use (OR = 1.13, 95% CI: 0.89–1.44, $p = 0.309$), age (OR = 1.02, 95% CI: 0.99–1.06, $p = 0.178$), or baseline HbA1c levels (OR = 1.14, 95% CI: 0.99–1.31, $p = 0.066$), respectively. Similarly, no notable association was observed between HF incidence and time trends between years (2017–2019 versus 2016).

5. Discussions

5.1 The prevalence and trends of CVD among patients with DM

According to our study results, the prevalence of CVD, such as AMI, stroke, and CAD, among T2DM patients in Hungary was 33.8% in 2009, 23.8% in 2024, and 29.4% in 2019. A decreasing trend was observed in these 10 years, especially for AMI and CAD.

Concerning the prevalence of CVD in individuals with DM, CVD is an important comorbidity among these patients, and the prevalence varies across studies and regions. A systematic review conducted worldwide found that CVD occurs in 32.2% of T2DM patients, and CVD is responsible for half of all deaths in this population. A study conducted in Spain found that the prevalence of CVD among patients with T2DM ranged from 6.9% to 40.8%. A German study found that the prevalence of CVD in patients with T2DM ranged from 36.3% to 57.1%, depending on the definition and follow-up period. A meta-analysis conducted in India found a prevalence of CVD of 21.1% (95% CI: 17.9–24.7%) among patients with T2DM. These studies highlight the significant burden of CVD in patients with DM and emphasize the importance of early prevention and integrated management of the disease to improve clinical and economic outcomes.

However, when considering the prevalence trends of CVD among patients with DM, most studies worldwide have observed a decreasing trend. For example, studies conducted in Asian countries, including Taiwan between 2005 and 2014 and South Korea between 2006 and 2013, found decreased trends of CVD in patients. The same pattern has also been observed in Australia and Russia.

This implies that although cardiovascular complications of DM continue to be the primary comorbidity in this population, the prevalence of CVD among patients with DM is declining. The increasing use of new generation of medications like SGLT-2 inhibitors and GLP-1, which have been demonstrated to have cardioprotective effects through multiple mechanisms, as well as socioeconomic factors that considerably affect blood sugar control in diabetes, such as the population's income, education, and the quality and accessibility of health care services, maybe the cause of this trend of declining CVD prevalence among patients with DM, which is primarily seen in developed nations. This pattern is consistent with the decreasing trend in CVD prevalence among patients with DM in Hungary, as identified in our study.

5.2 Risk factors for CVD in patients with DM

Our first study, which assessed the risk of CVD among patients with DM, found that demographic factors such as age group and gender, comorbidities such as high blood pressure,

dyslipidemia, and depression, and socioeconomic factors including education and perceived income levels influence the risk of CVD in patients with DM among the Hungarian population. This study is based on pooled data derived from three waves of EHIS data does not specify DM type, but given that about 90% of cases are T2DM, the findings can cautiously be interpreted as primarily reflecting T2DM.

Age is considered a risk factor for both DM and CVD. Most studies have shown that the risk of CVD in people with DM increases with age. This is explained by the fact that the duration of DM increases with age, risk factors such as hypertension and dyslipidemia worsen, and at the cellular level, it is explained by multiple mechanisms, including mitochondrial and endothelial cell dysfunction and chronic inflammation. When examining this pattern more closely, nevertheless, the age at which a patient receives a diagnosis of DM becomes more noteworthy. People who are diagnosed with diabetes early in life, for instance, are more vulnerable to developing CVD than those who are diagnosed later in life. Thus, in patients with DM, the length of DM duration is more important when examining the link between age and CVD risk. Therefore, from any perspective, age is a major factor affecting CVD in patients with DM, and our study results show that the risk of CVD increases with age in patients with DM, which is consistent with the abovementioned pattern.

Another non-modifiable factor that influences the risk of CVD in patients with DM is gender. This effect is seen to be due to the combination of biological, behavioral, and psychological factors. Several studies have demonstrated that women with T2DM exhibit a greater cardiovascular risk compared to men. For instance, Terzik et al. reported that women with diabetes have a 27% higher risk of stroke and a 44% higher risk of AMI than their male counterparts. The impact of gonadal hormones may be responsible in part for this difference. In premenopausal women, protective properties of estrogen against CVD are linked to a lower risk as compared to younger women and males. However, after menopause, this impact quickly decreases, resulting in a considerable rise in cardiovascular risk. This increased risk in women is also influenced by behavioral variables, such as inadequate glycemic control and insufficient management of cardiovascular risk factors. Furthermore, these disparities become even worse by socioeconomic determinants, such as women's poor access to healthcare, underscoring the complex nature of the issue. Despite this, additional research has shown that males with T2DM are more likely than women to experience macrovascular problems, especially CAD. This heightened risk is attributed to the greater prevalence of cardiovascular risk factors among men, including hypertension, dyslipidemia, smoking, and excessive alcohol consumption. All these factors combine to make men with DM more vulnerable to serious cardiovascular

consequences. Our study's results show that, in the Hungarian population, male DM patients are more likely to have cardiovascular problems than female patients. These findings highlight how urgently focused interventions are needed to reduce cardiovascular risk factors in this population.

One of the main factors that increases the risk of CVD in patients with DM is hypertension. For example, almost 70 percent of patients with DM have hypertension, which has been shown to increase their risk of CVD by 2.5 times. Considering the underlying risk factors for DM and hypertension are so interchangeable, patients with DM who also have hypertension are more likely to develop CVD. Several pathological mechanisms can explain these. First, hypertension impairs the normal function of endothelial cells. In patients with DM, endothelial normal function is also impaired due to hyperglycemia, then, the normal activity of the endothelium is further impacted by these combined circumstances. High blood pressure also increases the risk of chronic kidney disease (CKD) in patients with DM, and CKD is another risk factor for CVD in patients with DM. Hypertension associated with DM causes vascular inflammation, oxidative stress, and mitochondrial dysfunction, which strongly influences the risk of CVD in patients with DM. Our study results confirm the pattern, as hypertension increases the risk of CVD by 1.53 times in patients with DM in Hungary.

Dyslipidemia, a major risk factor for CVD, plays a primary role in the development of cardiovascular complications, including ASCVD, in patients with DM. It has been found that 70-90 percent of people with DM have dyslipidemia, which increases the likelihood of plaque formation in the vascular wall under the effects of hyperglycemia and IR during DM, and oxidative stress and inflammation also have a strong impact on this process. Due to these factors, the atherosclerotic plaques that form on the vessel walls in people with DM are more unstable than those in people without DM, which can rupture easily, further increasing the risk of cardiovascular complications. Our findings support earlier research by demonstrating that patients with dyslipidemia, particularly hypercholesterolemia, had an increased risk of CVD in Hungarian patients with DM.

Depression is one of the most common comorbidities in patients with DM, and it is associated with DM complications, such as CVD, through biological, psychological, and lifestyle factors. The biological factors that primarily link CVD and depression in patients with DM are hyperglycemia, chronic inflammation, and dyslipidemia. Chronic hyperglycemia induces chronic low-grade inflammation and oxidative stress, which are biological factors that contribute to the development of both CVD and depression. Consequently, depressed patients with DM are more likely to refuse to take regular blood sugar-lowering medications, monitor

their blood sugar regularly, and adhere to their diet and exercise regimens, which can worsen blood sugar control and increase the risk of complications such as CVD. On the other hand, the lifelong treatment and monitoring of a chronic condition like DM can predispose patients to depression, which exacerbates the biological and behavioral factors mentioned above, creating a vicious cycle of depression that worsens DM management. Our study also found that depression strongly influences the occurrence of CVD in patients with DM in the Hungarian population, which confirms the importance of psychological care in diabetes management.

Socioeconomic factors such as perceived income, education, and access to health care are considered to be strong factors that influence the development of diabetes complications. For example, a cross-sectional study conducted in Hungary found that diabetes-related mortality was 30% higher than the national average among the population in the lowest socioeconomic regions of the country and that low educational levels doubled the risk of DM-related mortality. Educational attainment is directly related to access to health care, and in many cases, higher educational attainment is associated with higher health literacy, which improves diabetes management and reduces CVD risk. Similarly, low levels of perceived income increase the risk of CVD in people with DM by increasing stress and the impact of risk factors such as poor diet and physical inactivity. In addition, people with low incomes are less likely to receive preventive screenings and visit the doctor for medical conditions such as DM, which may lead to late diagnosis, which further increases the risk of developing diabetes complications. According to our research, the risk of CVD is half that of those in the low-income category and is more than 30% lower for those with higher education than for those with only an elementary or secondary school. This emphasizes how crucial equality in society is to managing DM.

Lifestyle factors such as obesity, smoking, and alcohol consumption are considered risk factors for both DM and CVD. However, the direct contribution of these factors to CVD risk in DM patients is unclear due to the complexity of their interactions. For example, people with DM are at increased risk of CVD due to obesity, which is one of the major risk factors, and this risk is reduced when patients lose weight, as dyslipidemia and insulin sensitivity improve. Nonetheless, some research has indicated a U-shaped association between CVD and obesity in patients with DM. That is, compared to those of normal weight, those who are overweight or obese have a lower risk of CVD. Similarly, there is a paradox in the effects of alcohol consumption on CVD risk in patients with DM. Heavy alcohol consumption increases blood pressure and triglycerides and promotes cardiomyopathy, but moderate alcohol consumption has been shown to protect patients with DM from CVD risk. Smoking is also one of the main

risk factors for CVD in people with DM, but this risk may not be apparent depending on the presence of other risk factors, such as obesity, hypertension, and dyslipidemia. Additionally, smoking increases the risk of "silent ischemia," or asymptomatic CVD, which may be another factor contributing to the underreported CVD in patients with DM. Our study did not identify any association between these lifestyle factors and CVD risk in patients with DM, which may be related to the complex mechanisms described above.

5.3 Association between clinical laboratory parameters and the risk of CVD in patients with T2DM

The second study, which aimed to assess CVD risk among patients with T2DM using clinical laboratory parameters, found that variables such as lipid profile, creatinine, eGFR (as indicators of kidney function), and annual HbA1c testing—reflecting appropriate care—were associated with increased CVD risk, highlighting their potential utility in risk stratification and informing risk-based management.

One of this study's most important findings was the relationship between kidney function tests and CVD in patients with T2DM. Diabetic nephropathy (DN) is highly prevalent among patients with T2DM, with 25-40% having DN, a rate very close to that of CVD but the second most common co-morbidity in patients with DM. Moreover, DN has been shown to increase the risk of CVD in patients with T2DM, and it has been reported that the risk of CVD in diabetic patients with DN is almost twice that of patients without DN.

Multiple mechanisms explain this pattern. First of all, DN is caused by renal microangiopathy, which raises the risk of CVD by increasing arterial pressure and vascular resistance. Additionally, endothelial dysfunction and systemic inflammation are indicated by microalbuminuria, an early symptom of DN, which raises the risk of CVD. Also, inflammation caused by T2DM and DN can aggravate atherosclerosis, which can lead to CVD. The components of the metabolic syndrome in T2DM, including obesity, dyslipidemia, and IR, negatively affect both the cardiovascular system and renal function. Not only DN but also CKD contributes to the increased risk of CVD in patients with T2DM. One of the primary causes of CVD, including HF in patients with T2DM, is considerable left ventricular hypertrophy, which is brought on by hypertension and an increase in the volume of blood in circulation in patients with CKD. Given that both DN and CKD are known to increase the risk of CVD in patients with T2DM, kidney function tests can be used to evaluate this risk.

Our study results suggest that decreased eGFR levels are associated with an increased risk of CVD in patients with T2DM. This is further supported by strong evidence of a difference

in serum uric acid levels between diabetic patients with and without CVD. Both elevated and lowered blood creatinine levels were linked to an increased risk of CVD in patients with T2DM, according to the results of the Chi-square test. These findings suggest that other variables that lower blood creatinine levels also play a role in this occurrence, in addition to impaired kidney function brought on by the causes above. The main mechanism that could explain this pattern may be the accumulation of adipose tissue and loss of muscle mass in patients with T2DM. When there is a substantial loss of muscle mass and a large accumulation of fat in the body, serum creatinine levels decrease, increasing the risk of CVD. This hypothesis is further supported by the fact that this pattern is more pronounced in older adults who lose substantial muscle mass and in people diagnosed with sarcopenia.

Clinical laboratory parameters such as lipid profile, which includes triglycerides, LDL, and total cholesterol, which are laboratory indicators of dyslipidemia, are thought to be important in determining the risk of CVD. Dyslipidemia is characterized by elevated levels of TG, LDL, and total cholesterol, and reduced HDL. The pathophysiological mechanisms linking dyslipidemia to CVD in T2DM are multifaceted, involving accelerated atherosclerosis due to lipid accumulation in arterial walls, endothelial dysfunction, and increased inflammatory responses, all of which exacerbate macro- and microvascular damage in highly vascularized organs such as the heart, kidneys, and peripheral vasculature. The importance of lipid profiles in T2DM is further underscored by robust evidence demonstrating that lipid-lowering therapies, such as statins and, in some cases, fibrates or PCSK9 inhibitors, suggestively reduce the risk of cardiovascular events in patients with T2DM. These therapies work by lowering LDL cholesterol, stabilizing atherosclerotic plaques, and reducing systemic inflammation, thereby mitigating the progression of CVD. For instance, large-scale clinical trials, such as the Collaborative Atorvastatin Diabetes Study and the Heart Protection Study, have shown that statin therapy reduces major cardiovascular events by 20–30% in T2DM patients, even in those without prior CVD.

Our study findings align with this body of evidence, demonstrating that lipid profiles, particularly elevated triglyceride levels, are reliable markers for CVD stratification in patients with T2DM. Triglycerides, in particular, have emerged as a key biomarker due to their association with insulin resistance, a hallmark of T2DM, and their role in promoting atherogenic dyslipidemia, characterized by small, dense LDL particles and low HDL cholesterol. Elevated TG levels contribute to the formation of atherogenic plaques, increasing the likelihood of coronary artery disease, myocardial infarction, and stroke. Our results are consistent with other observational and interventional studies, which have similarly identified

TG as an independent risk factor for CVD in T2DM patients. For example, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study demonstrated that targeting TG with fibrates in T2DM patients reduced cardiovascular events, particularly in those with marked hypertriglyceridemia.

Because hyperglycemia is a major pathogenic factor in T2DM, and it has been proven that it contributes to the formation of atherosclerotic plaques in the vascular wall, it can be assumed that blood sugar levels and related clinical parameters, including HbA1c and TyG index, can be used to assess the risk of CVD in patients with T2DM. The direct relationship between blood glucose levels and CVD risk in T2DM is well-documented. For instance, it has been demonstrated that the risk of CVD in individuals with T2DM is directly correlated with fasting plasma glucose, 2-hour postprandial glucose. These markers reflect acute fluctuations in blood sugar, which can exacerbate vascular damage through mechanisms such as glycation of proteins, increased reactive oxygen species, and activation of pro-inflammatory pathways. Similarly, HbA1c, which measures average blood glucose levels over a 2–3-month period, has been consistently linked to CVD risk in T2DM patients. The American Diabetes Association (ADA) and other global guidelines recommend maintaining HbA1c levels below 7% for most T2DM patients to reduce CVD risk, although individualized targets may be necessary based on patient age, comorbidities, and risk of hypoglycemia.

In addition to traditional glucose markers, the TyG index, calculated as the product of fasting triglyceride and glucose levels, has emerged as a promising tool for CVD risk stratification in T2DM patients. The TyG index serves as a surrogate marker of insulin resistance, a key feature of T2DM that contributes to both dyslipidemia and hyperglycemia, thereby amplifying cardiovascular risk. TyG index is considered to predict the 10-year CVD risk of patients with T2DM, even though intermediate to high levels of prediction are questionable. Although there was no association between these clinical laboratory markers and the risk of CVD in individuals with T2DM, our investigation showed that blood sugar control is crucial for detecting CVD in these patients. In contrast, we created a variable, “proper care” based on the number of HbA1c measurements per year to assess the influence of better blood sugar control on the development of CVD in patients with T2DM. This is because measuring HbA1c every 6 months indicates that the patient's blood sugar control is sufficiently good. However, measuring it less or more frequently suggests that the person's blood sugar is either not controlled or is difficult to control and, therefore, requires more frequent measurements.

5.4 Cardioprotective effects of SGLT-2 inhibitors in patients with T2DM

The third study conducted within the framework of this thesis, which aimed to determine the effect of some novel blood sugar-lowering drugs, such as SGLT2 – inhibitors, on the risk of CVD in patients with T2DM, found that HbA1c, atherosclerosis, AMI, peripheral artery disease, and nephropathy were directly related to the risk of HF in patients with T2DM, while the use of SGLT2-inhibitors and increased eGFR were shown to have a protective effect against HF in these patients.

The primary outcome of this study is HF, which is defined as a condition in which the heart cannot supply the body with the necessary blood flow due to various pathological factors. These factors include atherosclerosis, AMI, peripheral artery disease, nephropathy, and long-term uncontrolled hyperglycemia or HbA1c, all of which were identified as risk factors in the study.

By inhibiting the proximal tubule of the kidney nephron from reabsorbing glucose from the primary urine into the blood flow, SGLT-2 inhibitors reduce blood sugar levels by increasing the quantity of glucose expelled from the body in the urine and lowering blood glucose levels. Its mechanism of action, however, goes beyond just lowering blood sugar; it also improves vascular function by restoring tubuloglomerular feedback, which lowers blood pressure and intratubular pressure. This reduces hypoxia and tubular workload, which in turn reverses the pathways of ketone body production and promotes autophagy. These medications have also been demonstrated to improve lipid profiles, modify mitochondrial activity, and have anti-inflammatory and antifibrotic effects. As a result of all these mechanisms, SGLT2-i has been shown to have cardioprotective effects in patients with DM, which is further confirmed by the results of our study.

The cardioprotective effects of SGLT2-i in patients with DM cannot be limited solely to the aforementioned mechanism of lowering blood sugar by increasing urinary glucose excretion. At the cellular level, SGLT-2i reduces inflammation and oxidative stress while improving mitochondrial function, which is important in reducing damage to heart muscle cells. Among these, the anti-inflammatory effects of SGLT-2 inhibitors have been shown to have a strong cardioprotective effect in patients with T2DM. Specifically, these agents reduce the synthesis of inflammatory mediators by reducing pro-inflammatory mechanisms through activating AMP-activated protein kinase (AMPK). It also helps to inhibit pathological mechanisms related to the inflammatory process, such as NLRP3 inflammasome and NF- κ B activation.

As mentioned above, oxidative stress is one of the main contributing factors to the development of cardiovascular complications in patients with T2DM, and SGLT-2 inhibitors have been shown to reduce oxidative stress by reducing key markers of oxidation and increasing main anti-oxidative enzymes in animal models and clinical trials.

SGLT-2 inhibitors have been shown to exert cardioprotective effects by reprogramming nutrient uptake and metabolism in heart muscle cells. In patients with HF, the amount of nutrients transported to the heart muscle cells increases, but their proper utilization is disrupted, leading to reduced ATP synthesis and the accumulation of harmful glucose and lipid byproducts. These byproducts downregulate cytoprotective nutrient deprivation pathways, thereby increasing cellular stress and reducing cell survival. SGLT2 inhibitors restore cellular homeostasis through three complementary mechanisms, including direct interaction with nutrient deficiency and nutrient excess sensors to activate cytoprotective functions; promotion of mitochondrial health (mediated by increasing autophagy flux) and increasing ATP synthesis by addressing cytosolic iron deficiency; direct inhibition of glucose transporter type 1. As a result of these effects, cytosolic accumulation of toxic metabolic byproducts reduces and promotes the oxidation of long-chain fatty acids.

Obesity is a major risk factor for both T2DM and CVD. Therefore, the cardioprotective effects of SGLT-2 inhibitors are thought to be directly related to their weight-reducing effects. For example, when overweight and obese people without T2DM were given an SGLT-2 inhibitor to lose weight, their weight and fasting blood sugar levels were reduced more than in the placebo group, but there were no changes in their waist circumference, fat mass, blood pressure, or lipid parameters. However, this weight loss effect may not be as pronounced due to the effects of counter-regulatory mechanisms for weight maintenance, such as increased appetite, decreased energy expenditure, and hormonal effects, which are activated by calorie restriction and increased glucose excretion from the body. Because weight loss reduces the risk of CVD, including HF, in patients with T2DM, it is clear that the cardioprotective effects of SGLT-2 inhibitors in patients with T2DM may be partly due to the effect of decreased body weight. GLP-1 receptor agonists have also been shown to reduce the risk of obesity-related HF and improve cardiac function by reducing body weight, supporting the idea that the cardioprotective effects of SGLT-2 inhibitors are a consequence of their weight-reducing effects. GLP-1 RAs use appetite-suppressing mechanisms to reduce body weight or act in opposition to the counter-regulatory mechanisms mentioned above, some researchers have suggested that combining SGLT-2 inhibitors with GLP-1 RAs may provide a clearer picture of how their weight-loss effects contribute to cardioprotection.

Results from clinical trials and systematic reviews based on their results have shown that SGLT-2 inhibitors reduce the incidence of CVD, cardiovascular death, and all-cause mortality in patients with T2DM. The findings of our study further support the idea that SGLT-2 inhibitors are a valuable therapeutic option for lowering the risk of CVD in patients with T2DM. However, as mentioned above, most of the studies currently conducted to determine the cardioprotective effects of SGLT-2 inhibitors are randomized clinical trials or laboratory experiments conducted *in vitro* and *in vivo*. These study designs, especially randomized clinical trials are considered the gold standard for evaluating the safety and effectiveness of new interventions, but their strict criteria limit the ability to generalize. In other words, RCTs cannot guarantee that the results of a clinical trial with strict criteria will be the same when a drug is used in real life in a population with different health, social, economic, and behavioral characteristics. Therefore, when evaluating the efficacy of a medication whose efficacy has been proven in clinical trials, real-world evidence is crucial. Everyday clinical practice is represented in real-world data, which offer important insights into the safety and effectiveness of medications in a variety of groups. Because our study examines the protective benefits of SGLT-2 inhibitors against HF in patients with T2DM using real-world data, it is deemed noteworthy.

The findings across all three studies have important implications for multiple stakeholders. For clinicians, the results emphasize the value of regularly monitoring metabolic and renal markers, such as triglyceride levels and eGFR, in diabetes care to identify patients at higher cardiovascular risk. For health policymakers, the studies highlight the role of equitable access to care and early screening—particularly for vulnerable groups—as essential components of chronic disease prevention strategies. Public health experts can use these insights to design more targeted educational campaigns and interventions aimed at improving diabetes self-management and preventing complications. Finally, for researchers, the studies offer direction for further exploration of risk-associated markers and treatment effectiveness using longitudinal and real-world datasets. By integrating these findings into clinical and policy frameworks, it may be possible to improve outcomes for people living with diabetes in Hungary and similar populations.

5.5 Strengths, and limitations

The main studies that form the basis of this thesis have several strengths and limitations, which allow for a balanced view of the scope and implications of the study.

First, in terms of limitations, there is an increased likelihood of reporting bias when self-reported data is used in a study to identify CVD risk factors in patients with DM. It should be noted again that the pooled dataset derived from the three waves of EHIS does not differentiate between diabetes types; therefore, the findings of the first study apply to DM in general, rather than specifically to T2DM. Furthermore, the absence of important characteristics like disease severity and duration in the data used in this study made it more difficult to account for them. Another limitation is the use of BMI as a measure of obesity, as it does not account for fat distribution (central obesity) or body composition (muscle mass), which may reduce its accuracy in assessing cardiometabolic risk. Plus, the data in this study lacked laboratory parameters required to evaluate the patient's metabolic status, which made it more difficult to determine their current state of health. However, in subsequent studies, we included these parameters and used other data based on hospital records to assess CVD risk in patients with T2DM, which reduces the limitations mentioned above for this thesis.

In the second study, the reliability of ICD-10 coding may be influenced by unknown clinical coding practices; however, as these codes are used in routine patient care, it is reasonable to assume that major coding errors are minimal. The second and third studies, which used laboratory parameters to determine the CVD risk of patients with T2DM, and the study evaluating the cardioprotective effect of SGLT2 inhibitors in patients with T2DM, used only hospital data (single-center design), which limits the possibility of representing the entire Hungarian population and all patients with DM in general. While the first study used nationally representative data, the subsequent hospital-based studies are inherently limited in their generalizability, and the findings should be interpreted in the context of the specific patient population examined, namely, individuals receiving care in a tertiary hospital setting, which may differ from those managed in primary care or community environments.

Also, the data used in these studies had a relatively short follow-up period, which limited the ability to assess the long-term effects of treatment and how laboratory test parameters change over time. These studies used real-world data and, because each patient received different types of treatment depending on their clinical condition, it was impossible to directly assess the effectiveness of each of these treatments in lowering blood pressure, cholesterol, and blood sugar. Therefore, we were able to address this limitation by using the frequency of HbA1c measurements as an indicator of the appropriateness and effectiveness of the healthcare provided to each patient.

In contrast, the studies included in this thesis have several strengths. In our first study, we used a comprehensive set of data, representative of the entire Hungarian population and

collected and processed using robust data collection tools under the supervision of Eurostat and the Hungarian Central Statistical Office. The results of this study are then combined with results from well-documented, large sampled, real-world data in this thesis. The aggregation of real-world data over a certain period provided valuable insights into clinical outcomes in a typical healthcare setting. The combination of datasets helped to mitigate the individual limitations of each, thereby enhancing the overall robustness of the study. One of the key strengths of this thesis is the use of comprehensive and representative data sources. Subsequently, more advanced and accurate statistical analysis methods, such as Cox proportional hazard regression, logistic regression, and sample weighting, were applied to these data. This further increases the authenticity and reliability of the research results.

Altogether, the strengths of the dissertation include its methodological rigor, the use of a representative dataset in the first study, and the consistency of findings with previous research. While this consistency supports the plausibility of the results, it does not by itself confirm their validity or generalizability for subsequent studies. On the other hand, limitations such as data discrepancies, potential bias, and the observational nature of the studies emphasize the need for further research, especially in broader and more diverse populations, to confirm and extend these findings.

Conclusions

The results of the thesis, which used the pooled dataset derived from the three waves of EHIS, shed light on the prevalence of CVD and related risk factors among adults with DM in Hungary. Our results indicated a decreasing trend in the prevalence of CVD in individuals with DM and highlighted the need of regular screening for hypertension and hypercholesterolemia in addition to continuously monitoring mental health in DM patients. The findings also showed that lower economic status was associated with a higher prevalence of CVD, even while lifestyle factors did not increase the burden of CVD among DM patients. To fully comprehend the possible reasons for the noted decline in the prevalence of CVD, more investigation is necessary.

The results of our next study show that in patients with T2DM, CVD is associated with decreased levels of eGFR, increased levels of triglycerides, and “proper care” (e.g., the number of annual HbA1c assessments). These results imply that laboratory markers, such as elevated triglycerides and decreased eGFR, have the potential as screening tools for detecting CVD in patients with T2DM. By using these markers, preventive interventions targeted at reducing cardiovascular complications in T2DM patients can be strategically implemented.

Finally, regardless of gender, age, or HbA1c levels, SGLT-2 inhibitors appeared to provide a protective effect against HF in patients with T2DM, suggesting that these drugs may be useful in reducing the risk of CVD in this population. To improve therapy recommendations and patient outcomes, more research should examine the underlying mechanisms causing this connection and evaluate the long-term advantages across various clinical and demographic groupings.

New findings

Study 1. Risk factors and prevalence of CVD among patients with DM

- Based on the EHIS datasets (2009, 2014, and 2019), the overall prevalence of DM among the Hungarian population has increased over time, while, in parallel, the incidence of CVDs and related events among patients with DM has shown a decreasing trend.
- According to the EHIS data, hypertension, hypercholesterolemia, depression, and low socioeconomic status were identified as significant risk factors for CVDs among Hungarian patients with DM. Conversely, lifestyle variables such as BMI, smoking, and alcohol consumption did not show a statistically significant association in the sample.

Study 2. Evaluation of CVD risk using clinical laboratory parameters

- A model for assessing CVD risk in patients with T2DM using laboratory test parameters.

CVD risk in Hungarian patients with T2DM is elevated by increased serum triglycerides and decreased eGFR, while low serum creatinine levels were identified as a potential protective factor. Effective blood glucose control—measured by the frequency of HbA1c testing and the quality of care—may substantially reduce cardiovascular risk in Hungarian patients with T2DM.

Study 3. Protective effect of SGLT-2 inhibitors against CVD in patients with T2DM

- The use of SGLT2 inhibitors has been shown to significantly reduce the risk of heart failure in Hungarian patients with T2DM, independent of age, sex, and HbA1c levels.

Summary

The incidence of DM is increasing worldwide, and CVD is one of the leading causes of mortality in these patients. Therefore, this thesis aims to identify risk factors for CVD among the Hungarian population with DM, to identify opportunities for evaluating the risk of CVD in these patients, and to find ways to prevent CVD in patients with DM. Within the framework of this thesis, we have completed three separate studies.

The results of this thesis indicate that, in addition to age and gender, cardiovascular risk factors such as hypertension and hypercholesterolemia increase the risk of CVD in patients with DM, which highlights the importance of interventions to regularly monitor and maintain these risk factors in patients with DM. In addition, depression is one of the risk factors for CVD in patients with DM, indicating the importance of ongoing mental health care for these patients. While socioeconomic factors such as education level and perceived income level have been found to negatively affect the risk of CVD in patients with DM, lifestyle factors such as BMI, smoking, and alcohol consumption have not been found to have effect among this population. When the period of data collection was included in the multivariate model for determining the risk factors for CVD in DM, a trend of decreasing the risk of CVD in the Hungarian population from 2009 to 2019 was observed, and it was considered necessary to determine in detail which factors contribute to this trend.

In a study evaluating the risk of CVD in patients with T2DM, the risk was found to be associated with age and gender, as well as clinical laboratory parameters related to lipid metabolism—such as total cholesterol, LDL, and triglycerides—and renal function markers including uric acid, creatinine, and eGFR, with strong evidence supporting these associations. In a Cox proportional hazards regression analysis evaluating the risk of CVD in patients with T2DM, there was evidence that elevated triglyceride levels and reduced eGFR were associated with an increased risk of CVD, while lower serum creatinine levels were associated with a reduced risk. This demonstrates these laboratory parameters are important in assessing the risk of CVD in patients with T2DM, and thus in reducing and preventing the risk. In addition, the risk of CVD was lower in patients with "proper care" or HbA1c measured once every 6 months, indirectly indicating that regular monitoring of blood sugar and maintaining it at an appropriate level is important in reducing the CVD risk in these patients.

Our initial research demonstrated that the prevalence of CVD is declining among patients with DM in Hungary, and lifestyle-related modifiable risk factors did not considerably affect CVD risk for these patients. We hypothesized that this pattern of declining CVD

prevalence in patients with DM may be related to the quality of diabetes care, particularly the effects of some new-generation blood sugar-lowering medications, as the second study found that the "proper care" variable had a substantial impact on the risk of CVD. Therefore, we examined the effects of blood sugar-lowering medications on the risk of CVD in patients with T2DM, and the third study conducted within the thesis found that SGLT-2 inhibitors have a protective effect against HF in patients with T2DM.

Acknowledgement

I would like to express my heartfelt gratitude to my parents, Ulambayar Norovvanchin and Uranchimeg Sharav, my siblings, and my friends, who have been a constant source of encouragement and support throughout the journey of completing this thesis. Their unwavering belief in me, countless discussions, and moments of laughter have made this challenging process far more bearable and memorable.

My deepest appreciation goes to my beloved family: my wife, Erdenetsetseg Nokhoijav, my son, Irmuun Battamir, and my daughter, Tselmuun Battamir. Their love, patience, and understanding have been my anchor. Their sacrifices and endless support have given me the strength to persevere and pursue my academic goals with determination.

I am immensely grateful to the faculty members and professors of the Faculty of Health Sciences, my colleagues, co-authors, editors, and the anonymous reviewers of academic journals, whose guidance, expertise, and dedication have profoundly shaped my academic journey. Their insightful feedback and encouragement have been instrumental in refining my work and broadening my perspective.

I would also like to extend my sincere thanks to the Stipendium Hungaricum, Tempus Public Foundation, and the people of Hungary for their generous financial support. Their funding has alleviated financial burdens and allowed me to focus wholeheartedly on my studies and research.

I owe an enormous debt of gratitude to my supervisor, Professor Nagy Attila Csaba, whose mentorship, wisdom, and unwavering support have been pivotal in the completion of this thesis. His crucial decision to accept me for the scholarship was a key factor in securing the support from the Tempus Public Foundation, enabling this academic journey. His constructive feedback, encouragement, and belief in my abilities have not only guided my research but also inspired me to strive for excellence.

In closing, I wish to express my deep respect for the book, the knowledge, and the teacher, the source of that knowledge. May this knowledge spread across the world, bringing happiness and enlightenment to people everywhere.



Registry number: DEENK/93/2025.PL
Subject: PhD Publication List

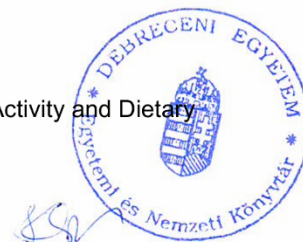
Candidate: Battamir Ulambayar
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Ulambayar, B.**, Ghanem, A. S., Nguyen, M. C., Faludi, E., Mór , M., Nagy, A. C.: Evaluation of cardiovascular disease risk in patients with type 2 Diabetes Mellitus using clinical laboratory markers.
J Clin Med. 13, 1-14, 2024.
DOI: <http://dx.doi.org/10.3390/jcm13123561>
IF: 3 (2023)
2. Nagy, A. C., T th,  ., Bak, N., **Ulambayar, B.**, Ghanem, A. S., Sztanek, F.: Protective Influence of SGLT-2 Inhibitors Against Heart Failure in Type 2 Diabetes Mellitus Through Longitudinal Clinical Database Analysis.
J. Clin. Med. 13 (23), 1-11, 2024.
DOI: <http://dx.doi.org/10.3390/jcm13237093>
IF: 3 (2023)
3. **Ulambayar, B.**, Ghanem, A. S., Kov cs, N., Tref n, L., M r , M., Nagy, A. C.: Cardiovascular disease and risk factors in adults with diabetes mellitus in Hungary: a population-based study.
Front Endocrinol (Lausanne). 14, 1-9, 2023.
DOI: <http://dx.doi.org/10.3389/fendo.2023.1263365>
IF: 3.9

List of other publications

4. **Ulambayar, B.**, Ghanem, A. S., T th,  ., Nagy, A. C.: Impact of Physical Activity and Dietary Habits on Mental Well-Being in Patients with Diabetes Mellitus.
Nutrients. 17 (6), 1-12, 2025.
DOI: <http://dx.doi.org/10.3390/nu17061042>
IF: 4.8 (2023)





5. Orosz, N., Gömöri, G., **Ulambayar, B.**, Nagy, A. C.: Hospital-based cross-sectional study on the clinical characteristics of children with severe acute respiratory infections in Hungary.
BMC Infect. Dis. 24 (1), 1-11, 2024.
DOI: <http://dx.doi.org/10.1186/s12879-024-10186-6>
IF: 3.4 (2023)
6. Varga, E., **Ulambayar, B.**, Szegedi, I., Hudák, L., Kovács, N., Nagy, A. C.: Seasonal patterns in the epidemiology of Bell's palsy in Hungary.
Front. Neurol. 14, 1-6, 2023.
DOI: <http://dx.doi.org/10.3389/fneur.2023.1188137>
IF: 2.7

Total IF of journals (all publications): 20,8

Total IF of journals (publications related to the dissertation): 9,9

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

18 March, 2025

