UNIVERSITY OF PÉCS MEDICAL SCHOOL

DOCTORAL SCHOOL OF MEDICAL AND PHARMACEUTICAL SCIENCES

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Investigating the risks of morbidity and mortality in patients with diabetes in Hungary.

Doctoral (PhD) thesis

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1. Introduction

There are more than half a billion people suffering from diabetes worldwide and the prevalence of the disease is increasing, which has made it a major public health concern.

The two most common forms of diabetes are type 1 and type 2 diabetes, which differ in terms of the incidence of cardiovascular complications, tumors, hypoglycemia, and diabetic ketoacidosis.

One of the main topics of my research was to investigate the complications of these two common, yet different, types of diabetes as well as to analyze the morbidity and mortality risks of young patients with type 1 and type 2 diabetes.

As the prevalence of diabetes increases, the incidence and mortality from cancer is also rapidly rising worldwide. Recent studies have shown that, alongside cardiovascular disease, cancer has become the main cause of death in diabetic patients. This trend has directed the attention of scientific research to investigating the impact of diabetes and antidiabetic drugs on cancer.

The other main topic of my research was to analyze the risk of developing different types of cancer in type 2 diabetic patient populations treated with SGLT2 inhibitors (SGLT2i) and DPP-4 inhibitors (DPP-4i).

2. Objectives

2.1 "Investigating the risks of morbidity and mortality in young adult patient populations with type 1 and type 2 diabetes"

1. Are there any differences in all-cause mortality between young adult patient populations with type 1 and type 2 diabetes? Which patient population has poorer 10-year survival?

2. What is the difference in the incidence of acute myocardial infarction (AMI) and stroke between the two patient populations?

3. Which young adult patient population (the one with type 1 or type 2 diabetes) is at higher risk of developing cancer?

4. How did the type of the diabetes affect the development of certain complications of diabetes (diabetic ketoacidosis, hypoglycemia, dialysis) in young diabetic adults? Is the risk of developing complications higher in the type 1 or type 2 diabetic patient population?

2.2 "Risk of developing cancer in patient populations treated with SGLT2i and DPP-4i"

1. How does treatment with SGLT2i and DPP-4i affect the risk of developing certain types of cancer in the studied patient populations?

Are there any differences in the risks of developing certain tumors (lung, laryngeal, lower gastrointestinal tract, rectal, pancreatic, breast, prostate, female genital, other and non-melanoma skin tumors) in the two patient populations treated with different antidiabetic drugs?

2. Is there a difference in the risk of developing urinary tract cancers and is there a difference in the risk of developing hematological malignancies between the two studied patient populations?

3. Does SGLT2i treatment increase the risk of developing certain tumors compared to patients treated with DPP-4i?

4. For which tumor types can an early or a late divergence be detected on the absolute risk difference curves?

3. Methods

Study design

Retrospective data analyses were performed using the National Health Insurance Fund (NHIF) database of Hungary in both studies.

3.1 "Investigating the risks of morbidity and mortality in young adult patient populations with type 1 and type 2 diabetes"

Patients and data collection

Data from all young adults with type 1 diabetes (aged 40 years or younger, n = 11 863) registered in the NHIF database between 1 January 2001 and 31 October 2014 were collected and compared with a population of young adults with type 2 diabetes of similar age (n = 47 931). We investigated the incidence of all-cause mortality, myocardial infarction, stroke, cancer, dialysis, diabetic ketoacidosis, and hypoglycemia starting with the onset of diabetes and ending with the time of death or the end of the study period. We compared two populations of similar age (young) but not matched on all parameters, with a ratio of type 1 to type 2 diabetic patients of - slightly more than - 1:4. The International Classification of Diseases 10th version (ICD-10) codes were used to determine the patients' diseases (type of diabetes and co-morbidities).

Our data source included all-cause mortality, myocardial infarction (ICD-10 I21-24), stroke (ICD-10 I61-63, G4630, G4640), dialysis, tumor (ICD-10 Class C and D), diabetic ketoacidosis (ICD-10 E1010, E1110 and E1410) and hypoglycemia (ICD-10 E1600, E1610 and E1620).

Statistical analysis

Survival analyses were performed using Cox regression. Kaplan-Meier curves were used to visualize the results. Data were stratified by sex and results were adjusted to take into account the differences in the proportion of men in the two groups. The mean of age and follow-up time were compared using

Welch's two-sample test. Follow-up time was calculated from the onset of diabetes.

3.2 "Risk of developing cancer in patient populations treated with SGLT2i and DPP-4i"

Patients and data collection

All patients were included, who met all three of the following criteria: (1) started SGLT2i or DPP-4i therapy in Hungary between 1 August 2014 and 1 July 2017, (2) had an ICD-10 'C' code after starting therapy, and (3) had no documented malignancies within one year prior to the start of the study. The two groups of patients (SGLT2i or DPP-4i novice) were matched for 54 clinical and demographic parameters using propensity score (PS) matching. Cancer types were categorized into larger groups based on their location to provide enough data in the monitored groups for statistical analysis.

Statistical analysis

Cancer-free survival analysis was performed using propensity score matching of patient populations matched 1:1 for SGLT2i and DPP-4i treatment. Cox multivariate analysis was used. The selected endpoints were plotted on Kaplan-Meier survival curves. The absolute risk difference between the investigated two arms were calculated and plotted during the follow-up time.

4. Results

4.1 *"Investigating the risks of morbidity and mortality in young adult patient populations with type 1 and type 2 diabetes"*

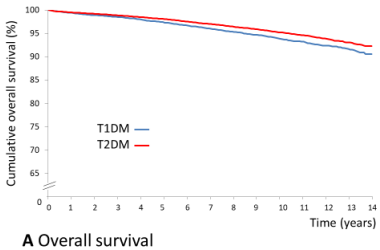
The mean age of the patients with type 1 diabetes (n=11 863) was 21.63 years (95% CI 21.42-21.85), 35.4% were female, and they had had no previous cardiovascular events. We also analyzed the data of 47 931 young adult patients with type 2 diabetes of similar age who were partially matched regarding to parameters of the group with type 1 diabetes.

Patients with type 1 diabetes had a significantly higher risk of all-cause mortality than those with type 2 diabetes [HR 2.17 (95% CI 1.95-2.41), p<0.0001] (Figure 1).

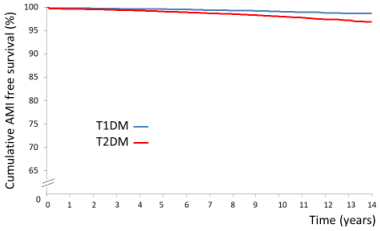
	Number of patients			Number of events			Hazard ratio (95% CI)				p value
T1DM0-40 vs T2DM0-40	**T1DM**		**T2DM**	**T1DM**		**T2DM**					
All-cause mortality	11 863	vs	47 931	521	vs	1 685	2.17 (	1.95	-	2.41)	<0,0001
Myocardial infarction	11 863	vs	47 931	82	vs	715	0.90 (	0.71	-	1.13)	0,3600
Stroke	11 863	vs	47 931	115	vs	913	1.06 (	0.87	-	1.29)	0,5820
Cancer	11 863	vs	47 931	194	vs	1 067	1.35 (	1.15	-	1.59)	0,0003
Diabetic ketoacidosis	11 863	vs	47 931	2895	vs	350	22.12 (	19.6	-	25.00)	<0,0001
Hypoglycemia	11 863	vs	47 931	725	vs	247	7.70 (	6.45	-	9.18)	<0,0001
Dialysis	11 863	vs	47 931	123	vs	360	2.20 (	1.76	-	2.75)	<0,0001

Figure 1: Risks of certain events, diseases, and mortality in young adult patients with type 1 diabetes and type 2 diabetes.

The 10-year survival of patients with type 1 diabetes (93.48%) was lower than that of patients with type 2 diabetes (95.23%), indicating a difference of 1.65% between the two groups at the end of the 167-month follow-up period (90.61% vs. 92.26%) (Figure 2).



A Overall survival



B Myocardial Infarction free survival

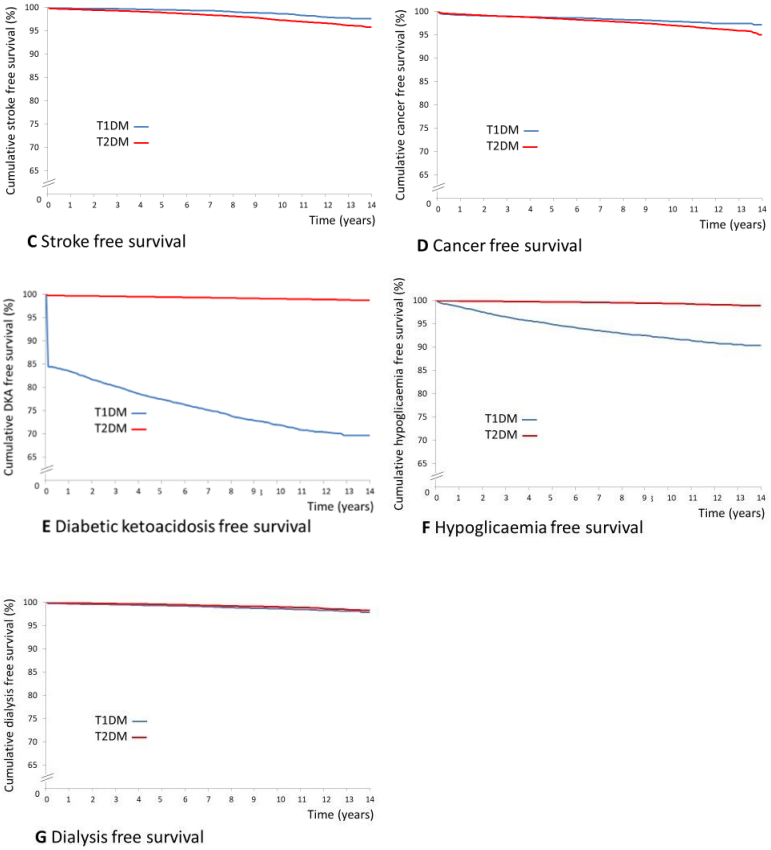


Figure 2: Overall survival (A), AMI (B), stroke (C), cancer (D), diabetic ketoacidosis (E), hypoglycemia (F) and dialysis-free survival (G) plotted on Kaplan-Meier curves in T1DM and T2DM young adult patient populations.

The risks of myocardial infarction (99.08% vs. 98.00%), stroke (98.64% vs. 97.31%) and cancer (97.90% vs. 97.07%) were higher in patients with type 2 diabetes when Kaplan-Meier curves showing event-free survival were plotted (Figure 2, B-D).

However, after adjusting for age and sex, no significant differences were found in the risks of myocardial infarction [HR 0.90 (95% CI 0.71-1.13),

p=0.3600] and stroke [HR 1.06 (95% CI 0.86-1.29), p=0.5820] between the two patient populations. In contrast, the adjusted risk of developing cancer was significantly higher in type 1 diabetes [HR 1.35 (95% CI 1.15-1.59), p=0.0003] than in type 2 diabetes, in our studied patient populations. The risks of diabetic ketoacidosis, hypoglycemia and dialysis were also significantly higher in patients with type 1 diabetes than in type 2 diabetic patients (Figure 1).

The 10-year event-free survival was 71.99% and 99.08% for diabetic ketoacidosis, 91.89% and 99.33% for hypoglycemia, and 98.62% and 99.02% for dialysis, respectively, in patient populations with type 1 and type 2 diabetes (Figure 2, E-G).

4.2 *"Risk of developing cancer in patient populations treated with SGLT2i and DPP-4i"*

Following propensity score matching of the two arms of the study, 18 583 patients were identified in each group. We compared the incidence of cancer between patients in the SGLT2i arm and the DPP-4i arm.

No significant difference in the risks of lung, laryngeal, lower gastrointestinal tract, rectal, pancreatic, breast, prostate, female genital, other, and non-melanoma skin tumors could be detected between the two patient populations.

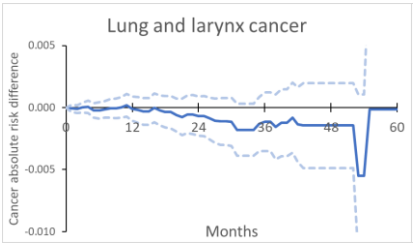
However, the risk was significantly lower for urinary tract [HR 0.50 (95% CI: 0.32-0.79)] and hematological cancers [HR 0.50 (95% CI: 0.28-0.88)] in patients treated with SGLT2i compared to patients receiving DPP4i. Treatment with SGLT2i did not significantly increase the risk of developing any type of cancer compared with patients treated with DPP-4i (Figure 3).

	Number of patients			Number of events			Hazard ratio (95% CI)	p value
Cancer type	**SGLT2i**		**DPP-4i**	**SGLT2i**		**DPP-4i**		
Lung & Larynx	18,028	vs	17,871	53	vs	61	0.80 (0.55 - 1.15)	0.2306
Lower GI	18,023	vs	17,869	48	vs	59	0.75 (0.51 - 1.09)	0.1346
Rectum	18,000	vs	17,833	25	vs	23	1.01 (0.58 - 1.79)	0.9591
Pancreas	18,009	vs	17,840	34	vs	30	1.06 (0.65 - 1.73)	0.8165
Non-melanoma	18,001	vs	17,841	26	vs	31	0.77 (0.46 - 1.30)	0.3337
Breast	18,018	vs	17,860	43	vs	50	0.82 (0.54 - 1.23)	0.3261
Prostate	18,088	vs	17,856	33	vs	46	0.65 (0.42 - 1.02)	0.0606
Urinary tract	18,044	vs	17,864	29	vs	54	0.50 (0.32 - 0.79)	0.0027
Haematology	17,993	vs	17,843	18	vs	33	0.50 (0.28 - 0.88)	0.0174

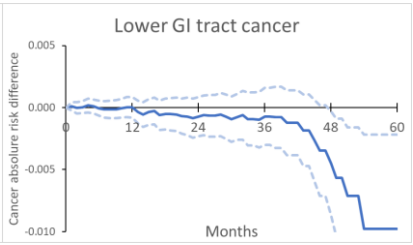
Figure 3: Risks of developing different types of cancer in patient populations treated with SGLT2i and DPP-4i. Hazard ratios less than 1.0 mean that the risk is higher in the DPP-4i group, while the ones more than 1.0 indicate that risk is higher in the SGLT2i group.

For lung, laryngeal, lower gastrointestinal and breast cancers, we observed late risk reduction on the curves showing absolute risk difference, while for prostate, hematological and urinary tract tumors, risk reduction occurred early, between months 2-12 (Figure 4).

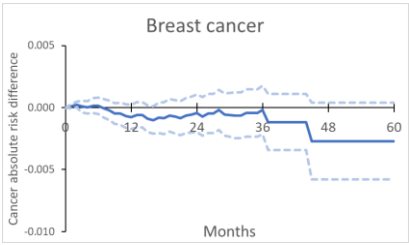
A



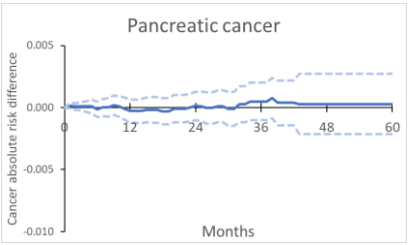
B



C



D



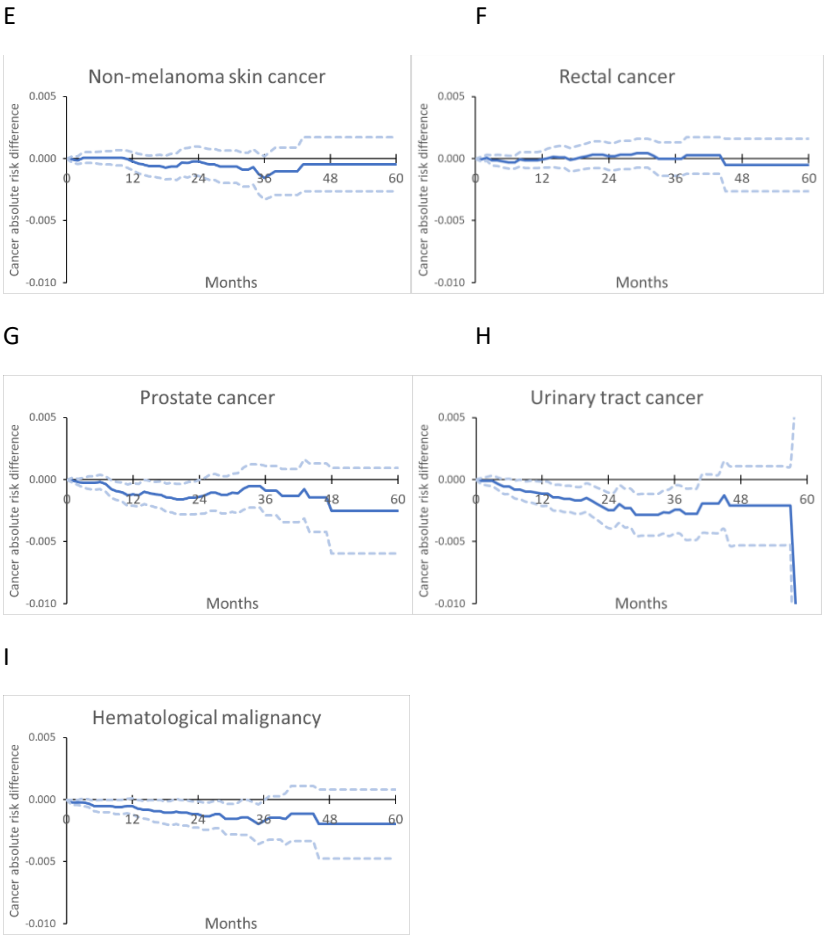


Figure 4: Absolute risk differences between the two investigated groups for different cancer types during the follow-up period. (A) lung and laryngeal, (B) lower gastrointestinal tract, (C) breast, (D) pancreatic, (E) non-melanoma skin, (F) rectal, (G) prostate, (H) urinary tract cancer, (I) hematological malignancies.

Where the difference was less than zero it indicated a lower risk in the SGLT2i arm compared to the DPP-4i arm. Dashed lines show 95% confidence intervals. The axis of the absolute risk difference is on the same scale for all

graphs (-0.010 to +0.005), allowing visual comparison of curves for different cancer sites.

5. Discussion

In our first retrospective, longitudinal, nationwide study, we compared the mortality and morbidity risks of young adult patients with type 1 and type 2 diabetes under 40 years of age and found that patients with type 1 diabetes had a higher risk of all-cause mortality than those with type 2 diabetes. Our results regarding mortality rates are similar to those published in Estonian and Lithuanian studies, which also described higher mortality rates for patients with type 1 diabetes.

Several studies have reported the importance of diabetic ketoacidosis as a major cause of premature mortality in type 1 diabetes. One study in the UK found that diabetic ketoacidosis was responsible for 83% of diabetes-related deaths. However, their analysis showed that hypoglycemia caused only 8% of the deaths in the young type 1 diabetic population. In line with this study, we also found an increased risk of ketoacidosis (HR 22.12) in patients with type 1 diabetes, but our analysis also showed an increased risk of hypoglycemia (HR 7.70), dialysis (HR 2.20), and cancer (HR 1.35) in type 1 diabetic patients compared to type 2 diabetic patients.

Since our study found no difference in the risk of cardiovascular diseases between the two diabetic populations, it is likely that, in addition to the increased risk of cancer, higher rates of dialysis in type 1 diabetic patients - as triggers of hypoglycemia and ketoacidosis - may have been responsible for the higher risk of mortality in type 1 diabetic patients. In addition, data in the literature suggest that the age at diagnosis of diabetes is an important prognostic factor for survival and all subsequent cardiovascular events. This finding may partly explain the higher mortality rates in type 1 diabetic patients in our analysis, given the earlier onset of diabetes in this population, than in the type 2 diabetic group.

Diabetes alone is linked to an increased risk of cancer compared to the non-diabetic population. Several studies have investigated the association between certain blood glucose-lowering drugs and the incidence of cancer, but the literature is rather contradictory.

In one of our previous studies, we reported that patients treated with SLGT2i had 25% lower risk of developing cancer compared to those treated with DPP-

4i, which provided us with an incentive to perform a more in-depth analysis. Therefore, we conducted a post-hoc nationwide study to analyze the prevalence of different cancer types in type 2 diabetic patients receiving SGLT2i and DPP-4i antidiabetic treatment.

Clinical data on the risk of cancer development due to DPP-4i treatment are conflicting. A large meta-analysis summarizing the results of 72 trials found no increased cancer risk in those treated with DPP-4i [relative risk (RR): 1.01 (95% CI 0.91-1.12)], while another meta-analysis of 157 studies reported that the overall cancer risk [OR: 0.90 (95% CI 0.82-0.99)] and colorectal cancer risk [OR: 0.70 (95% CI 0.52-0.94)] were found to be significantly reduced among DPP-4i users compared to those treated with placebo.

Surprisingly, in our study, patients using SGLT2i had half the risk of developing urinary tract [HR 0.50 (95% CI: 0.32-0.79)] and hematological cancers [HR 0.50 (95% CI: 0.28-0.88)] compared to patients taking DPP-4i.

Interestingly, the fear of an increased risk of urinary tract cancers was considered a real problem when SGLT2i drugs were first marketed. However, a later meta-analysis showed that SGLT2i did not increase the risk of bladder- or kidney cancer. In fact, recent studies have shown that SGLT2 inhibitors induce apoptosis at high concentrations and inhibit cell proliferation in breast cancer, renal cell carcinoma and hepatocellular carcinoma *in vitro*. Therefore, SGLT2 inhibitors have been investigated as potential anticancer drugs in *in vivo* experiments.

Furthermore, it should be highlighted that although no significant difference was found between the two groups of patients for other cancer types, the risk ratios for each cancer were below 1.0 in the group receiving SGLT2itreatment, with some exceptions, like rectal, hepatobiliary, and pancreatic cancers.

A meta-analysis published in 2019 comparing randomized controlled trials found no difference in cancer incidence between the groups treated with SGLT2i and the comparator groups [OR: 0.98 (95% CI 0.77-1.24)]. Similarly to our results regarding the effect of SGLT2i, however, a post-hoc analysis of the DAPA-CKD trial showed that cancer mortality was 58% lower among patients receiving dapagliflozin therapy [HR: 0.42 (95% CI 0.19-0.97)].

It should also be noted, that in the survival analysis the Kaplan-Meier curves varied by cancer type. For prostate, hematological, and urinary tract tumors, the curves depicting the absolute cancer risk difference showed an early divergence at 2-12 months, whereas for lung, laryngeal, breast and lower gastrointestinal cancers, the divergence occurred later. This may be due to several factors. Firstly, cell proliferation rates and consequently progression may differ between cancer types. Secondly, the studied antidiabetic agents may produce their effects in different ways and may affect various pathological abnormalities of the distinct cancer cell types. Given that the development of cancer is mostly multifactorial, involving both mutagenic and mitogenic factors, the early divergence of the curves may be due to the mitogenic effect, while the late divergence of curves may be related to the effect of mutagenesis.

6. Conclusions

We conducted retrospective, nationwide analyses of different diabetic populations in Hungary in our research. The strengths of our studies include the availability of data on a national level, the opportunity to perform analyses from real-world data (RWE) - which eliminates some of the weaknesses of randomized controlled trials-, and the use of propensity score matching in our 2nd study, which involved matching the two patient groups regarding a number of parameters, thereby significantly increasing the validity of our results.

The results of our first study suggest that the higher prevalence of diabetic ketoacidosis, hypoglycemia, dialysis, and cancer development observed in young type 1 diabetic patients, may be responsible for the higher mortality risk in this patient group compared to young type 2 diabetic patients.

In our second study, we analyzed the effect of SGLT2i and DPP-4i antidiabetic treatment on the development of cancer. We found that the type 2 diabetic patient population treated with SGLT2i had a significantly lower risk of developing cancer, which could be explained by the significantly lower risk of urinary tract and hematological cancers in this group. Furthermore, we observed an early as well as a late divergence in the cancer-free survival curves for different cancer types. Further studies are needed to elucidate the underlying reason for this phenomenon.

The significance of nationwide real-world data - which was the focus of our research - is to highlight the relevance of certain diseases, their complications, and important associations with treatment. RWEs are also important because they provide a basis for and thus help identify opportunities for primary and secondary prevention and possible new directions for both drug development and health promotion.

The results of our study may thus provide a starting point for further population-level analyses of diabetic and cancer patients and may also provide information for interventions to improve care for people with diabetes.

7. Main findings

7.1 *"Investigating the risks of morbidity and mortality in young adult patient populations with type 1 and type 2 diabetes"*

1. The risk of all-cause mortality was significantly higher in type 1 diabetic patients than in type 2 diabetic patients. The 10-year survival of type 1 diabetes patients was lower than that of type 2 diabetes patients, with a difference of 1.65% at the end of the 167-month follow-up.

2. No significant differences were found in the risks of acute myocardial infarction and stroke between the two patient populations.

3. The risk of developing cancer was significantly higher in the type 1 diabetic patients than in the type 2 diabetic patient population.

4. The risks of diabetic ketoacidosis, hypoglycemia and dialysis were significantly higher in the type 1 diabetic population than in the type 2 diabetic population.

7.2 *"Risk of developing cancer in patient populations treated with SGLT2i and DPP-4i"*

1. There were no significant differences in the risks for lung, laryngeal, lower gastrointestinal tract, rectal, pancreatic, breast, prostate, female genital, other, and non-melanoma skin tumors between the SGLT2i and DPP-4i-treated patient groups.

2. There was a significantly lower risk of developing urinary tract and hematological malignancies among patients treated with SGLT2i.

3. SGLT2i treatment did not increase the risk of developing cancer compared to patients treated with DPP-4i.

4. For lung, laryngeal, lower gastrointestinal and breast tumors, the curves depicting absolute cancer risk difference showed a late reduction in risk, whereas for prostate, hematological and urinary tract cancers, the curves showed an early divergence, between months 2-12.

8. Publications

8.1 Publications directly related to the thesis:

Zoltán Kiss*, **György Rokszin***, Zsolt Abonyi-Tóth, György Jermendy, Péter Kempler, László Barkai, István Wittmann:

Young adult patients with type 1 diabetes have a higher risk of mortality than those of similar age with type 2 diabetes: A nationwide analysis in Hungary

Diabetes/Metabolism Research and Reviews (2019)

DOI: 10.1002/dmrr.3190

*Equal contribution

IF: 3,314

György Rokszin, Zoltán Kiss, Gábor Sütő, Péter Kempler, György Jermendy, Ibolya Fábián, Zoltán Szekanecz, Gyula Poór, István Wittmann, Gergő Attila Molnár:

Sodium-Glucose Co-Transporter 2 Inhibitors May Change the Development of Urinary Tract and Hematological Malignancies as Compared With Dipeptidyl Peptidase-4 Inhibitors: Data of the Post-Hoc Analysis of a Nationwide Study

Frontiers in Oncology (2021)

DOI: 0.3389/fonc.2021.725465

IF: 5,738

Total number of impact factors associated with the thesis: 9.052

Total number of impact factors for all publications: 113,974

7.2 Publications not directly related to the thesis:

Vokó, Zoltán; Kiss, Zoltán; Surján, György; Surján, Orsolya; Barcza, Zsófia; Wittmann, István; Molnár, Gergő A.; Nagy, Dávid; Müller, Veronika; Bogos, Krisztina et al.: Effectiveness and waning of protection with different SARS-CoV-2 primary and booster vaccines during the Delta pandemic wave in 2021 in Hungary (HUN-VE 3 study) FRONTIERS IN IMMUNOLOGY (2022)

Gábor Sütő, Gergő A Molnár, György Rokszin, Ibolya Fábián, Zoltan Kiss, Zoltán Szekanecz, Gyula Poór, György Jermendy, Peter Kempler, István Wittmann: Risk of morbidity and mortality in patients with type 2 diabetes treated with sodium-glucose cotransporter-2 inhibitor and/or dipeptidyl peptidase-4 inhibitor: a nationwide study. BMJ OPEN DIABETES RESEARCH & CARE (2021)

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Kiss Zoltán; Márk László; Herczeg Béla; Aradi Dániel; Rokszin György; Fábián Ibolya; Horváth Krisztián; Wittmann István; Kiss Róbert; Dézsi Csaba et al.: Improvement in age- and sex-dependent mortality in patients with atrial fibrillation between 2011 and 2016 – a nationwide retrospective study from Hungary ARCHIVES OF MEDICAL SCIENCE (2021)

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Várnai Máté; Kiss, Zoltán; Gyulai Rolland; Oláh Judit; Holló Péter; Emri Gabriella; Csejtei András; Kenessey István; Benedek,Angéla; Polányi Zoltán et al.: Improving Quality Indicator of Melanoma Management – Change of Melanoma Mortality-to-Incidence Rate Ratio Based on a Hungarian Nationwide Retrospective Study FRONTIERS IN ONCOLOGY 11 Paper: 745550 , 10 p. (2021)

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