Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycemia

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A B S T R A C T

Aims: The objective of this nationwide study was to compare the risk of all-cause mortality, fatal and nonfatal cardiovascular disease (CVD), and severe hypoglycemia in patients with type 2 diabetes (T2D) on metformin monotherapy treatment starting second-line treatment with either insulin or dipeptidyl peptidase-4 inhibitor (DPP-4i).

Methods: All patients with T2D in Sweden who initiated second-line treatment with insulin or DPP-4i after metformin monotherapy during 2007–2014 identified in the Swedish Prescribed Drug Register were followed for outcome in the Cause of Death and National Patient Registers. Insulin and DPP-4i patients were matched 1:1 using propensity-score matching. Comparisons between groups were performed using unadjusted Cox regression models. Additionally, multivariate adjusted survival models were used to test the results using the full population without matching.

Results: Of 27,767 mono-metformin-treated patients, 55.7% started insulin and 44.3% a DPP-4i, and after matching both groups had 9278 patients each. Median follow-up (patient years) times were 3.84 (37,578) and 3.93 (37,983) for insulin and DPP-4i-groups, respectively. Insulin compared with DPP-4i was associated with higher risk of subsequent all-cause mortality, fatal and nonfatal CVD, and severe hypoglycemia; adjusted HR (95% CI): 1.69 (1.45–1.96); 1.39 (1.21–1.61); and 4.35 (2.26–8.35), respectively. When performing multivariate adjusted analyses on the full population similar results were found.
1. Introduction

International guidelines are currently recommending treatment with metformin as the first-line drug treatment in the majority of patients with type 2 diabetes (T2D) [1]. After varying time periods on metformin most patients with T2D need intensified treatment due to disease progression and insufficient glycemic control. The choice of second line glucose lowering drug (GLD) is open to a number of pharmacological treatments, i.e., insulin, dipeptidyl peptidase-4 inhibitors (DPP-4is), sulphonylureas, thiazolidinediones, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors and there is no consensus what to choose [2]. Sweden has a relatively high use of insulin compared with other European countries and insulin has now surpassed sulphonylurea as the most commonly used second-line drug after metformin [3,4]. Despite several benefits with early insulin initiation like rapid glucose control, insulin also carries a number of unwanted side effects like weight gain, hypoglycemia, reactions from injections, increased treatment complexity, and compromised quality of life [5,6]. Results from observational studies have raised safety concerns regarding increased risk of cardiovascular disease (CVD) and all-cause mortality in patients with T2D treated with insulin in contrast to results from the neutral insulin CV outcome trial, ORIGIN [7–11]. Also, sulphonylurea has been shown in several observational studies to be associated with increased risk of CVD and mortality compared with DPP-4i [12–16]. In the Western world DPP-4i are steadily increasing as a second-line therapy choice and have demonstrated a low risk of hypoglycemia and weight gain [17–19], and have a neutral effect on risk of cardiovascular death and myocardial infarction compared with placebo; although some conflicting signals on heart failure have been reported [20,22,23].

Most previous reports on choice of second line GLD and CVD risk are, however, hampered by the use of sulphonylurea (previous standard therapy) and not by placebo or metformin as the comparative drug with the possibility to disguise a more true complication risk [8,9]. To the best of our knowledge, no study has compared the risk of severe complications between insulin and DPP-4i added to metformin in second-line therapy.

The aim of this observational, full-population study was to investigate the risk of all-cause mortality, fatal and non-fatal CVD, and severe hypoglycemia associated with second-line treatment with either insulin or DPP-4i after mono-metformin, using national healthcare registries in Sweden.

2. Material and methods

2.1. Data sources

This observational registry study utilized data from Swedish national registries: the Prescribed Drug Register covering all drug prescriptions filled since 2005 using Anatomical Therapeutic Chemical (ATC) codes; the Cause of Death Register (established 1961); the National Patient Register covering all hospitalisations and discharge diagnoses since 1987 and all out-patient hospital visits since 2001. All three registers are held by the Swedish National Board of Health and Welfare (NBHW).

2.2. Study population

All patients with an initial metformin monotherapy treatment who filled a prescription for either insulin or DPP-4i (switch or add-on to metformin) during the time period January 1 2007 to December 31 2014 were identified. Metformin monotherapy treatment had to be for a duration of more than 6 months, and patients had to fill a prescription of metformin within one year prior to the start of second-line treatment. Index date was defined as the date of second-line treatment initiation with either insulin or DPP-4i. Patients with any history of cancer (n = 5942) or kidney disease (n = 331) were excluded. See Online-Only Supplementary Table 1 for ICD (International Classification of Diseases) diagnoses and ATC codes. The main analyses were done according to an on-treatment approach, and patients were observed from the index date until index drug discontinuation defined as treatment gap >6 months between filled prescriptions, death, or December 31, 2014. In addition, ITT (intention-to-treat) analyses were performed as above, also including those with interrupted or changed treatment.

Individual patient-level data from the national registers were linked using personal identification numbers, which are assigned at birth and their use is mandatory in dealing with the public healthcare system. Data linkage was performed by the NBHW and the linked database was managed at Statistic AB, Stockholm, Sweden. The study protocol was approved by the Stockholm regional ethics committee (registration number 2013/2206-31). Baseline treatments, defined by ATC codes, were defined as any identified filled prescription of the treatment of interest during the year prior to the index date.

Three endpoints were defined as follows: (1) Death of any cause. (2) Fatal and nonfatal CVD – a main diagnosis in the inpatient register of myocardial infarction (I21), ischemic
stroke (I63–I64), unstable angina pectoris (I20.0), or cardiovascular death (death with an ICD-10 code I diagnosis as primary cause of death). 3) Severe hypoglycemia — a main or secondary diagnosis in the inpatient register of hypoglycemia (E16.0, E16.1, or E16.2) or diabetes with coma (ICD-10 E10.0, E11.0, E12.0, E13.0, or E14.0), as these codes are typically used for hypoglycemia requiring third party assistance.

2.3. Statistical analyses

The time from initiation of second-line treatment to a clinical event (all-cause mortality, fatal or nonfatal CVD, or severe hypoglycemia) was visualized using Kaplan–Meier graphs. Patients were censored at treatment discontinuation, death, or study period end, which for clinical endpoints was 31 December 2014 and for all cause death 31 October 2015.

Propensity score was used to match each patient who added insulin with one patient who added DPP-4i and caliper 0.2 was used. The probability of being treated with DPP-4i was estimated using a logistic regression model with groups as the dependent variable and age, gender, diabetes duration, history of myocardial infarction, unstable angina, angina pectoris, coronary revascularization, heart failure, atrial fibrillation, stroke, transitory ischemic attack, peripheral artery disease, major organ specific bleeding, bariatric surgery, microvascular complications, severe hypoglycemia, lower limb amputations, chronic obstructive pulmonary disease, frailty (defined as ≥3 consecutive days of hospitalization the year prior to index), drugs to prevent or treat CVD (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, loop diuretics, thiazides, aldosterone, warfarin, statins, low-dose acetylsalicylic acid, antiplatelet drugs, calcium channel blockers, weight loss drugs) and calendar year of both index- and first line initiation. Propensity score distribution was used to study overlap between the two matched groups.

Statistical analyses comparing treatments (insulin vs. DPP-4i) in the matched cohort was performed using Cox proportional hazards models, where the dependence within the matched pairs were handled using a robust estimation of the variances. Sensitivity analyses of patients free from prevalent CVD was performed excluding patients with CVD before calculating the propensity score and performing the matching procedure. The matching was performed using the Match function in the R packageMatching [24].

In addition to the analyses of the matched cohort, a series of adjusted Cox proportional hazard models were used on the total unmatched population. Directed acyclic graphs [25] were used to minimize the risk of bias and identify the two adjustment models (Online-Only Supplementary Figs. 1 and 2). Separate adjustment models were determined for risk of severe hypoglycemia (Online-Only Supplementary Fig. 1), and for fatal and nonfatal CVD and all-cause mortality (Online-Only Supplementary Fig. 2).

The model for estimating the risk of severe hypoglycemia was adjusted for age and frailty) [12]. The model for fatal and nonfatal CVD was adjusted for age, sex, frailty, prior CVD as defined in Table 1, and use of statins, low-dose aspirin, and antihypertensives. Prior history of CVD was assessed in the National Patient Register from 1987 until index date. The proportional hazard assumptions were assessed by examining Schoenfeld residuals.

Add-on to metformin was studied separately by only including patients who filled prescriptions of both index drug and metformin within one week of index drug initiation. Separate analyses of the individual types of insulins were performed within the matched dataset to test for potential differences in risks. These survival models were additionally age-adjusted because of differences in baseline characteristics due to the sub-setting of the matched dataset. A P value below 0.05 was considered significant and all analyses were conducted using R statistical software (R version 3.2.3) [26].

3. Results

3.1. Patient characteristics and treatments

Of the 27,767 patients included in the study; 55.7% started insulin and 44.3% DPP-4i during 2007–2014, Table 1. Patients in the insulin group were older than those in the DPP-4i group, more often women, and had more frequently a history of cardiovascular and microvascular disease (Table 1). The insulin group was less treated with statins but more with other drugs associated with established CVD, e.g., low-dose aspirin, and beta-blockers.

3.2. Propensity matched analyses

We found a total of 18,556 insulin and DPP-4i patients who matched. The insulin and DPP-4i groups were very similar in all baseline parameters (Table 1) and with a propensity score distribution overlap of 96%. Low prevalence of severe hypoglycemia was found in both the insulin and DPP-4 inhibitor group at baseline 4% and 9%, respectively (detailed data not shown). Median follow-up (patients years) times were 3.84 (37,578 years) and 3.93 (37,983 years) for insulin and DPP-4i, respectively. The most frequently filled prescriptions for insulin were intermediate-acting, i.e. isophane (67.0%) followed by premixed insulin (intermediate + short-acting; 17.0%), long-acting (10.3%), and short-acting (5.8%), see Online-Only Supplementary Table 2.

In the insulin group, the crude numbers (incidence per 1000 patient-years) of all-cause death, fatal and nonfatal CVD, and severe hypoglycemia were 474 (20.7), 474 (25.2), and 53 (2.7), respectively. The corresponding results for the DPP-4i group were 254 (12.3), 313 (18.1) and 11 (0.6). As illustrated by the Kaplan–Meier curves (Fig. 1A–C), the increased incidence in the insulin group of all types of events can be observed already in the first 6 months, with a continued increase in separation between the curves with follow-up time. Hazard ratios (95% CI) between insulin vs DPP-4i group were 1.69 (1.45–1.96); 1.39 (1.21–1.61); and 4.35 (2.26–8.35) for all-cause mortality, fatal and non-fatal CVD, and severe hypoglycemia, respectively (Table 2). Hazard ratios for all-cause mortality, CVD and severe hypoglycemia were all highly significant and no further adjustment for multiplicity was needed. The intention-to-treat analyses show a lower hazard ratio for all events. Similar results were seen in the CVD-free cohort and numerical risk estimates seemed slightly higher.
for CVD and all-cause death in this cohort. (Online-Only Supplementary Table 3). Statin use was further investigated in patients with or without treatment, and the results remained similar. (Online-Only Supplementary Table 3). Compared with DPP-4i, insulin was associated with increased risk of cancer deaths (1.34 [1.16–1.54, p < 0.001], see Online-Only Supplementary Table 4).

When breaking down the different types of insulins, the same risk pattern was observed, with various degrees of significance. However, these patterns have to be cautiously interpreted due to lower patient numbers, as well as outcomes. (Online-Only Supplementary Table 5).

Small differences in causes of death were noted, the insulin group died less by cardiovascular causes (~6%) and more by other causes (~4%) compared with the DPP-4i group, Online-Only Supplementary Table 6.

### 3.3 Multivariate adjusted survival analyses

When applying multivariate adjustment on the full cohort of 27,767 patients, insulin compared with DPP-4i second-line treatment was associated with similar higher risk of all-cause mortality, fatal and nonfatal CVD, and severe hypoglycemia compared with the propensity matched model.

<table>
<thead>
<tr>
<th>Number of patients, N</th>
<th>Insulin</th>
<th>12,301</th>
<th>p</th>
<th>Propensity matched patients (1:1)</th>
<th>Insulin</th>
<th>9278</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.9 (13.5)</td>
<td>61.4 (11.0)</td>
<td>&lt;0.001</td>
<td>62.2 (13.1)</td>
<td>62.1 (11.1)</td>
<td>0.544</td>
<td></td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>6127 (40%)</td>
<td>4501 (37%)</td>
<td>&lt;0.001</td>
<td>3448 (37%)</td>
<td>3516 (38%)</td>
<td>0.310</td>
<td></td>
</tr>
<tr>
<td>Time on mono-metformin, years</td>
<td>3.4 (2.0)</td>
<td>3.6 (2.1)</td>
<td>&lt;0.001</td>
<td>3.6 (2.1)</td>
<td>3.6 (2.1)</td>
<td>0.729</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Cardiovascular disease (unstable angina, myocardial infarction, or stroke); CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; DPP, dipeptidyl peptidase; NSTEMI, non-ST-segment-elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment-elevation myocardial infarction.

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(Table 2). The intention-to-treat analyses yielded lower risk estimates but similar results compared with the propensity matched model.

When excluding patients that switched we found 8031 patients who initiated on insulin or DPP-4i, as add-on to metformin: 3463 (43%) and 4568 (57%), respectively. Similar risks

![Kaplan–Meier curves and adjusted HRs](image-url)
were found compared with the multivariate adjusted model using the full cohort, Table 2.

4. Discussion

We have shown that in Sweden a high proportion of patients with T2D are initiated on second line insulin compared with DPP-4i, 56% and 44%, respectively. In this clinical setting, we have also shown that insulin, when initiated after metformin monotherapy, is associated with increased risk of all-cause mortality, fatal and nonfatal CVD, and severe hypoglycemia compared with add-on DPP-4i, 1.7-, 1.4-, and 4.4-fold, respectively. These results remained robust when using a different analysis approach like multivariate adjusted survival models on the full (unmatched) population of all insulin patients as well as in T2D without prevalent CVD. The results also remained stable when only including patients with continued metformin treatment, add-on, which were the majority of patients.

Only two observational studies have previously reported on second-line use of insulin and CVD outcome, but the comparator was sulphonylurea [8,9]. Roumie et al. [9] recently showed that risks of a fatal and nonfatal CVD event was increased 1.3-fold in patients adding insulin to existing mono-metformin treatment versus sulphonylurea. The strength of their study was the additional adjustments of important laboratory data, e.g., HbA1c, kidney function markers, blood pressure, and cholesterol as well as diabetes duration. Interestingly, even with these additional factors the numerical risk estimate was comparable to that of our study. Similarly to Roumie et al., Ekström et al. also used sulphonylurea as comparator to basal insulin (medium long acting) after monotherapy with metformin and found that insulin was associated to increased risk of all-cause mortality but not for CVD in the Swedish National Diabetes Register (NDR) [8]. This study used a wide range of important variables collected specifically to address treatment challenges in Swedish diabetes care and included a wider range of variables compared with those studied by Roumie et al. Both studies report a 1.2- to 1.4-fold increased risk of all-cause mortality when comparing insulin with sulphonylurea. One could speculate if this risk had been even higher if DPP-4i had been chosen as the comparator as in the present study that showed a 1.7-fold increased risk. In comparison to second-line sulphonylurea vs DPP-4i, we have previously shown that the former was associated with 1.3-fold increased risk of all-cause mortality using the same analytical method [12]. Thus based on our observational data, both insulin and sulphonylurea show the same pattern compared with DPP-4i when used as second-line therapy with high risks of all-cause death, fatal and nonfatal CVD, and severe hypoglycemia [12].

Currie et al. used a slightly different approach, but in principal similar, using observational data from the UK Clinical Practice Research Datalink in which they compared monometformin treatment versus mono-insulin treatment [7]. In this very large cohort, they showed increased risks of major adverse cardiac events, similar to our CVD and all-cause death, 1.74 (1.44–2.09) and 2.20 (1.98–2.43), respectively. Using the same data source, Holden et al. later reported significant

<table>
<thead>
<tr>
<th>Table 2 – Hazard ratios (HRs) in patients treated with metformin + insulin versus metformin + dipeptidyl peptidase-4 inhibitors (DPP-4i) using propensity-matched patients (1:1). Multivariate adjusted Cox proportional hazard analyses were performed to test the results with different statistical methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard ratios (HRs)</strong></td>
</tr>
<tr>
<td><strong>Propensity-matched (Insulin vs DPP-4i)</strong></td>
</tr>
<tr>
<td><strong>CVD free cohort</strong></td>
</tr>
<tr>
<td><strong>Multivariate adjusted (Insulin vs DPP-4i)</strong></td>
</tr>
<tr>
<td><strong>Add-on treatment</strong></td>
</tr>
</tbody>
</table>

*Adjusted for age, frailty, comorbidity and treatment.*

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Diabetes Research and Clinical Practice 123 (2017) 199–208
association between increasing insulin dose and increased risk of CVD and all-cause mortality [27]. Both studies support our findings that insulin is associated with risk of severe complications in the treatment of T2D. This may suggest, and could additionally suggest that combination of antidiabetic therapy, add-on to insulin, might reduce the doses of insulin and thereby possibly improve the prognosis.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not specifically address insulin in second-line therapy, but randomized patients into intensive control and standard of care [28]. This study prematurely terminated because of 1.2-fold (HR 1.22; 95% CI 1.01–1.46) increase of all-cause death in the intensive control group. Importantly, insulin was more frequently used in the intensive control group compared with the standard of care, 77% and 55%, respectively, and higher risks of hypoglycemia were reported in the former compared with the latter group [29,30].

The Outcome Reduction with an initial Glargine Intervention (ORIGIN) trial, in dysglycemic patients with either prediabetes or established type 2 diabetes, showed that treatment with insulin glargine vs. standard of care in a randomized control care setting did not increase the risk of CVD but modestly increased the risk of hypoglycemia and weight gain [10]. However, the intensity of blood glucose control was surprisingly small over six years in the insulin glargine group compared with the standard of care group and this might explain the modest risk of hypoglycemia. The results of the ORIGIN trial show that mild glucose-lowering drug treatment very early in the disease with insulin glargine, and relatively small changes in glucose levels, is CVD neutral. However, the ORIGIN study included less representative patients and treatments compared to a real clinical setting represented by the present and other observational studies performed in a real world setting [8–10].

Although our study was not designed for the purpose we found the same risk pattern for different types of insulin used in second line compared with DPP-4i. However, although the risk estimates are of similar numerical magnitude, the low number of patients cause variable significance levels except for the largest group of medium acting insulin in which results are robust.

The cause of increased risks of CVD and all-cause mortality seen with second-line insulin use is not clear. One partial explanation could be the high risk of severe hypoglycemia associated with insulin and sulphonylureas compared with DPP-4i and subsequently a risk substrate for CVD and death [31]. In this study, we have demonstrated a markedly increased 4.4-fold risk of severe hypoglycemia associated with insulin, compared with DPP-4i. It is already well known that insulin in comparison with DPP-4i treatment is associated with increased risk of hypoglycemia, which was further demonstrated in current study. Hypoglycemias have been reported to be associated with CVD and mortality through different pathways [12,31]. Hypoglycemic responses, such as sympathoadrenergic activation, have been suspected to trigger CVD and might act as a causal pathway between insulin treatment and risk of CVD and mortality, and may contribute to serious cardiac arrhythmias [31]. In previous studies, similar associations between occurrence of severe hypoglycemia and CVD events were found, supporting this suggested causal mechanism [12,31].

Other mechanisms negatively affecting the thrombotic status and endothelial function, e.g., inflammation [32] and platelet dysfunction [33], could also explain associations between insulin and CVD. Another partial explanation for the increased CVD risk shown with insulin could be that treatment with DPP-4i is not associated with any weight gain, in contrast to the association of insulin treatment with moderate/significant weight gain [5,10,28]. Moderate weight gain has been strongly associated with increased risk of cardiovascular death and all-cause mortality [34,35].

Patients treated with insulin had an increased risk of all-cause mortality, and CVD death was the most common cause of death closely followed by cancer. Although the current study was not designed to look at any associations with cancer, we found a significant 1.3-fold increased risk of cancer death in insulin-treated patients compared with DPP-4i-treated patients. This has been reported previously by Currie et al. who showed a 1.4-fold increased risk with mono-insulin vs. mono-metformin [7]. Furthermore, Holden et al. recently showed an insulin-dose association between insulin and the risk of cancer [27]. Albeit interesting, we need to design a new study to specifically address this question, because the multivariate models were not designed to adjust for cancer associations.

4.1. Strengths

A strength of the present work is the population-based, nationwide, and unselected real-world study design, which provides high external validity. In addition, this is a study with full (100%) register coverage for hospitalizations, filled drug prescriptions, and cause of death in a country with an established and complete public healthcare system. Diagnoses in the Swedish Patient Registry have been reported to have high validity [36], and few patients are lost to follow-up. Patients with diseases that per se might lead to choice of insulin treatment, rather than non-insulin, was excluded, e.g., history of cancer and manifest kidney disease. Moreover, for the multivariate adjusted analyses, directed acyclic graphs were used to create the optimal adjustments of hazard models and should have provided minimal bias [25]. The frequent and early, low threshold, use of insulin in Sweden increased the possibility of finding 1:1 matched patients initiated on DPP-4i in second-line therapy. The reason for the high use of insulin use in Sweden [3], compared with other European countries [4], is not clearly understood, but a potential explanation is the Swedish national guidelines [37] that give treatment with medium–long acting insulin the highest priority after metformin in pharmacological treatment of T2D. Moreover, the relatively frequent use of diabetes nurses in primary care enables closer and dedicated patient follow-up needed for insulin treatment.

4.2. Limitations

Observational studies such as this have limitations. The present study has no information on laboratory measurements,
lifestyle parameters, primary healthcare data, or socioeconomic data, and consequently there may be remaining confounding factors. Parameters on kidney function are lacking and to minimize potential effects we have excluded any patient with kidney disease. Beside exclusion of kidney disease, we have included a number of important covariates in the propensity score that to some extent will indirectly reflect likelihood of kidney dysfunction and lower the likelihood of imbalanced kidney function at baseline between the two groups, e.g. age, atherosclerotic burden (prior myocardial infarction, unstable angina, ischemic stroke, peripheral artery disease), heart failure diagnosis, heart failure drug treatments (aldosterone antagonists, betablockers, loop diuretics) and drugs affecting the renin-angiotensin system. Furthermore, all patients had to be on metformin monotherapy before index which is contraindicated in patients with moderate to severe kidney failure. Despite this, as in any observational study we cannot rule out that residual confounding factors affected our results. However, the close matching with an extensive number of important variables and relative high hazard ratios could minimize the risk of unknown confounding.

We have little information on the duration of diabetes and age of onset of diabetes (diabetes age). However, by matching in index year and also the year of first-line therapy initiation, we believe that this is a robust proxy for diabetes age.

We have no information on emigration, which could result in loss to follow-up. However, the on-treatment analyses used in this study should have minimized the effects of patients moving out of Sweden. Furthermore, our assessment of severe hypoglycemia is crude, including only events leading to hospital admission. It was not possible to evaluate other hypoglycemic events in this register-based study. Another limitation is that patients with a recorded hypoglycemia had to survive until this occasion and, if anything, this would underestimate the total mortality rate in these patients compared with those without a hypoglycemic event. Daily insulin dosages has not been taken into consideration because of inconsistent structure of dosage advice from prescriber in the prescribed drug register.

In summary, despite insulin’s strong glucose-lowering effect and prevention of microvascular disease, there is increasing evidence that other complications may limit its benefits in the treatment of patients with T2D. During the last few years, newer glucose-lowering drugs with less risk for hypoglycemia and potentially also for CVD have entered the market and might offer therapeutic alternatives with less risk of serious adverse effects [38,39].

5. Conclusion

In this observational study initiation of insulin after metformin monotherapy treatment was associated with an increased risk of subsequent all-cause mortality, cardiovascular adverse events, and severe hypoglycemia compared with initiation of DPP-4i. In order to elucidate causal relationships for the associations found in this study, randomized trials will be needed, especially using newer glucose lowering drugs with proven cardiovascular safety as comparators.

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Author contributions

All authors participated in the study design. MT performed the data collection and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing the manuscript. All authors took final responsibility in the decision to submit for publication.

Conflict of interests

JWE has received honoraria or research grants from AstraZeneca, NovoNordisk, Bristol-Myers-Squibb, Sanofi and MSD. JB holds a full-time position at AstraZeneca as epidemiologist. DN has received consultancy fees from Novo Nordisk, AstraZeneca and Eli Lilly. MT is employed by an independent statistical consultant company, Statisticon AB, Uppsala, Sweden, for which AstraZeneca Nordic-Baltic is a client. TN has received research grants from AstraZeneca and NovoNordisk, and is on the national board of NovoNordisk, Sanofi-Aventis and Eli Lilly. AN has received honoraria from MSD, AstraZeneca, Eli Lilly, Boehringer Ingelheim.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2016.12.004.

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