Mortality in Individuals Treated with Glucose Lowering Agents: a Large, Controlled Cohort Study

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Context: Several observational studies and meta-analyses have reported increased mortality of patients taking sulfonylurea and insulin. The impact of patient profiles and concomitant therapies often remains unclear.

Objective: To quantify survival of patients after starting glucose-lowering agents (GLAs) and compare it to control subjects, matched for risk profiles and concomitant therapies.

Design: Retrospective controlled cohort study.

Setting: The study is based on health expenditure records of the largest Belgian health mutual insurer, covering over 4.4 million people.

Patients: 115,896 patients starting metformin, sulfonylurea or insulin (alone or in combination) between January 2003 and December 2007. Control subjects without GLA therapy were matched for age, gender, history of cardiovascular events and therapy with antihypertensives, statins and blood platelet aggregation inhibitors.

Intervention(s): None.

Main Outcome Measure: 5-year survival after start of GLA.

Results: Profiles of patients using different GLAs varied, with patients on sulfonylurea being oldest and patients on insulin having more frequently a history of cardiovascular disease. Excess mortality differed across GLA therapies compared to matched controls without GLAs, even after adjusting for observable characteristics. Only metformin monotherapy was not associated with increased 5-year mortality compared to matched controls, while individuals on combination of sulfonylurea and insulin had highest mortality risks. Age and concomitant use of statins strongly affect survival.

Conclusions: Differences exist in 5-year survival of patients on GLA, at least partly driven by the risk profile of the individuals themselves. Metformin use was associated with lowest 5-year mortality risk and statins dramatically lowered 5-year mortality throughout all cohorts.

Glucose lowering therapy in type 2 diabetes is challenging, due to the progressive nature of the disease by the underlying failure of the insulin-secreting β-cells (1). Algorithms and guidelines are proposed by international bodies, guiding clinicians through the maze of possibilities of glucose-lowering agents, but guidance is mostly based on evidence from the original UKPDS study, reported in the middle of the 1990's (2). Evidence on the

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Abbreviations:

impact of glucose-lowering agents on the hardest endpoint, survival, is limited. In particular, sulfonylurea and insulin have been associated with higher mortality risks in cross-sectional studies or population studies (3–8) with criticisms arising that comparing the mortality risk in these individuals to the global population is unfair as the profile of this population may be different, predisposing them to a higher mortality risk. On the other hand, many studies report a lower mortality risk in type 2 diabetes patients treated with metformin (3–9) but again, the profile of these people may be different by itself, thus influencing risk. Finally, in the high cardiovascular risk disease that is type 2 diabetes, use of statins has been debated frequently, with doubts being cast over the usefulness of these drugs in this population, in particular in the young or very old age groups. This study investigated the survival of patients starting therapies involving various glucose-lowering agents (GLAs) compared to fully matched control subjects. We particularly analyzed the effect of age and concomitant use of statins.

This study was performed in collaboration with the largest mutual health insurance fund in Belgium (National Alliance of Christian Mutualities - NACM), which has access to a large database containing health expenditure records of 4.4 million people throughout the country. The Belgian health care insurance is a broad solidarity-based form of social insurance. Mutual health insurers like NACM are the legally-appointed bodies for managing and providing the Belgian compulsory health care and disability insurance. To implement its operations, NACM disposes of a large database containing health expenditure records of all its members. These records hold all financial reimbursements of drugs, procedures and contacts with health care professionals so that long-term follow-up and full matching of people using GLAs to people identical in age, gender, concomitant medications and start of follow-up are possible. This allowed us to assess the excess mortality in patient cohorts defined by their GLA therapy compared to references without GLA therapy but with otherwise similar observable characteristics.

Research Designs and Methods

NACM population

This study is based on records of the NACM, the largest Belgian mutual health insurer with over 4.4 million members (market shares of over 40% and 60% in Belgium and Flanders, respectively). All data extractions and analyses were performed at the Medical Management Department of the NACM under supervision of the Chief Medical Officer.

NACM disposes of a longitudinal overview of its members' medical resource use, embedded in health expenditure records. Only 2% of the subpopulation under study left the NACM to switch to another mutual health insurer, emigration or employment by a foreign employer during the 5-year follow-up period, leading to a retention rate of 98% in our study. Patients that joined NACM after December 1999 were excluded from all analyses to minimize the chance of missing glucose-lowering therapy and/or cardiovascular events prior to starting follow-up.

Each medication record corresponds to one or several active substances as defined in the fifth level of the anatomical therapeutic chemical (ATC) classification system. This association is known via the metadata of each drug unit/package, which contains a mapping to active substances and defined daily doses as presented in the ATC system. The ATC system classifies drugs based on the targeted organ or system and their therapeutic and chemical characteristics (10). Patients were partitioned into treatment groups based on ATC codes listed in their individual histories. Exact definitions of all pharmacological groups can be consulted in Supplemental Table 1. In addition to pharmacotherapy, we considered a set of cardiovascular events prior to follow-up, which were identified via a combination of medicinal and surgical interventions (also described in Supplemental Table 1). Based on usual prescription behavior in Belgium, exposure of oral glucose lowering drugs was assumed to be uninterrupted between the dates of the first record and up to six months after the final record in the insurance database.

Study Cohort selection

The selection process is illustrated in Figure 1. 115 896 patients over 18 years old in whom glucose-lowering therapy was prescribed between first of January 2003 and 31st of December 2007 were eligible for the study. Eligible patients were assigned to study cohorts based on their glucose-lowering pharmacotherapy: more specifically metformin (MET), sulfonylurea (SU) and insulin (INS). Every combination of these three drug types defines a study cohort. Patients on DPP4 inhibitors or GLP-1 receptor agonists were not included as these were only introduced in Belgium around 2008.

Follow-up started on the first day of therapy intake, based on the patient's purchase of the prescribed agent(s). In each study and control group, subjects were followed until death or censoring over a maximum period of 5 years since inclusion. For control subjects, the start of follow-up was determined at random within the year of inclusion of the associated study patient to avoid bias related to the time of entry into the study.

Monotherapy study cohorts denote the first glucose-lowering therapy consisting of a single type of GLA, given to a patient without prior use of other GLAs (n = 74,938), based on historical records from 1990 onwards. Patients are excluded from monotherapy cohorts if they transition to combination therapy within three months. Patients who started a combination therapy during the selection interval for at least 3 months (or until death) were included in the associated study cohorts, regardless of potential prior glucose-lowering therapy (n = 47,149).

Patients could successively enter multiple study cohorts *and* be included in multiple cohorts during follow-up. For instance, a patient without prior GLA therapy who started metformin in 2003 and added sulfonylurea in 2005 is included in both the metformin monotherapy and the metformin and sulfonylurea combination therapy cohorts (5-year follow-up starting in 2003 and 2005, respectively), with some period of overlap (2005–2008).

Only patients with at least one month between the first and

last purchase of associated GLAs were included in study cohorts. We accounted for potential bias by consistently matching control patients who survived for at least one month (11, 12). Patients who started treatment and died during a single hospital admission were excluded from the analysis.

Control Cohort selection

We compared study groups to controls with similar observable characteristics. Controls were sampled without replacement from the NACM population with matched characteristics to the study cohort, but without records of GLA therapy up to and including 2013 so that the only observable difference between study and control cohorts was the intake of GLA's or not.

Unless stated otherwise, the control groups contained 5 subjects per subject in the study cohort, matched exactly on age at the start of follow-up, gender, cardiovascular history (had event/no event before the start of the follow-up), associated therapy (use of statins, antiplatelet and antihypertensive drugs) and the year of start of follow-up. Matching based on associated therapy was performed dichotomously (subject has/has not received the therapy for more than half of the individual's effective follow-up period).

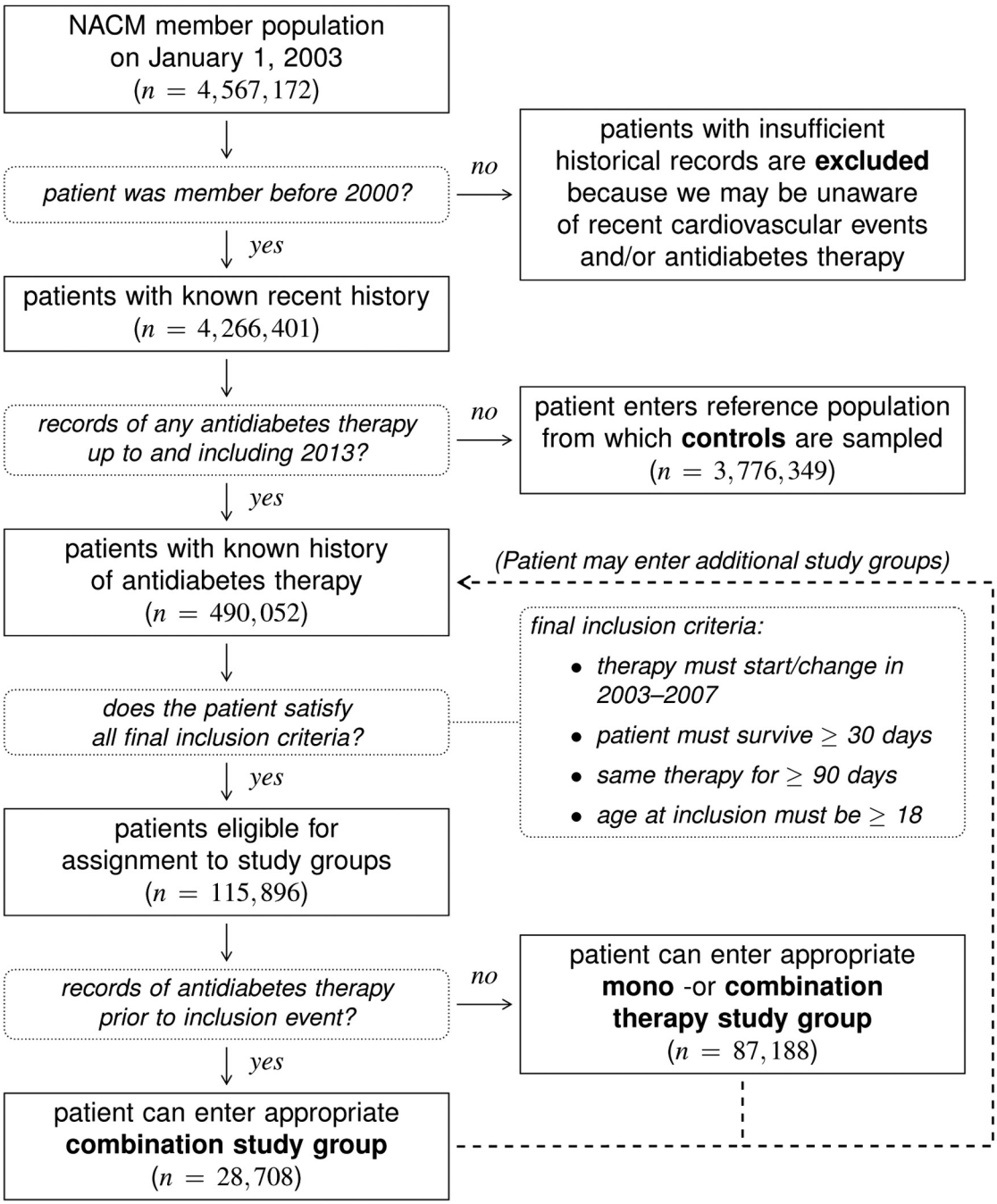

Figure 1. Flowchart describing the selection protocol for study and control patients. Patients can move from the bottom right (monotherapy) to the bottom left group (combination therapy), but not vice versa. All listed counts are for unique patients.

Therapy changes within cohorts

Most patients remained on the same GLA therapy during the entire follow-up (Supplemental Table 2). 15.4 to 28.5% of patients starting on monotherapy moved to a combination therapy by the end of the follow-up. Patients on combination therapy at start were still on the same regimen in 47.7 to 66.5% of cases: changes were often due to stopping of sulfonylurea (9 to 20%) or eliminating metformin from combination regimens that include insulin (15.2 to 18.7%).

Censoring

As we were primarily interested in prognoses for patients starting a certain therapy, no censoring was done based on therapy changes (such as adding additional GLAs) or poor compliance. Censoring based on therapy changes would be informative and hence bias the survival estimates of interest. Patients that discontinued all GLA therapy for nine consecutive months are right censored, as this was considered to indicate that the patient was not using GLAs to manage glucose levels (eg, using metformin for weight loss). Right censoring also occurred when subjects left the health insurer (lost to follow-up), which was rare (less than 2% of all patients in follow-up in each cohort). Switching health insurer was considered unrelated to a patient's medical condition and can therefore be considered noninformative.

Statistical analysis

Empirical survival curves were obtained using the Kaplan-Meier estimator. The associated 95% CIs were computed using the exponential Greenwood formula (13).

We used Cox proportional hazards (PH) models to quantify excess mortality between study and control cohorts while controlling for all observable patient characteristics. Adjusting for concomitant medication was particularly important, as controls were only matched in a binary fashion. Unless mentioned otherwise, the PH models contained the following set of predictors: continuous covariates describing age at start of follow-up and associated therapy (specifically statins, antiplatelet and antihypertensive drugs) and dichotomous factors for gender and the group a subject belonged to (study or control). Associated therapy-related predictors quantify the fraction of the subject's effective follow-up time during which he/she was exposed to the agent. Finally, an interaction term between age and gender is consistently included.

The PH assumption was assessed via the Grambsch-Therneau test on scaled Schoenfeld residuals from the PH models (14). The proportionality assumption was tested for each reported hazard ratio (HR) at the 1% significance level and rejections are indicated in all tables.

A sensitivity analysis was performed to assess the uncertainty on the hazard ratios associated with statin use within study groups. Two thousand resamples (with replacement) of each data set were used to estimate the reported hazard ratios and estimated new models on each resample. Subsequently, stability of the distribution of hazard ratios across these simulated models was verified.

Software

Statistical analyses were conducted in *R* using the *survival* package (15, 16). Statistical plots were made in *R* using the *ggplot2* package (17).

Results

Baseline cohort characteristics

An overview of the study cohorts and their baseline characteristics is given in Table 1. The study group with the youngest patient population was the group on insulin monotherapy without CV history ($P < .001$ compared to all other groups), followed by patients on metformin monotherapy without CV history ($P < .001$ compared to all remaining groups). The oldest patients were those who received sulfonylurea regardless of CV history ($P < .001$ compared to all other groups). Patients with a history of CV disease were consistently older than others ($P < .001$ in all pair-wise comparisons to groups without CV history) except in the sulfonylurea-insulin combination group.

Patients without insulin in their GLA therapy were less likely to have a history of CV disease (less than 9% percent of the total group) than patients with insulin on board (more than 20% percent of total group) ($P < .001$).

The percentage of males and intake of associated therapies (statins, antiplatelet and antihypertensive therapies) were consistently higher in the patients with a history of CV disease than in those without, irrespective of the glucose lowering therapy ($P < .001$ for all groups). Most patients with a CV history were taking statins for over half the follow-up period, ranging from 58% in the SU + INS group to 79% in the metformin monotherapy group. In contrast, only a minority of patients without CV history were taking statins: ranging from 23% in the insulin monotherapy group to 47% in the MET + INS group.

Five-year survival in individuals on different glucose lowering agents

Compared to their associated matched controls, patients on metformin monotherapy showed no significant excess mortality during the follow-up. In contrast, patients started on SU, and certainly on insulin, did much worse than their respective controls (Figure 2). The excess mortality was highest in patients starting on insulin (23.8%), followed by SU (4.1%) and finally metformin (0.3%, though not statistically significant at the 5% significance level). Patients who started with bitherapy (MET + SU or MET + INS) or tritherapy (MET +SU +INS) also exhibited reduced 5-year survival compared to matched controls, with the highest difference in survival (12.9 and 15.6%) when insulin was part of the regimen from the start of follow-up.

Comparable differences were seen in survival of patients without a history of cardiovascular (CV) events, with the lowest survival rates in therapies involving both insulin and SU (up to 29% difference after 5 years) (Table 2). Patients with a history of CV events consistently ex-

Table 1. Baseline characteristics of study cohorts

			gender	associated therapy		
	subjects	age	female	statins	antiplatelet	AHT
study cohort	n	mean ± SD	n (%)	n (%)	n (%)	n (%)
metformin	**42 900**	**62.0 ± 12.3**	**21 759 (51)**	**19 747 (46)**	**7725 (18)**	**33 785 (79)**
no cv history	39 578	61.6 ± 12.4	20 913 (53)	17 127 (43)	5579 (14)	30 592 (77)
cv history	3322	66.8 ± 10.3	846 (25)	2620 (79)	2146 (65)	3193 (96)
sulfonylurea	**19 231**	**68.4 ± 12.6**	**10 100 (53)**	**7479 (39)**	**3825 (20)**	**15 507 (81)**
no cv history	17 438	68.0 ± 12.8	9576 (55)	6325 (36)	2739 (16)	13 786 (79)
cv history	1793	71.8 ± 9.7	524 (29)	1154 (64)	1086 (61)	1721 (96)
Insulin	**12 807**	**62.8 ± 17.8**	**5818 (45)**	**3842 (30)**	**4270 (33)**	**10 214 (80)**
no cv history	10 372	61.0 ± 18.7	5125 (49)	2395 (23)	2410 (23)	7827 (75)
cv history	2435	70.6 ± 10.2	693 (28)	1447 (59)	1860 (76)	2387 (98)
metf + sulf	**25 218**	**65.8 ± 12.0**	**12 632 (50)**	**11 718 (46)**	**5521 (22)**	**20 913 (83)**
no cv history	22 830	65.4 ± 12.1	11 966 (52)	9973 (44)	4038 (18)	18 612 (82)
cv history	2388	69.6 ± 9.4	666 (28)	1745 (73)	1483 (62)	2301 (96)
metf+insulin	**9506**	**64.8 ± 13.9**	**4880 (51)**	**4891 (51)**	**3562 (37)**	**8305 (87)**
no cv history	7874	64.0 ± 14.5	4330 (55)	3716 (47)	2333 (30)	6710 (85)
cv history	1632	68.7 ± 10.1	550 (34)	1175 (72)	1229 (75)	1595 (98)
sulf+insulin	**6.087**	**74.1 ± 11.0**	**3201 (53)**	**2285 (38)**	**2730 (45)**	**5580 (92)**
no cv history	4580	74.1 ± 11.6	2639 (58)	1415 (31)	1584 (35)	4108 (90)
cv history	1507	74.1 ± 8.8	562 (37)	870 (58)	1146 (76)	1472 (98)
metf+sulf+insulin	**10 653**	**69.1 ± 11.4**	**5570 (52)**	**5405 (51)**	**4680 (44)**	**9746 (91)**
no cv history	8380	68.7 ± 12.0	4800 (57)	3827 (46)	2933 (35)	7520 (90)
cv history	2273	70.5 ± 9.1	770 (34)	1578 (69)	1747 (77)	2226 (98)

All differences in use of associated therapy are statistically significant between study cohorts, except for use of antihypertensives (AHT) in insulin and sulfonylurea mono cohorts. For each cohort, associated therapy use was significantly higher in subgroups with prior cardiovascular events. All comparisons of study group characteristics use significance level $\alpha = 0.05$ and are computed using Tukey's test in conjunction with ANOVA to adjusts for multiple comparisons.

hibited lower survival than patients without a CV history, but excess mortality compared to matched controls was comparable for both subgroups. Of note, the survival of patients with a CV history on metformin monotherapy was not significantly different from the survival of the associated controls. The observed survival benefit of metformin monotherapy disappeared in combination therapy cohorts (Table 2).

Age-dependent 5-year survival of individuals on different glucose lowering agents

Figure 3 illustrates the 5-year survival of patients as a function of age at the start of follow-up. Compared to the general population, 5-year survival was lower at any age in all cohorts on glucose lowering monotherapy except the metformin monotherapy cohort, which exhibits comparable survival to the general population. At any certain age, survival was highest in patients on metformin, worse in patients on sulfonylurea, and worst in patients on insulin. In patients starting on combination therapy, survival was also lower at any age than associated controls. Again, if the regimen contains insulin, survival is worse at any age category, with or without sulfonylurea on board.

The differences in survival at any age were slightly reduced when comparing to fully matched controls, though they remain large and statistically significant (illustrations are given in Supplemental Figure 1). This reduction in excess mortality appears to be mainly attributable to the fact that the fully matched control groups have a higher frequency of prior cardiovascular events than the unmatched general population.

Patients starting metformin monotherapy at a very young age (between 18 and 40 years; n = 1446; 83.3% male) had a 5-year survival rate of 99.2% [98.4%–99.6%] compared to 99.3% [99.1%–99.5%] for fully matched controls ($P = .644$). Of note, all females in this study group (n = 242) survived the entire follow-up. In the age category 18 to 40 years, the 5-year survival rate of patients on insulin monotherapy (n = 1873) was reduced compared to fully matched controls ($P < .001$), with survival rates of 94.7% [93.4%–95.6%] and 99.5% [99.3%–99.6%] respectively.

Statins and survival in individuals on different glucose lowering therapy

Survival was compared between patients with and without statins. Survival was consistently higher for patients that used statins in conjunction with GLA therapy (Table 3), irrespective of CV history. The observed mortality rate when using statins along with GLAs was 57 to 64% lower in patients without a history of CV disease and by 50 to 68% in patients with a CV history, compared to

Table 2. 5-year survival of study cohorts and fully matched controls, stratified by history of cardiovascular disease

	no history of cardiovascular disease				history of cardiovascular disease			
	5-year survival (%)		hazard ratio		5-year survival (%)		hazard ratio	
study cohort	study cohort	control			study cohort	control		
metformin	92.6 [92.3–92.2]	92.9 [92.8–93.0]	1.07 [1.02–1.11]		86.7 [85.4–87.8]	85.2 [84.6–85.7]	0.92 [0.83–1.02]	
sulfonylurea	82.5 [81.9–83.1]	86.5 [86.3–86.8]	1.45 [1.40–1.52]	*	72.5 [70.2–74.6]	77.2 [76.4–78.1]	1.35 [1.22–1.50]	
Insulin	63.9 [62.9–64.9]	88.1 [87.8–88.3]	4.32 [4.14–4.51]	*	56.1 [53.9–58.3]	78.6 [77.9–79.3]	2.69 [2.49–2.90]	
metf+sulf	87.0 [86.5–87.4]	90.3 [90.1–90.5]	1.40 [1.35–1.46]		79.1 [77.4–80.7]	81.8 [81.1–82.5]	1.18 [1.07–1.30]	*
metf+insulin	77.1 [76.1–78.0]	89.8 [89.5–90.1]	2.71 [2.56–2.87]	*	69.2 [66.9–71.4]	82.7 [81.8–82.5]	2.07 [1.87–2.30]	
sulf+insulin	50.3 [48.8–51.7]	78.4 [77.8–78.9]	3.07 [2.92–3.23]	*	48.8 [46.2–51.3]	74.3 [73.3–75.2]	2.66 [2.44–2.89]	
metf+sulf+ins	71.5 [70.5–72.5]	87.5 [87.2–87.8]	2.71 [2.58–2.85]		67.4 [65.6–69.3]	81.5 [80.8–82.2]	2.05 [1.89–2.23]	

Overview of survival for the study cohorts compared to a fully matched control cohort, stratified by cardiovascular history. The control groups are sampled from the general population and matched for age, gender and use of statins, antihypertensives and antiplatelet drugs. For every patient in the study cohorts, 5 patients with completely matching profiles were used in control. Stars (*) indicate that the proportional hazards assumption was rejected for the associated hazards ratio ($P < 0.01$), which means that the resulting effect size is an average over the entire follow-up period, rather than a true hazard ratio.

patients using only GLAs. Sensitivity analysis showed that the bootstrap confidence intervals largely agree with the confidence intervals estimated via the proportional hazards procedure itself, indicating reliable estimates (Supplemental Table 3).

In a second analysis, cohorts in which all patients on glucose lowering therapy were taking statins were compared to the general age and gender matched population. Patients on metformin monotherapy (with and without a CV history) and sulfonylurea mono (without CV history) that were also taking statins exhibited higher survival rates than age and gender matched control groups without glu-

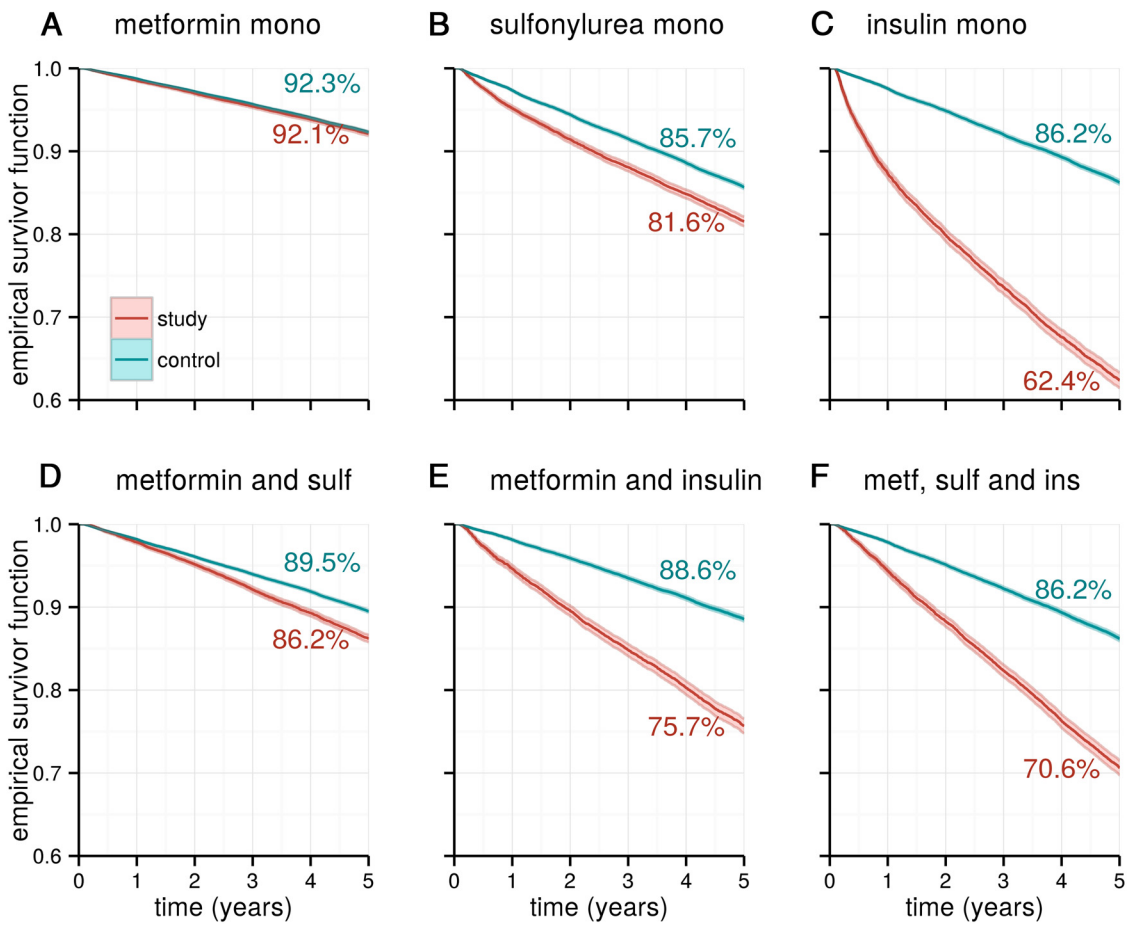

Figure 2. *Survival of the main study cohorts (red line) compared to fully matched controls (blue line). Data are shown for patients on monotherapy with:* A. *metformine,* B. *sulfonylurea and* C. *insulin and for patients on combination therapy with* D. *metformine and sulfonylurea (sulf),* E. *metformin and insulin and* F. *metformin (metf), sulf and insulin (ins). Percentages shown in the graft indicate the percentage of surviving patients after a study follow-up of five years. Data are empirical survival function +/- 95 confidence interval (CI).*

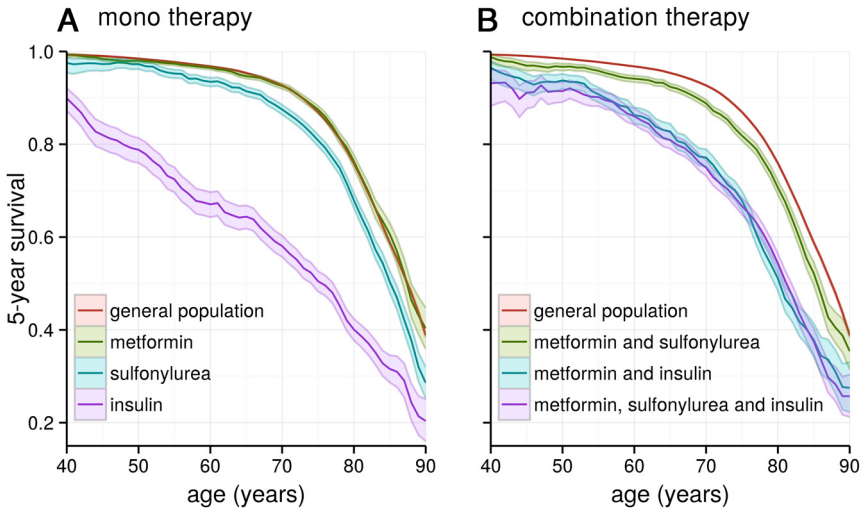

Figure 3. 5-year survival for increasing age per cohort and in the general population. Data are shown for patients on A. monotherapy with metformin (green line), sulfonylurea (blue line) and insulin (purple line) and B. combination therapy with metformin and sulfonylurea (green line), metformin and insulin (blue line) and metformin, sulfonylurea and insulin (purple line). 5-year Survival at a given age X was computed as the survival of the subgroup of age X-3 years to X+3 years. Data are empirical survival function +/- 95 CI.

cose lowering therapy (of which resp. only 32,4%, 24.7%, and 29.9% were taking statins during most the follow-up). Patients on the combination of MET and SU and statins had the same survival rate than their controls, irrespective of CV history (Supplemental Table 4).

Conclusions

The main objective of this large controlled cohort study was to investigate the survival of patients on various glucose lowering therapies in comparison to a reference population with similar observable characteristics. It was found that 5-year survival rates vary between glucose lowering therapies, at least partly driven by the risk profile of the individuals themselves, and substantially influenced by the intake of statins and the age at the start of GLA therapy.

Increased 5-year mortality rates were observed in patients on GLAs compared to matched references not on GLAs. This confirms the study of Bannister et al (9) showing an increased mortality in patients on SU monotherapy and extends the evidence to other groups on insulin monotherapy and different combination therapies. Although we did not see a better survival rate in patients on metformin monotherapy, our data show that these patients have similar survival rates compared to matched controls, especially if a positive history of CV disease is present.

Our study confirms data from many other observational studies that patients on metformin monotherapy have a lower mortality risk than patients on other glucose lowering therapy (3–8), characterized by reduced excess mortality compared to matched controls. This study does determine whether this excess mortality of patients on SU and insulin is mainly caused by the vulnerability of the background population or by negative properties of the therapies themselves. The extra mortality risk can, at least partially, be explained by the risk profile of the individuals themselves. First of all, this might reflect the progressive nature of type 2 diabetes such that patients with less pronounced hyperglycemia are started on metformin monotherapy whereas uncontrolled patients are started on insulin or combination therapies including SU. Age is another important independent predictor of mortality and can explain why younger patient groups (ie, metformin mono) have better survival rates than older patient groups (ie, SU mono). Age however does not explain the lower survival rates in younger patients on insulin monotherapy and survival differences throughout all age categories. A positive history of cardiovascular events also increases the background risk of our populations and explains the lower survival rates in any study cohort with a positive CV history. As in Morgan et al (7), a combination of several other elements will probably play a role such as hypertension and factors that were not available in our study such as presence of chronic kidney disease and albuminuria, the level of glycemic control, smoking and heart failure. Especially a background of chronic kidney disease might explain important differences in mortality risk between groups with or without metformin on board.

Differences in survival benefit of the different GLAs might also explain excess mortality in patients on SU and insulin. Data from literature are conflicting concerning differences between agents. On the one hand several studies report no difference in survival when comparing metformin with SU (18–20) or SU with insulin (19). Also in the ORIGIN trial, insulin glargine was not associated with higher mortality rates than controls (21) despite the lower use of metformin in the insulin glargine group. On the other hand, many clinical and observational studies have indicated an increased mortality risk associated with the use of SU and insulin compared to metformin (3–8), although differences were shown to depend on the type of SU (22, 23), and the dose of insulin (24) used. In fact only a well-controlled RCT with sufficient power comparing different treatment strategies might answer this question,

Table 3. Analysis of the effect of statins within each study cohort.

	no history of cardiovascular disease				history of cardiovascular disease			
	5-year survival (%)		hazard ratio		5-year survival (%)		hazard ratio	
study cohort	without statins	with statins			without statins	with statins		
metformin	90.2 [89.8–90.6]	95.5 [95.2–95.9]	0.43 [0.39–0.47]	*	71.3 [67.5–74.6]	90.6 [89.4–91.7]	0.36 [0.29–0.45]	
sulfonylurea	76.9 [76.1–77.8]	91.7 [91.0–92.4]	0.36 [0.32–0.40]	*	53.1 [48.8–57.2]	82.5 [80.1–84.6]	0.32 [0.26–0.40]	
insulin	59.6 [58.4–60.8]	77.3 [75.4–79.0]	0.37 [0.33–0.41]	*	40.5 [37.0–43.9]	66.5 [63.7–69.1]	0.45 [0.39–0.53]	*
metf + sulf	82.5 [81.8–83.2]	92.6 [92.0–93.1]	0.42 [0.38–0.46]	*	62.8 [58.8–66.5]	85.0 [83.2–86.6]	0.42 [0.34–0.51]	
metf + insulin	68.2 [66.7–69.6]	86.8 [85.7–87.9]	0.39 [0.35–0.44]		46.7 [42.0–51.2]	77.9 [75.4–80.2]	0.40 [0.33–0.49]	
sulf + insulin	41.3 [39.6–43.1]	69.9 [67.4–72.3]	0.43 [0.38–0.48]		32.3 [28.6–36.0]	60.8 [57.4–63.9]	0.50 [0.42–0.59]	
metf + sulf + ins	61.5 [60.0–62.9]	83.4 [82.1–84.5]	0.43 [0.39–0.48]	*	46.6 [42.8–50.3]	76.6 [74.4–78.6]	0.42 [0.35–0.49]	

Presented hazard ratios are associated to the fraction of follow-up on statins. Patients are classified as statin users if they were on statins for at least half the follow-up. The proportional hazards models used here control for age, gender, use of antihypertensive and antiplatelet drugs and an age-gender interaction. Stars (*) indicate that the proportional hazards assumption was rejected for the associated hazards ratio ($P < 0.01$), in which case the result should be interpreted as the average effect size over the entire follow-up rather than a true hazard rate.

but it is very unlikely that these RCT's will ever be undertaken. Observational studies are in that view considered complementary as they do not omit patients on the basis of strict criteria and will usually have enough follow-up time to evaluate hard endpoints such as mortality risk.

This study is the first to show a beneficial impact of intake of statins on real-life survival data in a large population study of patients on glucose lowering therapy. This is not unexpected, since available evidence from RCT's convincingly showed beneficial effect of statins on survival and prevention of cardiovascular events in secondary prevention (reviewed in (25)). Data in primary prevention are scarce with the only RCT in diabetic patients lacking power to show an overall mortality benefit (26). Our trial shows a beneficial effect of statins in patients with diabetes, both in primary and secondary prevention, with mortality risks being 60 to 80% lower independent of the type of glucose lowering therapy or presence of a CV disease history. Of note, patients taking statins in combination with metformin or SU monotherapy even showed better survival than the general population.

An asset of this study was the use of health expenditure records to assess the survival of patients on various glucose lowering therapies in comparison with a similar reference cohort from the general population. Claims records constitute a valuable source of information for observational epidemiological studies by embedding long-term longitudinal medical information of a large number of patients. Additionally, claims records aggregate proxies of medical information from various caregivers into a complete patient-wide overview which is often unavailable to individual caregivers and other medical stakeholders.

Through exact pair-wise matching of the reference cohort and regression adjustment in the proportional hazards models we were able to exclude important observable confounders in comparisons of the study cohorts with their respective references (27). Having access to a large population from which to sample control subjects allowed us to find references with exact matches on key confounding variables. Matching on these observable factors excludes the confounding effect and yields an efficiency gain (28). Some residual confounding resulting from uncontrolled and unobservable factors may remain.

Our study also has limitations. The large subject numbers are both a strength and a weakness as they add sufficient power to the study but also introduce the potential for confounders which are not self-evident. While there are considerable benefits in using claims data for epidemiological research, the absence of detailed clinical parameters prohibits causal inference because we could not control for level of glycemic control (eg, fasting blood glucose or HbA1c), BMI, or other modifiable cardiovascular risk factors (eg, smoking). However, we controlled for age, sex, concomitant medication, and presence of history of CV disease. Due to its observational nature our study remains susceptible to confounding by indication (29–31). Therefore our study is not suitable to compare GLA therapies directly as the patients' underlying conditions yield indications for their treatment, preventing comparisons (29, 32).

We conclude that 5-year survival in subjects on glucose lowering therapy is lower than in matched controls except for metformin monotherapy. Intake of metformin is associated with lowest 5-year mortality. In all groups, the intake of statins was associated with a reduced mortality rate.

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