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Cause-specific mortality in endometrioid endometrial cancer patients with type 2 diabetes using metformin or other types of antidiabetic medication

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Abstract

AIM: To obtain further evidence of the association between metformin or other types of antidiabetic medication (ADM) and mortality from endometrial cancer (EC) and other causes of death in patients with endometrioid EC and type 2 diabetes (T2D).

MATERIALS AND METHODS: A retrospective cohort of women with existing T2D and diagnosed with endometrioid EC from 1998 to 2011, obtained from a nationwide diabetes database (FinDM), were included in the study. Cumulative mortality from EC and that from other causes was described by using the Aalen-Johansen estimator. Cause-specific mortality rates were analyzed by using Cox models, and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were estimated in relation to the use of different forms of ADM during the three-year period preceding EC diagnosis.

RESULTS: From the FinDM cohort we identified 1215 women diagnosed with endometrioid EC, of whom 19% were metformin users, 12% were users of other types of oral antidiabetic medication, 25% used other types of oral antidiabetic medication plus metformin, 26% used insulin and 14% had no antidiabetic medication. Mortality from EC was not found to be different in women using metformin (HR 0.89, 95% Cl 0.52–1.54) but mortality from other causes was lower (HR 0.52, 95% Cl 0.31–0.88) compared with women using other types of oral ADM.

CONCLUSIONS: Our findings are inconclusive as to the possible effect of metformin on the prognosis of endometrioid EC in women with T2D. However, use of metformin may reduce mortality from other causes.

KEYWORDS: EC; Endometrial cancer; Metformin; Antidiabetic medication; Cause-specific mortality; Endometrioid; Retrospective cohort study

1. Introduction

Endometrial cancer (EC) is the most common cancer of the female genital tract in Europe, the cumulative rate up to 75 years of age being 1.8 per 100 women [1]. The incidence of EC is increasing in parallel with the pandemic of obesity, physical inactivity and the increasing incidence of type 2 diabetes (T2D) [2,3]. Other known risk factors of EC include age, diabetes, low parity, late menopause, genetic predisposition and postmenopausal estrogen therapy without progestin support [4,5]. These risk factors have particularly been linked to the endometrioid type of endometrial cancer, but they also seem to be connected to non-endometrioid EC [6].

Metformin is an oral biguanide derivative that is the first-line drug in the treatment of T2D [7]. It acts by decreasing hepatic gluconeogenesis and by increasing insulin sensitivity and glucose uptake in muscle tissue. Metformin use in diabetic patients has been associated with decreased cardiovascular mortality [8] and a lower incidence and better prognosis as regards some types of cancer [9-13]. The possible anticancer mechanisms of metformin are hypothesized to be mediated both indirectly via diminished insulin levels and directly on cancer cells by its antiproliferative effects via AMPK and mTOR pathways [14-17]. Additionally, in vitro studies have shown metformin to inhibit proliferation [18] and invasion [19] of endometrial cancer cells as well as to increase their sensitivity to cytostatic chemotherapeutic agents [20-21] and progestin therapy [22].

In most retrospective studies metformin has been linked to improved prognosis in cases of endometrial cancer [23-25], but in one study, after controlling for several confounding factors, metformin was not found to be associated with overall survival (OS) or progression-free survival (PFS) in EC patients [26]. However, the numbers of diabetic patients in these studies were limited and the duration of metformin use (pre- and post-diagnostic) was unknown.

Finnish healthcare registers are among the most reliable in the world. A Finnish diabetes database (FinDM) [27] has been established for epidemiological monitoring of diabetes and its complications. In FinDM the duration of diabetes, information on antidiabetic medication used and the amount of drugs purchased is recorded. Thus, we have a solid database which gives us an excellent opportunity to evaluate the role of metformin in the survival of diabetic patients with endometrial cancer. We analyze the cause-specific mortality of these patients from EC and from other causes of death in relation to the use of antidiabetic medication during three years before the diagnosis of cancer. Our main focus is on the comparison of mortality between users of metformin and users of other types of oral ADM.

2. Materials and methods

This article was written following STROBE guidelines for the reporting of observational studies [28]. FinDM is an individual-level nationwide diabetes register which has been linked to information from the National Institute for Health and Welfare, Statistics Finland, the Social Insurance Institute and the Finnish Cancer Registry. Patients are entered into the database either through receiving reimbursement for any type of ADM or by diagnosis of diabetes in hospital records or in the Cause of

111 Death Register. Categorization of the patients into type 1 (primarily insulin-dependent) and type 2
112 diabetics is made according to the types of first-line ADM purchased. A good coverage of diabetic
113 patients by FinDM was shown when it was compared with data from a local diabetes register of the
114 Helsinki region [29].
115 There were about 240 000 women with prevalent (at the beginning of 1996) or incident (from 1
116 January 1996 to 31 December 2011) T2D in FinDM. Women diagnosed with endometrioid-type
117 endometrial cancer (ICD-O-3 codes C54.1/C54.9 plus M-8380/3) between the 1st of January 1998 and
118 the 31st of December 2011, and in whom the estimated duration of T2D was at least 180 days before
119 EC diagnosis were included in this study. Data on the histology and stage of cancer was collected from
120 the Finnish Cancer Registry. Stage was defined as local, advanced (including growth to adjacent
121 tissues, metastasis in regional lymph nodes and distant metastasis) or unknown. Patients with non-
122 endometrioid EC (including serous, clear cell and mixed carcinoma) or unknown histology,
123 leiomyosarcomas, carcinosarcomas and endometrial stromal sarcomas were excluded. Patients with
124 prior cancer (with the exception of non-melanoma skin cancers: ICD-O-3 codes C44 plus M-8090-
125 8095/3, M-8097-8098/3, M-8102/3, and M-8110/3) were also excluded (Figure 1).
126 According to the antidiabetic medication used during the three years before EC diagnosis, the patients
127 were categorized as follows: 1) metformin only, 2) other oral antidiabetic medication only, 3)
128 metformin plus other oral antidiabetic medication, 4) insulin at any time and 5) no antidiabetic
129 medication. The ATC codes for different types of ADM are listed in Appendix 1. In groups 1-3 the
130 duration of medication use had to be 180 days or longer and thus the data on 42 patients who had
131 used metformin and/or other oral forms of ADM 1-179 days is not shown in the results section. One
132 purchase of insulin was enough to locate the patients in group 4. The exposed time to all types of

133 medication was defined during the three years preceding EC diagnosis starting from the first purchase
134 and ending 90 days after the last purchase or on the date of EC diagnosis if it came earlier. The
135 cumulative amount of metformin used was estimated according to daily defined doses (DDDs)
136 purchased during the three years preceding EC diagnosis.
137 Follow-up started at the time of diagnosis of endometrioid EC and ended on the date of death,
138 emigration, or 31 December, 2013, whichever was first. Follow-up information was obtained from the
139 Finnish Cancer Registry, the records of which are annually matched through computerized linkage
140 (based on personal identity codes) with the Cause of Death Register maintained by Statistics Finland,
141 so that the dates and causes of death (including noncancerous causes, both underlying and
142 contributory causes of death, categorized on the basis of ICD-10 codes) are added to the records in
143 the Registry. Personnel at the Finnish Cancer Registry compare the official causes of death of each
144 patient with cancer with all data available for that cancer, and make a judgment as to whether or not
145 the patient died of that cancer or of something else. The classification of deaths into the two
146 categories in this study, i.e. (1) deaths from EC, and (2) deaths resulting from other causes, was based
147 on that judgment. Deaths resulting from other causes were then further divided into the following
148 three subgroups: (1) deaths from other cancer (ICD-10 codes C00-C97), (2) deaths from cardiovascular
149 disease (ICD-10 codes I00-I99) and (3) deaths from other causes (all the remaining ICD-10 codes).
150 The records of the Finnish Cancer Registry are also regularly linked with the Central Population
151 Register of Finland, at which time the correctness of the personal identity codes is checked, and the
152 complete name, vital status, possible date of death, or emigration, as well as the official place of
153 residence before the date of diagnosis are obtained [30].
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3. Statistical analysis

Mortality from EC and from other causes of death, respectively, were described in different antidiabetic medication groups by using the Aalen-Johansen estimator of cumulative incidence function for competing risks [31-32]. The effects of year, age and stage at diagnosis of EC and the duration of DM were adjusted for by using the Cox proportional hazard models, from which hazard ratios (HRs) with 95% confidence intervals were estimated. Statistical analyses were performed by using SPSS (version 24) and R (version 3.4.1) software [33].

4. Results

Our final study cohort consisted of 1215 women with T2D, who were diagnosed with endometrioid EC at least 180 days after the diagnosis of T2D. The patients in the cohort were between 30 and 98 years of age at the diagnosis of EC. 236 (19%) patients were metformin users, 147 (12%) were users of other types of oral antidiabetic medication, 301 (25%) used other types of oral antidiabetic medication plus metformin, 316 (26%) used insulin and 173 (14%) had no antidiabetic medication. Metformin users were on average younger than the patients in the other ADM groups. Women using combination treatment, insulin or no ADM had longer durations of diabetes than those using only metformin or other oral forms of ADM. The stage distribution of EC was quite similar in the various ADM groups (Table 1). The mean follow-up time was 5.8 years.

492 patients died during the follow-up period, the 10-year unadjusted cumulative mortality being 48%. 190 deaths resulted from endometrial cancer (10-year mortality 17%). Some variability was

observed in the unadjusted mortality from EC between the different ADM groups (from 13% in metformin users to 20% in users of other oral ADM). However, mortality from other causes was overall lower in the metformin group compared with all the other groups. In particular, the unadjusted mortality from cardiovascular disease in the metformin group was lower (8% by 10 years) compared with the other ADM groups (20% in users of other oral ADMs) (Figure 2, Table 2).

In the Cox regression analysis older age and more advanced stage were associated with an increased mortality from EC, but no discernible difference was observed between the different ADM groups (Table 3). The estimated hazard ratio (HR) for metformin users vs. users of other oral ADM was 0.89 (95% Cl 0.52-1.5). Mortality resulting from other causes of death was found to be lower in metformin users (HR 0.52, 95% Cl 0.31–0.88) and higher in ever users of insulin (HR 1.80, 95% Cl 1.24–2.61) compared with users of other types of oral ADM. Duration of T2D was not observed to be associated with mortality from other causes. There was no evidence for cumulative use of metformin (DDDs) to be associated with mortality from EC (data not shown).

5. Discussion

In our study endometrioid EC-related mortality was not observed to be different in metformin users compared with users of other forms of ADM, and with diet-controlled diabetics, even when adjusted for age and year of EC diagnosis, stage of cancer, and duration of diabetes. The estimated hazard ratios had, however, wide error margins, so that one is not entitled to interpret these results to support the null hypothesis of no effect. In contrast, mortality resulting from other conditions, dominated by deaths from cardiovascular diseases, was found to be clearly lower in the metformin

group also in the adjusted analysis. This finding is apparently at least to some extent affected by residual confounding due to unavailable risk factors, many of them being associated with age, considering the fact that metformin users were on average seven years younger than the patients on other oral ADM. The result is, however, qualitatively well in line with previous reports concerning diabetes-related deaths (mainly cardiovascular) among metformin-treated patients [8]. Moreover, use of insulin at any time was observed to be associated with an increased mortality from other causes, which can be explained by the fact that patients with more advanced diabetes are more prone to cardiovascular complications of the disease. In our analysis the duration of T2D was not found to predict either EC-specific mortality or mortality from other causes in diabetic women with endometrioid EC.

In this study we were able to overcome several of the limitations encountered in previous studies. Our cohort was quite large comprising a total of 1215 women with T2D who were diagnosed with endometrioid-type endometrial cancer. All type 2 diabetics in the FinDM database are diagnosed according to WHO criteria [34]. Data on the duration of diabetes is relatively reliable in the FinDM database, although some delays are possible because diet-controlled diabetics treated in an outpatient setting are not recorded in it. All diabetic patients are registered in the FinDM database at the time of receiving their first reimbursement for antidiabetic medication. We were able to obtain precise data on the duration and used amounts of metformin and other types of antidiabetic medication and the temporal relationship between medication use and endometrial cancer diagnosis. Use of ADM was estimated for the three years preceding EC diagnosis. The Finnish Cancer Registry is a nationwide database with 99% coverage of cancer cases in Finland [35]. In this registry, deaths attributable to endometrial cancer are probably more reliably separated from other causes of death.

An important limitation of our study was the lack of data on many essential risk factors for mortality from other causes of death, including smoking, Body Mass Index, common age-related comorbidities, and certain markers of the severity of diabetes. Therefore, the estimated reduction of the hazard of death from other causes by nearly 50%, as indicated by the point estimate for metformin vs. other oral ADM, may well be exaggerating the possible benefit associated with the use of metformin. In addition, the data on ADM in institutionalized and elderly diabetics is apparently not as reliable as in the rest of the study population, and most of them are more likely classified in the no-ADM category. The effect of this possible misclassification, however, is negligible when considering the overall results.

Diabetic patients have an increased incidence of several cancers including endometrial carcinoma [36]. Many growth-promoting and potentially carcinogenic mechanisms have been associated with diabetes. Insulin and insulin-like growth factor 1, circulating levels of which are increased in diabetic patients, act as proliferative agents at a cellular level. The suggestion of a cancer-promoting effect of insulin is supported by the finding of an increased cancer incidence among insulin-using diabetics [37]. Hyperglycemia can also have a tumor-promoting effect by providing energy for the growth of tumor cells. Type 2 diabetes is strongly connected to metabolic syndrome, obesity and increased level of several cytokines [36]. Especially in endometrial cancer, obesity is an important risk factor as a result of increased estrogen formation in adipose tissue.

The results of several preclinical studies have indicated potential anticancer properties of metformin which could affect cancer incidence and survival in diabetic patients [16]. However, in these studies the drug concentrations have been well above those used for the clinical treatment of diabetes [14]. The possible anticancer effects of metformin could be hypothesized to be mediated in two different

ways: either through a direct antiproliferative effect on cancer cells mediated via AMPK and mTOR pathways, or indirectly via the physiological consequences of better controlled diabetes through lower blood sugar and insulin levels [14,16].

Only a few studies have been carried out to explore the connection between metformin and endometrial cancer survival. A retrospective cohort study by Ko et al., in which metformin users were compared with other diabetics, suggested improved OS and RFS but not TTR in EC patients using metformin possibly as a result of decreased all-cause mortality [24]. Greater OS in metformin-treated patients with advanced EC (stage III-IV/recurrent) receiving chemotherapy has also been observed [23]. In another study the beneficial effect of metformin on OS in diabetics with EC was limited to non-endometrioid endometrial cancer [25]. Weaknesses in these studies included the lack of information about the diagnostic criteria or the duration of diabetes, low numbers of patients and missing information on the dose and duration of use of metformin and other types of oral ADM. Additionally the primary endpoint in these studies was overall survival, and cause-specific mortality from EC was not analyzed.

In the line with our study Al Hilli et al. did not find either any difference in OS or PFS between metformin users and other diabetics, or metformin users and nondiabetic patients when using propensity score matching to account for confounding factors [26]. However, in this study the duration of diabetes and the duration and dose of metformin use were also unknown.

Our findings are inconclusive as to the possible effect of metformin on the prognosis of endometrioid EC in women with T2D. However, use of metformin may reduce mortality from other causes.

Conflict of interest statement

This work was supported by grants from Jane and Aatos Erkko Foundation, the Finnish Cancer Foundation and the Finnish Government Research Funds admitted for University Hospital of Oulu. These instances had no role in the study design, the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

Details of ethics approval

Local Ethical Committee approval is not requested for research based on registry data in Finland. The data of each individual in FinDM is handled according to the Finnish data protection legislation. The data received by the research group was anonymized so that the personal identity codes unique to each resident of Finland were transformed into unidentified codes.

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373 **Table 1.** Baseline characteristics in different antidiabetic medication groups. The entries are numbers

374 of patients (percentages in parentheses) if not otherwise stated.

	Other oral ADM[1]	Metformin[1]	Metformin and other oral ADM[1]	Insulin ever	No ADM	Total[2]
Number of Patients (%)	147 (12.1)	236 (19.4)	301 (24.8)	316 (26.0)	173 (14.2)	1215 (100)
Age at diagnosis (years)						
Median	75	68	71	71	71	71
IQR[3]	69-81	61-75	65-77	64-78	63-78	63-78
Age categories (years)						
30-59	10 (7)	41 (17)	32 (11)	48 (15)	31 (18)	177 (15)
60-69	32 (22)	85 (36)	98 (33)	94 (30)	44 (25)	363 (30)
70-79	55 (37)	81 (34)	122 (41)	109 (34)	67 (39)	448 (37)
80-98	50 (34)	29 (12)	49 (16)	65 (21)	31 (18)	227 (19)
Duration of DM (years)						
Median	3.8	3.0	6.5	11.4	7.6	6.6
IQR[3]	2.2-7.2	1.6-5.3	4.0-9.8	8.3-15.2	4.5-12.2	3.1-11.0
Stage						
Local	93 (63)	152 (64)	179 (59)	202 (64)	113 (65)	765 (63)
Advanced	22 (15)	43 (18)	56 (19)	46 (15)	18 (10)	193 (16)
Unknown	32 (22)	41 (17)	66 (22)	68 (22)	42 (24)	257 (21)

[1]Duration of medication ≥180 days

[2] Includes 42 patients with <180 days of metformin and/or other oral ADM use

[3] Interquartile range

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382 **Table 2**. Mortality from various causes of death during the follow up in different antidiabetic
383 medication groups. The entries are absolute numbers of deaths, and 10-year unadjusted cumulative
384 mortality proportions (% in parentheses).

Cause of death (ICD-10 code)	Other oral ADM[1]	Metformin[1]	Metformin and other oral ADM[1]	Insulin ever	No ADM	Total
Endometrioid EC (C54)	28 (19.7)	30 (13.4)	50 (18.6)	50 (16.5)	24 (15.1)	190 (17.0)
Other cancer (C00-C97)	8 (5.5)	5 (4.2)	6 (2.8)	12 (5.3)	7 (5.2)	38 (4.3)
Cardiovascular disease (I00-I99)	29 (20.2)	11 (7.6)	41 (16.0)	69 (27.3)	18 (11.0)	171 (17.4)
Other causes (All other codes)	20 (12.4)	4 (2.3)	23 (8.6)	33 (12.4)	13 (10.2)	93 (9.5)
All causes	85 (57.8)	50 (27.5)	120 (45.9)	164 (61.4)	62 (41.5)	492 (48.3)
Total number of patients[2]	147	236	301	316	173	1215

[1]Duration of medication ≥180 days

[2]Includes 42 patients with <180 days of metformin and/or other oral ADM use

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Table 3. Estimated results from Cox proportional hazard models of mortality from endometrial cancer and from other causes of death. The entries are hazard ratios (HR) and their 95% confidence intervals (CI) associated with the available prognostic factors. Patients on any oral ADM less than 180 days were excluded from the analysis.

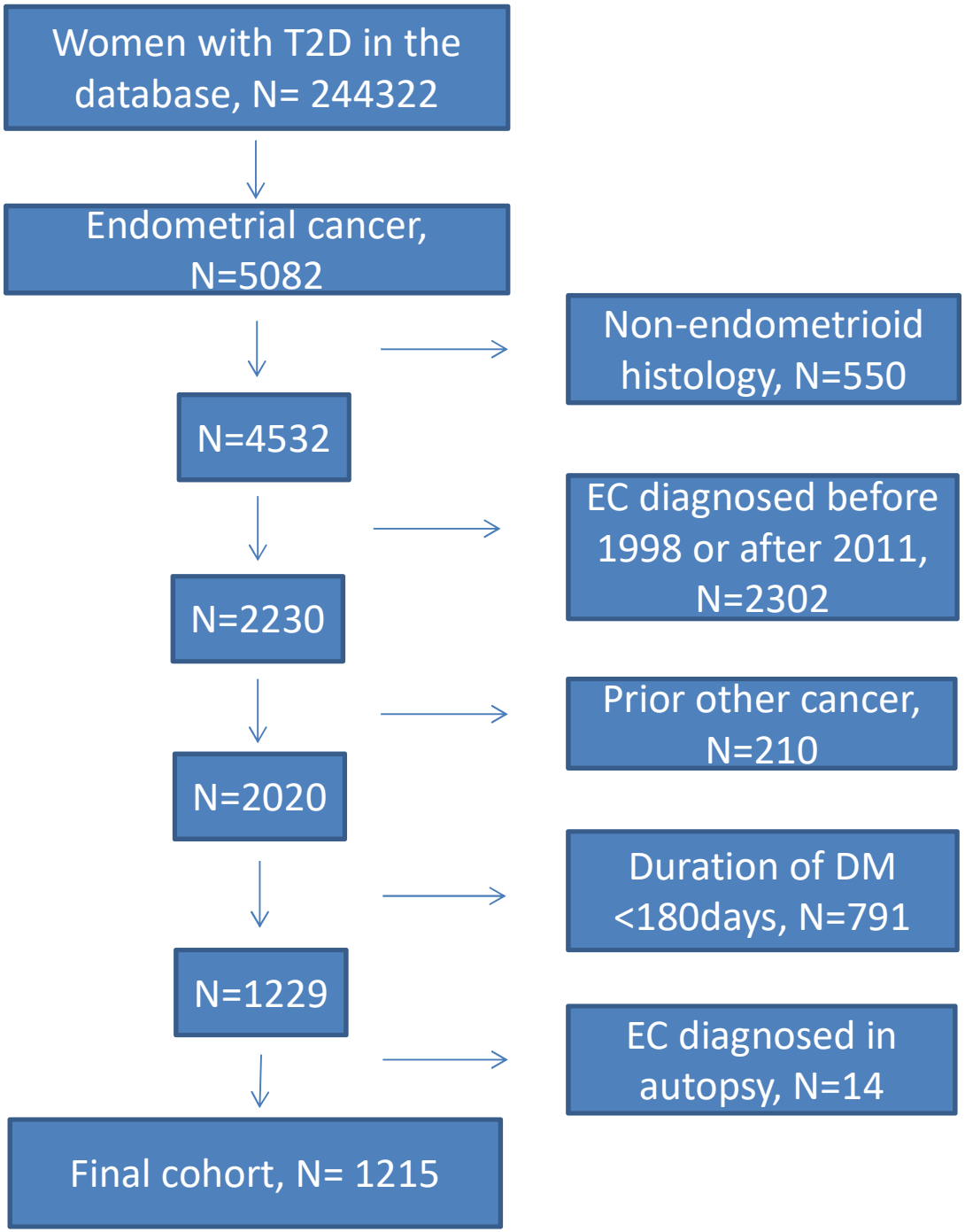
			Endometrial cancer	Other causes
		N	HR (95% CI)	HR (95% CI)
Age at EC diagnosis (years)	<60	177	1	1
	60-64	160	1.14 (0.55-2.38)	0.96 (0.52-1.77)
	65-69	203	1.78 (0.91-3.50)	1.26 (0.72-2.21)
	70-74	227	2.08 (1.09-3.97)	2.55 (1.54-4.22)
	75-79	220	2.44 (1.27-4.69)	5.18 (3.18-8.45)
	80-84	145	4.66 (2.45-8.88)	7.72 (4.61-12.95)
	≥85	83	7.78 (3.96-15.27)	15.70 (8.96-27.52)
Year of EC diagnosis	1998-2002	334	1	1
	2003-2007	433	0.93 (0.65-1.33)	0.77 (0.59-1.02)
	2008-2011	448	0.70 (0.47-1.04)	0.64 (0.44-0.94)
Stage of EC	Local	765	1	1
	Advanced	193	10.31 (7.35-14.47)	1.20 (0.79-1.81)
	Unknown	257	2.19 (1.44-3.32)	1.20 (0.91-1.58)
Duration of DM (years)	0.5-3	279	1	1
	3-6	280	1.03 (0.66-1.61)	1.01 (0.70-1.47)
	6-12	402	0.92 (0.59-1.41)	0.93 (0.64-1.35)
	12-40	254	0.91 (0.55-1.51)	1.00 (0.66-1.51)
Antidiabetic medication	Other oral ADM[1]	147	1	1
	Metformin[1]	236	0.89 (0.52-1.54)	0.52 (0.31-0.88)
	Metformin and other oral ADM[1]	301	0.99 (0.61-1.62)	0.86 (0.60-1.25)
	Insulin ever	316	1.30 (0.77-2.20)	1.80 (1.24-2.61)
	No ADM	173	1.06 (0.60-1.86)	0.90 (0.58-1.38)

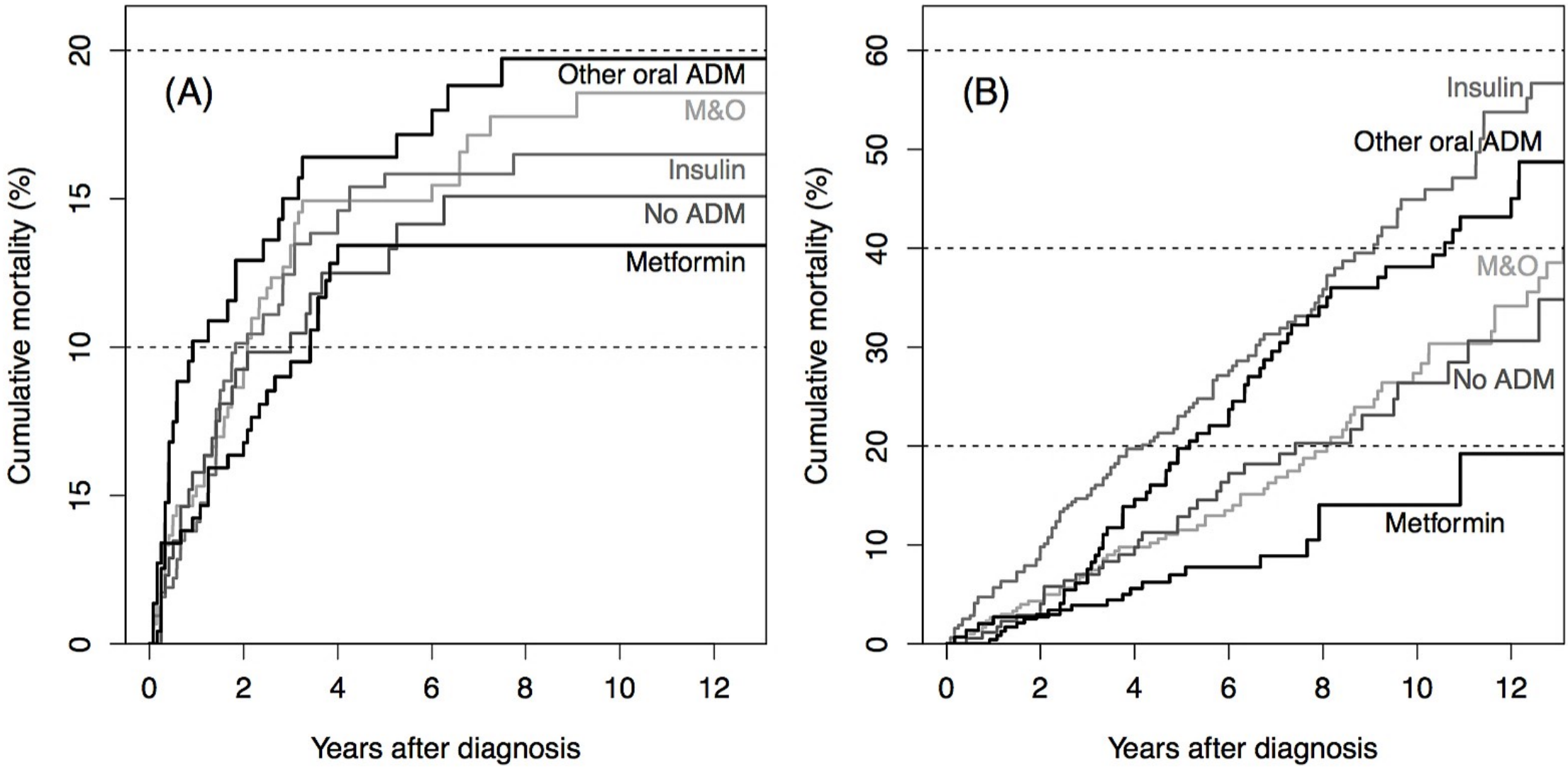
[1]Duration of medication ≥180 days

Figure legends

Fig. 1 Flow chart showing how the study cohort was formed.

Fig. 2. Cumulative mortality (%) from endometrial cancer (A) and from other causes of death (B) after diagnosis of endometrioid endometrial cancer in different antidiabetic medication groups. The curves are based on unadjusted Aalen-Johansen estimates. Note the different scaling of the vertical axis in (A) and (B). M&O = Metformin and other oral ADM.


Women with T2D in the database, N= 244322
Endometrial cancer, N=5082
Non-endometrioid histology, N=550
N=4532
EC diagnosed before 1998 or after 2011, N=2302
N=2230
Prior other cancer, N=210
N=2020
Duration of DM <180days, N=791
N=1229
EC diagnosed in autopsy, N=14
Final cohort, N= 1215


(A)
Other oral ADM
M&O
Insulin
No ADM
Metformin
Cumulative mortality (%)
0
15
10
15
20
0
2
4
6
8
10
12
Years after diagnosis
(B)
Insulin
Other oral ADM
M&O
No ADM
Metformin
Cumulative mortality (%)
0
10
20
30
40
50
60
0
2
4
6
8
10
12
Years after diagnosis

APPENDIX A: Supplementary Data

ATC codes for different types of ADM

Subgroup	ATC Code
METFORMIN	A10BA02
OTHER TYPES OF ORAL ADM	
Sulfonylurea	A10BB01
Sulfonylurea	A10BB07
Sulfonylurea	A10BB12
Dipeptidyl peptidase-4 inhibitor	A10BH01
Dipeptidyl peptidase-4 inhibitor	A10BH02
Dipeptidyl peptidase-4 inhibitor	A10BH03
Thiazolidinedione	A10BG02
Thiazolidinedione	A10BG03
Glinide	A10BX02
Glinide	A10BX03
Combination other oral ADM	A10BD04
Combination metformin and other oral ADM	A10BD05
Combination metformin and other oral ADM	A10BD07
Combination metformin and other oral ADM	A10BD08
Guar gum	A10BX01
INSULINS	
	A10AB01
	A10AB02
	A10AB04
	A10AB05
	A10AB06
	A10AC01
	A10AC03
	A10AC30
	A10AD01
	A10AD04
	A10AD05
	A10AE01
	A10AE02
	A10AE04
	A10AE05