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Antidiabetic medication, statins and the risk of endometrioid endometrial cancer in patients with type 2 diabetes

Reetta Arima[a,*], Mikko Marttila[b], Ari Hautakoski[b], Martti Arffman[c], Reijo Sund[d], Pirjo Ilanne-Parikka[e], Jenni Kangaskokko[f], Esa Läärä[g], Ulla Puistola[a], Marianne Hinkula[a]

[a]Department of Obstetrics and Gynecology, PEDEGO Research Unit, Medical Research Center Oulu, University of Oulu and University Hospital of Oulu. P.O. Box 23, FIN-90029 Oulu, Finland. reetta.arima@gmail.com. Telephone number +358503777122, fax number +35883154310, ulla.puistola@oulu.fi, marianne.hinkula@oulu.fi

[b]Children, Adolescents and Families Unit, Department of Welfare, National Institute for Health and Welfare, P.O. Box 310, FIN-90101 Oulu, Finland. mikko@mikkomarttila.com, ari.hautakoski@gmail.com

[c]Service System Research Unit, National Institute for Health and Welfare. P.O. Box 30, FIN-00271 Helsinki, Finland. martti.arffman@thl.fi

[d]Centre for Research Methods, Department of Social Research, University of Helsinki, Helsinki, Finland. Institute of Clinical Medicine, University of Eastern Finland. P.O. Box 1627, FIN-70211 Kuopio, Finland. reijo.sund@helsinki.fi

[e]Science Center, Tampere University Hospital, Tampere, Finland. The Diabetes Center, Finnish Diabetes Association, FIN-33680, Tampere, Finland. pirjo.ilanne-parikka@diabetes.fi

[f]Department of Pathology, Medical Research Center Oulu, University of Oulu and University Hospital of Oulu. P.O. Box 50, FIN-90029 Oulu, Finland. jenni.kangaskokko@ppshp.fi

[g]Research Unit of Mathematical Sciences, University of Oulu. P.O. Box 8000, FIN-90014 Oulu, Finland. esa.laara@oulu.fi

[*]Corresponding author

Abstract

Objective. To gain further evidence of an association between the incidence of endometrial cancer (EC) and the use of metformin, other antidiabetic medication (ADM) and statins in women with type 2 diabetes (T2D).

Methods. A retrospective cohort of 92,366 women with newly diagnosed T2D was obtained from a diabetes register (FinDM). 590 endometrioid ECs were observed during the follow-up time. Poisson regression was utilized to estimate the hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the endometrioid EC in relation to the use of metformin, other oral ADM, insulin and statins. Nested case-control analyses were performed, where up to 20 controls were matched for age and duration of DM for each EC case. The HRs were estimated by conditional logistic regression for never/ever and cumulative use of different forms of ADM and statins.

Results. In the case-control analyses the use of metformin (HR 1.24, 95% CI 1.02-1.51) and other oral ADM (HR 1.25, 95% CI 1.04-1.50) was associated with an increased incidence of endometrioid EC compared to no ADM use. No difference was observed between metformin users and those using other oral ADMs. The use of statins was inversely related to the incidence of endometrioid EC (HR 0.78, 95% CI 0.65-0.94). Results from the full cohort analysis supported this finding.

Conclusions. In our study the use of metformin or other oral forms of ADM was not associated with a lowered risk of endometrioid EC in women with T2D. Instead statins were observed to be inversely associated with endometrioid EC in this population.

Keywords: metformin; antidiabetic medication; endometrial cancer; cancer incidence; cohort study; case-control study

1. Introduction

Endometrial cancer (EC) is the fourth most common female cancer in developed countries, with a cumulative rate up to 75 years of age of 1.8 per 100 women [1]. The incidence of EC is rising worldwide, partly due to the increasing prevalence of obesity and diabetes [2-4]. In addition, age, lack of physical activity, genetic predisposition and hormonal factors including low parity, late menopause and postmenopausal unopposed estrogen therapy augment the risk of EC [5,6].

Metformin is an oral form of antidiabetic medication (ADM) that has become the recommended first-line treatment in cases of type 2 diabetes [7]. In epidemiological studies use of metformin has been linked to decreased incidence and/or mortality in cases of at least some cancer types [8-12]. Metformin has shown antiproliferative and anti-invasive effects on endometrial cancer cells in preclinical studies [13,14].

The association between metformin use and endometrial cancer risk has been investigated in a few retrospective cohort studies, which have methodological challenges as a result of their observational nature [15]. Three recent studies could not find any association between metformin use and the incidence of endometrial cancer [16-18], but lowered incidence of EC in metformin users has also been reported [19].

Statins (HMG-CoA inhibitors) reduce plasma cholesterol levels and are used in primary and secondary prevention of coronary heart disease. They are among the most commonly prescribed kinds of

89 medication worldwide. Statins have been shown to reduce levels of mevalonate and induce apoptosis
90 of cancer cells in vitro [20]. A previous Finnish record-linkage study did not find an association
91 between statin use and endometrial cancer incidence in the general population [21]. A meta-analysis
92 carried out by Liu et al. also could not find an association between statin use and EC incidence, but in
93 a subset of studies conducted in Asian populations a decrease in the risk of EC was observed among
94 statin users [22].
95 We studied the associations between metformin, other forms of oral antidiabetic medication, insulin
96 and statins with the incidence of endometrioid EC in a nationwide register-based cohort and case-
97 control study in diabetic women.
98
99 **2. Materials and methods**
100
101 *2.1 Data sources*
102
103 This article was written following STROBE guidelines for the reporting of observational studies [23].
104 The data was obtained from the FinDM register, in which information about diabetic patients from
105 several nationwide registers is combined [24]. FinDM includes precise information about the amount
106 and the date of purchase of antidiabetic and other kinds of medication starting from 1994.
107 Information about diagnosis set in hospital records is available from 1969 for inpatient and from 1998
108 for outpatient setting. Data about surgical procedures performed in hospitals are recorded from 1987.
109 Patients with diabetes are entered in the register on the basis of diabetes diagnosis noted in hospital
110 records or by receiving reimbursement for antidiabetic medication. A comparison of data from FinDM

against a local diabetes register of the Helsinki region has demonstrated good coverage of diabetic persons in the nationwide register [25]. In some cases the duration of diabetes may be longer than indicated in the register, as FinDM does not contain information about diet-controlled diabetics treated solely in outpatient primary care setting. The classification of patients in the register to type 1 (primary insulin-dependent) and type 2 diabetes was based on the antidiabetic medication used as first-line treatment.

The records of FinDM are linked to those from the Finnish Cancer Registry, which has an excellent coverage of over 99% of all cancer cases in Finland [26], and it contains among other things the date of cancer diagnosis and the morphology of cancer. Information about the date of death from Statistics Finland is linked to FinDM. Data linkage between different registers is made based on the personal identification codes unique to each resident of Finland.

2.2 Identification of the study cohort

Details of the cohort selection process are presented in the flow chart. There were a total of 244,322 women resident in Finland with T2D in the FinDM register including patients with prevalent T2D at the beginning of 1996 and with incident diabetes diagnosed after that but no later than 31 December 2011. A total of 172,070 female patients, who were diagnosed with type 2 diabetes between the 1st of January 1996 and the 31st of December 2011 were identified from the FinDM register. The data were handled anonymously according to Finnish data protection legislation. Women with a diagnosis of EC before cohort entry were excluded. Also patients diagnosed with EC during the first year after the diagnosis of diabetes were excluded, as it is generally suggested that the increased medical

surveillance following newly diagnosed diabetes leads to increased detection of occult cancers during the first year after diagnosis [27]. Women with prior hysterectomy were excluded from the cohort. Data about hysterectomies was available post-1987, leaving the possibility of some hysterectomized women remaining in the cohort. This especially concerned women in the older age categories. Patients who had used systemic hormone replacement therapy (HRT) were removed from the cohort to eliminate the effect of HRT on the incidence of EC and to exclude some of the women who had had hysterectomy before 1987. The final number of diabetic women in the cohort was 92,366. Follow-up for the incidence of EC started at the age of 40 years whereas follow-up concerning the duration of T2D and the use of different types of ADM and statins began at the time of diagnosis of diabetes regardless of the age of the patient at that moment. Follow-up of each patient ended on the date of diagnosis of endometrioid EC, hysterectomy for other reasons, starting of systemic hormone replacement therapy, death or the end of the study period. We also performed nested case-control analyses, where up to 20 controls (n=11,792) were matched for age and the duration of diabetes within the range of ±182 days for each of the 590 women in the final cohort who were diagnosed with endometrioid EC during the study period. Controls were selected among those being alive and at risk of EC at the date of EC diagnosis of the case.

2.3 Classification of used medication

Exposure to anti-diabetic medication was assessed in three categories: metformin, other types of oral ADM and insulin (classification by ATC codes is shown in appendix 1). In addition the use of statins was evaluated. Exposure to any medication was defined to begin 365 days after its purchase date in

155 order to avoid reverse causality. Both in nested case-control analyses and in the full cohort analysis
156 patients were classified as exposed to the drug from this moment onwards throughout the follow-up
157 time (never-/ever-exposed). In addition, cumulative use of ADM and statins was estimated in nested
158 case-control analyses as summed amount of daily defined doses (DDD) during the follow-up period.
159
160 *2.4 Statistical analysis*
161
162 In the full-cohort analysis a Poisson regression model was used to estimate hazard ratios (HRs) with
163 95% confidence intervals (95% CIs) of the incidence of endometrioid EC in relation to metformin use
164 and other variables [28]. A multiple Poisson regression model included in addition age, duration of
165 diabetes and use at any time of other forms of medication (ADM and statins). Conditional logistic
166 regression was utilized in the nested case-control analyses to estimate HRs with 95% CIs as regards
167 the use of different forms of ADM and statins. Estimates for use at any time ("ever use") and
168 cumulative use were obtained from separate models. The cumulative dose was categorized according
169 to the tertiles of the total amount of daily defined doses (DDDs) used. We investigated the combined
170 effect of metformin and statin use by including an interaction term in the conditional logistic
171 regression model estimated in the case-control analyses. The event-based data was transformed into
172 individual level data for statistical analysis by using SAS/STAT® software version 9.4 of the SAS System
173 for Windows. We used R environment version 3.3.0 for all the figures, estimates and data analyses
174 [29].
175
176

3. Results

The final cohort consisted of 92,366 women diagnosed with type 2 diabetes between 1996 and 2011. The total follow-up covered 503,937 person-years at risk. The mean follow-up time was 5.5 years. The patients in the cohort were between 40 and 106 years of age. 590 women were diagnosed with endometrioid endometrial cancer during the study period. From now on when regarding results from our study, EC refers to endometrioid endometrial cancer.

The incidence of EC was age-dependent, reaching its peak in the group of women aged 65-69 years. The incidence of EC was higher in patients in whom the duration of DM was over 8 years, compared with those with a shorter duration of the disease. Of the 590 women diagnosed with EC, 411 (69.7 %) were metformin ever-users. The corresponding numbers were 351 (59.5%) as regards other forms of oral antidiabetic medication and 91 (15.4%) for insulin use. Sixty-seven patients (11.4%) diagnosed with EC had no record of any ADM use (Table 1a-b).

The EC incidence in the chosen reference group (age 70-74 years, diabetes duration less than three years, no previous record of drug use) was estimated to be 103.21/100 000 person-years. In the multiple Poisson regression model, “ever use” of metformin and other forms of oral ADM, respectively were both associated with an increased incidence of EC compared to never use. A similar effect was noted as regards insulin. The risk of developing EC was not observed to be different when metformin ever-users and ever-users of other types of oral ADM were compared (HR 1.00, 95% Cl 0.87-1.12). In contrast, use of statins at any time was inversely related to EC incidence (Table 2).

In line with the results of the full-cohort analysis, “ever use” of metformin or other forms of oral ADM was associated with an increased incidence of EC in nested case-control analyses. Ever use of insulin

199 also appeared to be positively associated with the risk of EC. As in the full cohort analysis in nested
200 case-control analysis the incidence of EC was not found to be different between metformin ever-users
201 and ever-users of other forms of oral ADM (HR 1.00, 95% CI 0.87-1.15). A trend towards an elevated
202 EC risk was also seen with increasing cumulative use of metformin and insulin. Ever use of statins was
203 inversely related to EC incidence, while no clear trend regard to additional risk was observed with the
204 cumulative use of statins (Table 2, Figure 1).
205 We tested the possible interaction between metformin and statin use in the case-control population
206 by dividing the patients into following subgroups: 1) Neither metformin nor statin use, 2) Metformin
207 use +, no statin use, 3) No metformin use, statin use + and 4) Both metformin and statin use +. No
208 evidence for combination effects was found (interaction hazard ratio 0.94, 95% CI 0.64-1.37).
209 In the nested case-control analyses the most frequently used types of other oral ADM based on
210 numbers of ever-users (at least one purchase) of the medication in question were sulfonylureas
211 n=6301 (94.1%) and thiazolidinediones n=579 (8.7%). The most common statins were simvastatin
212 n=4296 (68.6%), atorvastatin n=2159 (34.5%) and fluvastatin n=1307 (20.9%). The sum of percentages
213 is over 100% because some of the patients had used more than one type of other oral ADM or statins
214 during the follow up time.
215
216 **4. Discussion**
217
218 In the present study metformin use was associated with an increased incidence of endometrioid
219 endometrial cancer in the full cohort (HR 1.23) as well as in the case-control analysis (HR 1.24)
220 compared to metformin “never use”. Additionally, increasing cumulative use of metformin showed a

tendency to predict an elevated risk of EC. Thus, our results speak against the EC risk-reducing effect of metformin.

Other forms of oral ADM were also related to an increased incidence of EC in our study. In our cohort the oral types of ADM mostly included sulfonylureas (94.1%). In previous studies sulfonylureas have been suggested to increase the incidence of cancer [30]. Our results are in line with these findings.

In our study insulin use was associated with an elevated risk of EC, both in the full-cohort (HR 1.19) and in the case-control analyses (HR 1.22). The incidence of EC tended to be higher with increasing cumulative use of insulin. These findings are consistent with earlier observations of the cancer-promoting effects of the exogenous use of insulin [10,27].

In our cohort (HR 0.82) and case-control analyses (HR 0.78) statin use was observed to be inversely related to the risk of EC, but there was no clear dose-dependent pattern. It has been suggested that hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, atorvastatin, lovastatin and fluvastatin) statins might have different impacts on cancer risk.

One of the major strengths of our study lies in its time-dependent design. We were able to calculate the time-related use and to make a good estimate of the cumulative amounts (DDD) of metformin and other types of ADM. A patient's details are entered into the diabetes register at the time of the first reimbursement for any form of ADM. Thus data in the register concerning the duration of DM is considered to be quite reliable.

A major limitation in our study is the lack of data on body mass index (BMI) as well as reproductive history of the women in the diabetes cohort. In previous studies metformin users have often been heavier than other diabetics [9,12,17], which could bias our results towards an increased EC risk in metformin users. In an Italian nested case-control study Franchi et al also found metformin use to be

connected with an increased EC risk in diabetic women (OR 1.30, 95% CI 1.00-1.70) [31]. This estimate is comparable to results from our own nested case-control analyses (HR 1.24, 95% CI 1.02-1.51). However, when Franchi et al took BMI into account using a Monte Carlo sensitivity analysis based on data about BMI of diabetic patients resident in the same region the association between metformin and excess risk of EC disappeared (OR 1.07, 95% CI 0.82-1.41). FinDM does not contain direct measures of the severity of diabetes such as hemoglobin A1c. However, we had data about duration of T2D and insulin use which are surrogate markers for the severity of diabetes. Another limitation in our study is missing information on hysterectomies before 1987. This leaves the possibility that some hysterectomized women were in the cohort, but this should not affect the results concerning metformin use and the risk of EC, as the probability of hysterectomy is not connected to the use of metformin. Moreover, this problem was partly compensated for when women with systemic HRT were excluded from the cohort. The grade was not available for a substantial proportion of endometrioid endometrial cancers in the Finnish Cancer Registry which prevented us from analyzing low grade (grade 1-2) and high grade (grade 3) tumors separately.

Diabetes is associated with an increased incidence of several other cancers besides endometrial carcinoma [3,27]. Several possible carcinogenic mechanisms arise from physiological changes seen in diabetes. These include obesity, elevated levels of steroid hormones, chronic inflammation, hyperglycemia, insulin resistance leading to hyperinsulinemia, and elevated IGF-1 (Insulin-like Growth Factor-1) [32]. Different forms of antidiabetic medication may have varying effects on cancer risk, based on their diverse mechanisms of action. A recent meta-analysis of 265 studies indicated the use of metformin or thiazolidinediones to be associated with a lower incidence of cancer, while insulin, sulfonylureas and alpha glucosidase inhibitors were related to an increased incidence [30].

Metformin is recommended as a first-line treatment in type 2 diabetes and it has a favorable safety profile and a low cost. The antidiabetic effects of metformin are mediated by diminished gluconeogenesis in the liver and increased glucose uptake by skeletal muscle, leading to lower circulating glucose and insulin levels and the amelioration of insulin resistance. Preclinical, epidemiological and clinical data concerning the anticancer properties of metformin have been promising [33,34]. Several potential antitumor mechanisms of metformin have been suggested. These include indirect effects through diminished blood sugar and insulin levels, direct cellular-level effects via AMPK-mediated inhibition of mTOR and activation of anti-inflammatory and antioxidative pathways [8]. This has led to the idea of repurposing metformin as a preventive agent and co-treatment for cancer [35-38].

In a nested case-control study by Becker et al. neither the use of metformin or other types of ADM were observed to have any association with the incidence of EC [16]. Another retrospective cohort study was carried out to compare EC incidence after the initiation of metformin vs. sulfonylureas and no difference was found between the medication groups [17]. Neither did Luo et al. find an association between metformin use and the risk of EC in a prospective cohort study based on a Women´s Health Initiative (WHI) questionnaire [18]. Unfortunately there were no data on the time or dose of metformin or other types of antidiabetic medication used in relation to EC diagnosis in this study. In a Taiwanese cohort study an inverse dose-dependent pattern was reported between metformin use and the risk of endometrial cancer [19]. However, it is remarkable that the prevalence of obesity in the study was <1%, which is considerably lower than that in such patient groups in western countries (31%) [39].

In one prospective questionnaire-based cohort study the use of cholesterol-lowering drugs (predominantly statins) for five or more years was associated with a lower incidence of endometrial cancer [40]. However, a Finnish register linkage study of the general population, with an average of 8.8 years of follow-up could not observe any connection between statin use and the incidence of EC or any other cancer [21]. A review article by Boudreau et al. and the meta-analysis carried out by Liu et al. also indicated no convincing connection between statin use and EC risk [20,22]. It is also possible that to some degree the lower cancer incidence observed in statin users in our study is related to differences in health-seeking behavior compared with nonusers (healthy-user effect).

Most earlier studies carry a risk of potentially significant time-related biases [15,41]. Data on the duration of diabetes is often missing. In addition, data on the duration, timing, dose and cumulative amounts of antidiabetic medication in relation to cancer diagnosis is commonly missing. The short follow-up times in some of the previous studies lead to bias concerning endometrial cancer incidence connected to newly-diagnosed diabetes (ascertainment bias). Immortal time bias occurs when the categorization of drug exposure is time-fixed. For example, if the follow-up time preceding the initiation of medication is counted for the ever-user group in never-/ever-exposed designs the incidence of the disease is overestimated in never-users and underestimated in ever-users. In time-lag bias, comparison of a first-line treatment of a certain chronic disease with a second- or third-line treatment can cause bias if the stage of the disease affects the outcome. In type 2 diabetes this means that it is reasonable to compare metformin with other types of oral ADM but not later-stage medication such as insulin. In our study these possible biases have been considered.

To conclude, in our study in patients with T2D the use of metformin or other types of oral ADM was not observed to be in concordance with the hypothesis that these forms of medication would have a

protective effect as regards the risk of EC. Insulin users seemed to be at an increased risk of EC. According to what we know, our results suggest, for the first time, that there can be a beneficial effect of statins as regards the risk of EC in women with T2D.

Conflict of interest statement

The authors declare that they have no conflicts of interest in regard to this manuscript.

Details of ethics approval

Local Ethical Committee approval is not demanded for research based on registry data in Finland. The data of individual persons in FinDM is stored according to the Finnish data protection legislation. The data received by the research group was anonymized so that the personal identity codes were converted into unidentified codes.

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417

Table 1a. Distribution of the cases, matched controls, person-years at risk in the cohort and endometrioid EC incidence/100 000 person-years by age[1] and duration of diabetes[1].

Variable	Value	Person-years in cohort	Cases (%)	Controls (%)	Incidence
Age (years)	40-44	11 222	4 (0.7)	79 (0.7)	35.6
	45-49	18 145	5 (0.8)	107 (0.9)	27.6
	50-54	25 159	28 (4.7)	545 (4.6)	111.3
	55-59	33 529	42 (7.1)	847 (7.2)	125.3
	60-64	43 572	67 (11.4)	1321 (11.2)	153.8
	65-69	55 902	94 (15.9)	1909 (16.2)	168.2
	70-74	77 105	99 (16.8)	1987 (16.9)	128.4
	75-79	91 366	128 (21.7)	2532 (21.5)	140.1
	80-84	81 070	82 (13.9)	1631 (13.8)	101.1
	85-89	47 495	29 (4.9)	627 (5.3)	61.1
	90-106	19 373	12 (2.0)	207 (1.8)	61.9
Duration of diabetes (years)	1-<3	160 744	175 (29.7)	3569 (30.3)	108.9
	3-<5	118 799	138 (23.4)	2736 (23.2)	116.2
	5-<8	120 018	135 (22.9)	2657 (22.5)	112.5
	8-<16	104 377	142 (24.1)	2830 (24.0)	136.0
	Total	503 937	590 (100)	11792 (100)	117.1

[1] Cases and controls were matched for age and the duration of diabetes

Table 1b. Distribution of the cases, matched controls and person-years at risk in the cohort by medication use.

Variable	Value	Person-years in cohort	Cases (%)	Controls (%)
Statin use	Ever	235 758	270 (45.8)	5993 (50.8)
	Never	268 179	320 (54.2)	5799 (49.2)
Metformin use	Ever	321 349	411 (69.7)	7671 (65.1)
	Never	182 588	179 (30.3)	4121 (34.9)
Other oral ADM use	Ever	266 793	351 (59.5)	6342 (53.8)
	Never	237 145	239 (40.5)	5450 (46.2)
Insulin use	Ever	58 963	91 (15.4)	1449 (12.3)
	Never	444 974	499 (84.6)	10343 (87.7)
Any ADM use	Ever	417 730	523 (88.6)	9805 (83.1)
	Never	86 208	67 (11.4)	1987 (16.9)
	Total	503 937	590 (100)	11792 (100)

Table 2. Unadjusted (HR^u) and adjusted (HR^a, HR^c) estimates of hazard ratios regarding the association between endometrioid EC incidence and use (at any time) of the studied forms of medication. The reference group is "never use" of that medication. The estimates are based on Poisson regression from full-cohort data and conditional logistic regression from nested case-control data.

Ever-use	**HR^u**	**HR^a (95% CI)**	**HR^c (95% CI)**
Statin	0.96	0.82 (0.70-0.97)	0.78 (0.65-0.94)
Metformin	1.30	1.23 (1.03-1.48)	1.24 (1.02-1.51)
Insulin	1.38	1.19 (0.93-1.52)	1.22 (0.95-1.58)
Other oral ADM	1.31	1.26 (1.06-1.50)	1.25 (1.04-1.50)
^{u} = unadjusted			
^{a} = adjusted from full cohort for age, duration of diabetes and use at any time of other forms of medication			
^{c} = adjusted from case-control for age, duration of diabetes and use at any time of other forms of medication			

460 **Figure legends**

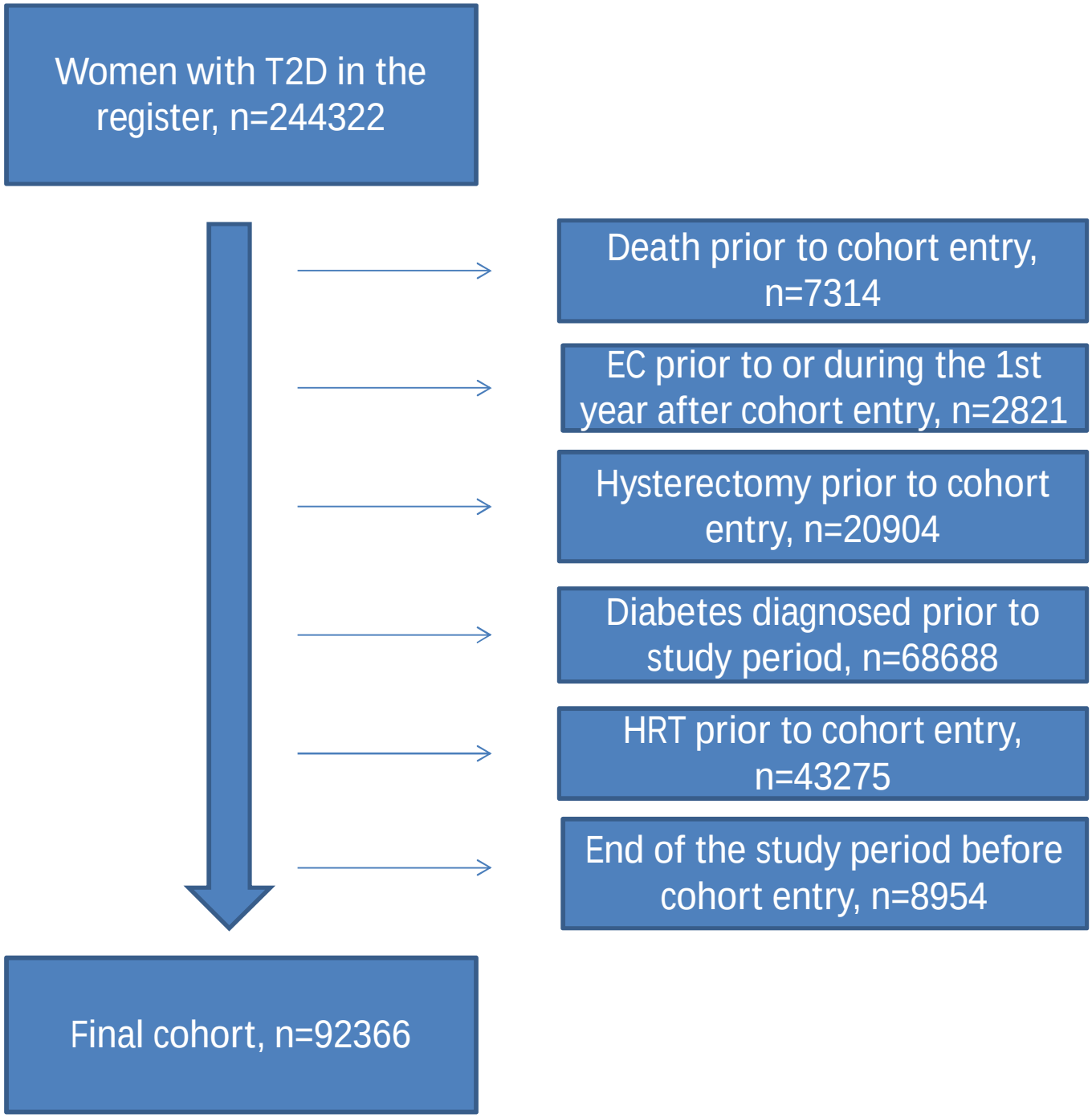
461

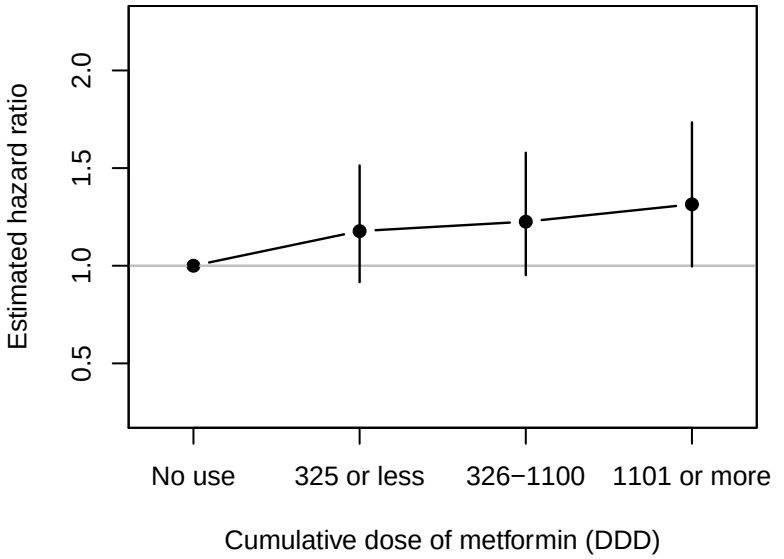
462 **Flow chart.** Forming of the cohort.

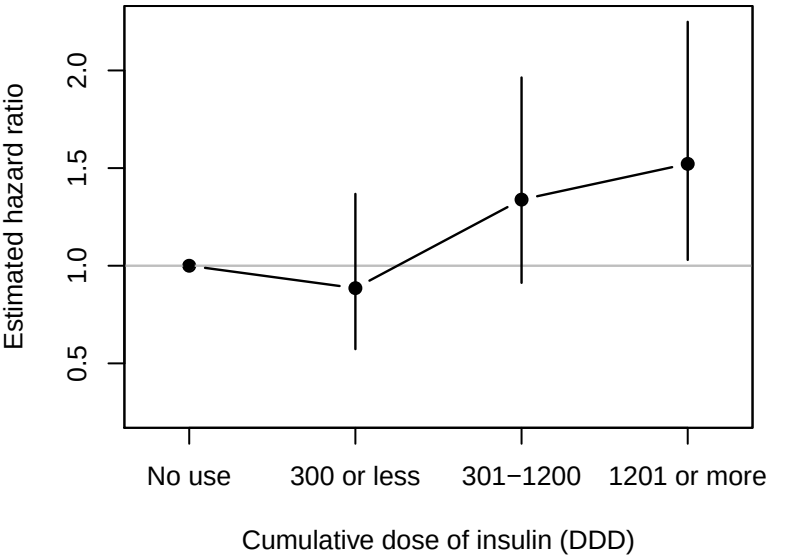
463

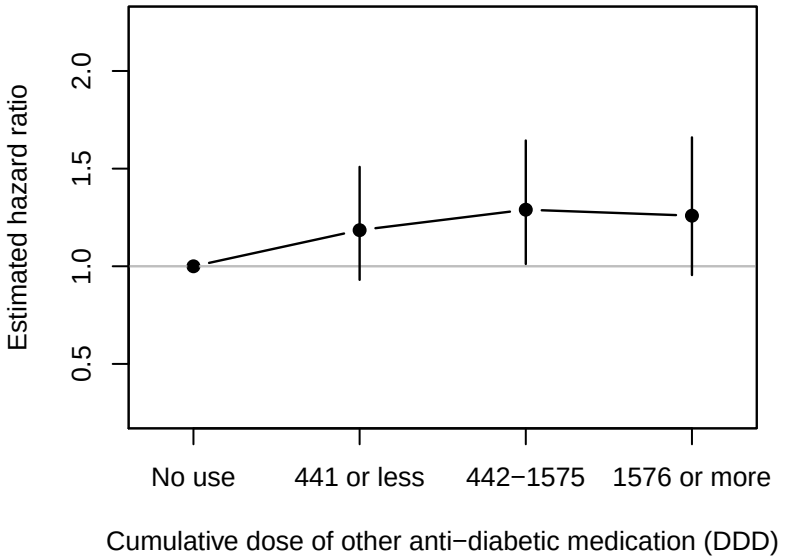
464 **Figure 1.** Estimated hazard ratios (with 95% confidence intervals) of endometrioid EC by cumulative
465 doses of different forms of ADM, and statins, adjusted for age, duration of diabetes and the use of
466 other medication.

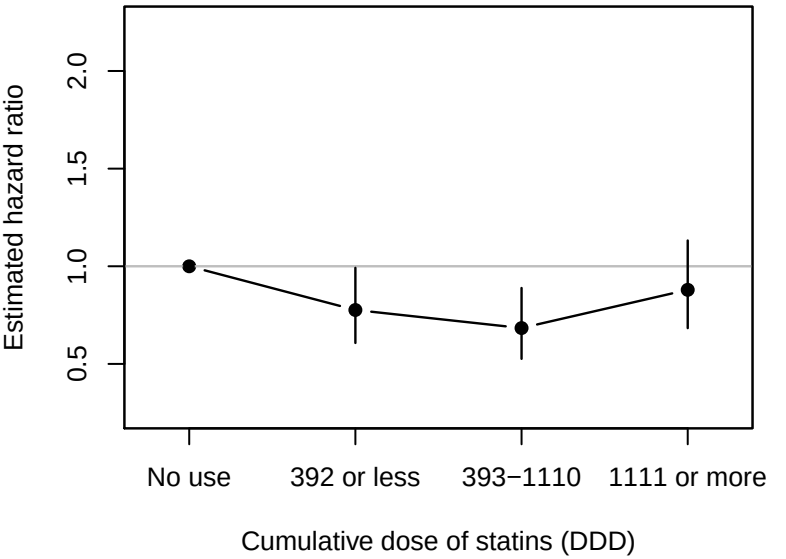
467


Women with T2D in the register, n=244322
Death prior to cohort entry, n=7314
EC prior to or during the 1st year after cohort entry, n=2821
Hysterectomy prior to cohort entry, n=20904
Diabetes diagnosed prior to study period, n=68688
HRT prior to cohort entry, n=43275
End of the study period before cohort entry, n=8954
Final cohort, n=92366


Estimated hazard ratio
0.5
1.0
1.5
2.0
No use
325 or less
326−1100
1101 or more
Cumulative dose of metformin (DDD)


Estimated hazard ratio
0.5
1.0
1.5
2.0
No use
300 or less
301−1200
1201 or more
Cumulative dose of insulin (DDD)


Estimated hazard ratio
0.5
1.0
1.5
2.0
No use
441 or less
442−1575
1576 or more
Cumulative dose of other anti−diabetic medication (DDD)


Estimated hazard ratio
0.5
1.0
1.5
2.0
No use
392 or less
393−1110
1111 or more
Cumulative dose of statins (DDD)