OULU 2019
D 1529

ACTA UNIVERSITATIS OULUENSIS

Reetta Arima

METFORMIN, STATINS AND THE RISK AND PROGNOSIS OF ENDOMETRIAL CANCER IN WOMEN WITH TYPE 2 DIABETES

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
FACULTY OF SCIENCE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL;
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

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REETTA ARIMA

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Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital, on 11 October 2019, at 12 noon

UNIVERSITY OF OULU, OULU 2019

Acta Univ. Oul. D 1529, 2019

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ISBN 978-952-62-2345-2 (Paperback)
ISBN 978-952-62-2346-9 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

JUVENES PRINT
TAMPERE 2019

Arima, Reetta, Metformin, statins and the risk and prognosis of endometrial cancer in women with type 2 diabetes.

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Faculty of Science; Medical Research Center Oulu; Oulu University Hospital; National Institute for Health and Welfare

Acta Univ. Oul. D 1529, 2019

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Abstract

Endometrial cancer (EC) is the fifth most common female cancer worldwide and its incidence is increasing. The prognosis of EC is fairly good. Histologically, ECs are categorized into endometrioid and non-endometrioid subtypes.

Lately, the idea of repurposing existing medications for the prevention and co-treatment of EC has evoked interest in the scientific community. The results of preclinical studies involving various forms of antidiabetic medication (ADM) such as metformin, or cholesterol-lowering statins have been promising.

In the previous epidemiological studies, the results of metformin and/or statin use and the risk and prognosis of EC have indicated either neutral or beneficial effects. At least some of these studies have several limitations, including a potential for several types of bias, and missing information on the dose and timing of medication, cancer-specific mortality or the histology of EC.

The aim of this study was to find reliable further evidence on whether the use of metformin or statins could have beneficial effects on the risk and prognosis of EC in women with type 2 diabetes (T2D). Endometrioid and non-endometrioid EC were analyzed separately based on data from the Finnish Cancer Registry (FCR).

In our study cohort of 92 366 women obtained from a nationwide diabetes database (FinDM) (1996 to 2011), the incidence rates of endometrioid (n = 590 cases) and non-endometrioid (n = 57 cases) EC were not found to differ between metformin users and users of other forms of oral ADM when adjusted for age, duration of T2D and use at any time of other forms of medication under study. We found insufficient evidence that metformin affects the prognosis of patients diagnosed with endometrioid (n = 1215) or non-endometrioid (n = 105) EC (1998 to 2011) after adjusting for year, age and stage at diagnosis of EC, and duration of T2D. However, in patients with endometrioid EC, mortality from other (predominantly cardiovascular) causes of death was decreased in metformin users compared with users of other types of oral ADM. Despite promising preclinical data, we were not able to confirm a beneficial effect of metformin use on the risk or prognosis of EC in women with T2D. In statin users, a lower risk of both EC subtypes and reduced cancer-specific mortality from non-endometrioid EC were observed.

Keywords: antidiabetic medication, cancer incidence, case-control study, cohort study, endometrial cancer, metformin, prognosis, statins

Arima, Reetta, Metformiini, statiinit ja kohdun runko-osan syövän riski ja ennuste tyypin 2 diabetesta sairastavilla naisilla.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Luonnontieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala; Terveyden ja hyvinvoinnin laitos

Acta Univ. Oul. D 1529, 2019

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Kohdun runko-osan syöpä on naisten viidenneksi yleisin syöpä, ja todettujen tapauksien määrä kasvaa. Syövän paranemisennuste on melko hyvä. Histologisesti syöpä jaetaan endometrioidimuotoon ja ei-endometrioidi -muotoon.

Alun perin muihin tarkoituksiin kehitettyjen lääkkeiden käyttö kohdun runko-osan syövän ehkäisyssä ja hoitoyhdistelmissä on ollut viime aikoina tieteellisen mielenkiinnon kohteena. Prekliinisten tutkimusten tulokset diabeteslääke metformiinin ja hyperkolesterolemian hoitoon käytettyjen statiinien osalta ovat olleet lupaavia.

Aiemmissa epidemiologisissa tutkimuksissa metformiinin tai statiinien käytön vaikutukset kohdun runko-osan syövän riskiin ja ennusteeseen ovat olleet vaihtelevia. Osassa tutkimuksista on ollut ongelmia liittyen tilastollisten harhojen riskiin, puutteellisiin tietoihin lääkityksen kestosta ja kumulatiivisista annoksista sekä spesifisestä syöpäkuolleisuudesta ja syövän histologiasta.

Kansalliseen diabetestietokantaan (FinDM) perustuvan tutkimuksemme tavoitteena oli selvittää, onko metformiinin tai statiinien käytöllä (Kelan lääkekorvaustilastot) kohdun runko-osan syövän riskiä vähentävää tai ennustetta parantavaa vaikutusta tyypin 2 diabetesta sairastavilla naisilla. Endometrioidit-syövät ja ei-endometrioidit -syövät analysoitiin erikseen Suomen Syöpärekisterin tietoihin perustuen.

Kohortissamme (n = 92 366) ei todettu eroa endometrioidin (n = 590) tai ei-endometrioidin (n = 57) kohdun runko-osan syövän ilmaantuvuudessa metformiinia tai muita oraalisia diabeteslääkkeitä käyttävien naisten välillä (1996-2011), kun ikä, diabeteksen kesto ja muiden lääkitysten käyttö vakioitiin. Emme löytäneet näyttöä metformiinin käytön yhteydestä syöpäkuolleisuuteen endometrioidissa (n = 1 215) tai ei-endometrioidissa (n = 105) alatyypeissä verrattuna muihin diabeteslääkityksiin (1998-2011), kun ikä, syövän diagnoosivuosi ja levinneisyys sekä diabeteksen kesto vakioitiin. Endometrioidiin syöpään sairastuneilla metformiinia käyttävillä naisilla muu, valtaosalla sydän- ja verisuonitautiperäinen, kuolleisuus oli vähentynyt verrattuna muiden oraalisten diabeteslääkkeiden käyttäjiin. Aiemmista lupaavista tutkimustuloksista huolimatta emme todenneet metformiinilla olevan edullisia vaikutuksia kohdun runko-osan syövän kannalta. Statiinien käyttöön liittyi vähentynyt tämän syövän riski sekä vähentynyt syöpäkuolleisuus ei-endometrioidissa alatyypissä.

Asiasanat: diabeteslääke, ennuste, kohdun runko-osan syöpä, kohorttitutkimus, metformiini, statiinit, syövän ilmaantuvuus, tapaus-verrokkitutkimus

Acknowledgements

This study was carried out in collaboration with the Department of Obstetrics and Gynecology, Oulu University Hospital, and the Research Unit of Mathematical Sciences, University of Oulu, in 2015–2019.

I wish to express my gratitude to Professor Hannu Martikainen and Heads of the Departments of Obstetrics and Gynecology Docent Eila Suvanto (Oulu University Hospital) and Docent Jyrki Jalkanen (Central Finland Central Hospital) for providing me with the facilities to conduct this research.

I give my warmest thanks to my excellent supervisors. Professor Ulla Puistola has provided education and guidance in the field of gynecological oncology and her professional expertise and enthusiasm in both clinical work and research have been inspirational for me. Professor Esa Läärä has guided me with endless patience in the often complex areas of statistical and epidemiological questions. Marianne Hinkula, M.D., Ph.D., is both my supervisor and a dear friend who has always encouraged me during difficult times in this project.

I´ve been privileged to work with several accomplished co-authors and researchers. I´m grateful to Ari Hautakoski, M.Sc., and Mikko Marttila, M.Sc., who carried out the statistical analysis for this study under the guidance of Professor Esa Läärä. They have always answered my questions quickly and patiently. I thank Martti Arffman, M.Soc.Sc., and Professor Reijo Sund, who have been our contact persons in regard to the FinDM database and provided us with register data. I greatly appreciate the invaluable contribution of Professor Eero Pukkala in establishing this research project.

I wish to acknowledge the official reviewers, Professor Sarah Wild and Docent Maija Jakobsson, whose corrections and comments have improved the quality of this thesis. I also thank the members of the official advisory group, Docent Eila Suvanto and Docent Jussi Koivunen for their support. I´m grateful to Nick Bolton, Ph.D., for revision of the English language and to Sanna Järvinen for proofreading the Finnish abstract.

I´ve been honored to work with superb colleagues in the Departments of Obstetrics and Gynecology, both in Oulu and in Jyväskylä, and feel deeply grateful for all the support I´ve received.

I want to thank my parents Tuula and Risto for bringing me up, loving me and always believing in me. I´m grateful to my sister Tiia, brother Eetu and long-term friends Maija Vesanen, Suvi-Talvikki Oksanen and Marjo Kuosa for being at my side in spite of the geographical distance which has separated us during the last few

years. My brother-in-law Esa Arima is appreciated for aiding me in the technical aspects of this research.

I want to give the warmest love and appreciation to my husband Aki who has always supported me, and during this project provided his help in all areas from childcare to technical problems. Finally, I want to thank our children Otso, Iivo and Isla from the bottom of my heart; you are the lights of my life.

This work was financially supported by grants from the Jane and Aatos Erkko Foundation, the Finnish Cancer Foundation, Finnish Government Research Funds allocated to the University Hospital of Oulu, the University of Oulu Scholarship Foundation and the Ida Montin Foundation.

Jyväskylä, May 2019 *Reetta Arima*

Abbreviations

ADM	antidiabetic medication
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
DDD	daily defined dose
DPP-4	dipeptidyl peptidase-4
EC	endometrial cancer
e.g.	exempli gratia
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESTRO	European SocieTy for Radiotherapy & Oncology
FCR	the Finnish Cancer Registry
FIGO	Federation of Gynecology and Obstetrics
FinDM	Finnish diabetes (database)
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HR	hazard ratio
HRT	hormone replacement therapy
ICD-10	International Classification of Diseases-10
ICD-O-3	International Classification of Diseases for Oncology-3
i.e.	id est
IQR	interquartile range
MMR	mismatch repair
OGTT	oral glucose tolerance test
OR	odds ratio
OS	overall survival
PFS	progression-free survival
POLE	(DNA) polymerase epsilon
RFS	recurrence-free survival
RR	relative risk
SEER	Surveillance, Epidemiology, and End Results (program)
SGLT2	sodium-coupled glucose cotransporter 2
SU	sulfonylurea
T2D	type 2 diabetes

TCGA	The Cancer Genome Atlas
TTR	time to recurrence
TZD	thiazolidinedione
WHI	Women´s Health Initiative
WHO	World Health Organization

Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Arima, R., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Kangaskokko, J., Läärä, E., Puistola, U., & Hinkula, M. (2017). Antidiabetic medication, statins and the risk of endometrioid endometrial cancer in patients with type 2 diabetes. *Gynecologic Oncology, 146*(3), 636–641. doi:10.1016/j.ygyno.2017.06.011

II Arima, R., Hautakoski, A., Marttila, M., Arffman, M., Sund, R., Ilanne-Parikka, P., Kangaskokko, J., Hinkula, M., Puistola, U., & Läärä, E. (2017). Cause-specific mortality in endometrioid endometrial cancer patients with type 2 diabetes using metformin or other types of antidiabetic medication. *Gynecologic Oncology, 147*(3), 678–683. doi:10.1016/j.ygyno.2017.10.014

III Arima, R., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Kangaskokko, J., Urpilainen, E., Läärä, E., Hinkula, M., & Puistola, U. (2018). Antidiabetic medication, statins and the risk and prognosis of non-endometrioid endometrial cancer in women with type 2 diabetes. *Anticancer Research, 38*(7), 4169–4178. doi:10.21873/anticanres.12710

Contents

1 Introduction

Endometrial cancer (EC) is the fifth most common cancer affecting women worldwide, with around 380 000 new cases diagnosed in 2018 (Ferlay et al., 2019). The incidence of EC is rising, partly due to the pandemic of obesity, physical inactivity and type 2 diabetes (T2D), all of which are risk factors of EC (Liao, Zhang, Mungo, Tompkins, & Zeidan, 2014; Raglan et al., 2018; Schmid et al., 2015).

The majority of EC cases are diagnosed at an early stage (Morice, Leary, Creutzberg, Abu-Rustum, & Darai, 2016). In a recent US study based on the nationally representative Surveillance, Epidemiology, and End Results (SEER) program population data, 5-year survival in cases of localized EC was 95%, but the figure declined to 16% in stage IV disease (Siegel, Miller, & Jemal, 2019). Histologically, about 80% of ECs belong to the endometrioid subtype, which has better prognosis than the less common non-endometrioid subtype (Practice bulletin no. 149: Endometrial cancer, 2015).

New options are needed for the prevention of EC and improvement of prognosis of the disease, particularly in the case of advanced (recurrent or metastatic) EC. One option is to repurpose existing, commonly prescribed drugs that were originally meant to be used in the treatment of other conditions, e.g. adjuvant treatment of EC (Gupta, Sung, Prasad, Webb, & Aggarwal, 2013). One such candidate is metformin, which is used as first-line antidiabetic medication (ADM) in patients with T2D (Inzucchi & Majumdar, 2016) and which has shown promising anticancer potential in preclinical studies. The results of previous epidemiological studies carried out to assess the associations between metformin use and the risk and prognosis of EC have been variable.

Statins inhibit HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase and are the most commonly used types of medication in the prevention of cardiovascular morbidity and mortality in patients with hypercholesterolemia (Rutishauser, 2011). Statins have also been demonstrated to exert anti-neoplastic effects on EC cells in vitro (Kato et al., 2010; Schointuch et al., 2014). However, the results of earlier epidemiological studies on the relationship between statin use and the incidence of and mortality from EC remain inconsistent. Moreover, at least some of the earlier epidemiological studies carried out to evaluate the possible associations between metformin or statin use and the risk and prognosis of EC have had several limitations including time-related biases (Klil-Drori, Azoulay, & Pollak, 2017; Suissa & Azoulay, 2012; Suissa & Azoulay, 2014), missing information on

the dose and timing (in relation to EC diagnosis) of ADM or statin use, duration of diabetes and EC histology. Furthermore, in many of the prognostic studies, overall mortality instead of cancer-specific mortality has been estimated.

This study was conducted to shed more light on the potential associations between the use of metformin and/or statins and the risk and prognosis of EC in women with T2D. The data were obtained from a nationwide record-linkage diabetes database, FinDM (Sund & Koski, 2009), containing reliable information about medication use (ADM and statins) of individual patients, linked to data from the Finnish Cancer Registry (FCR).

2 Review of the literature

2.1 Endometrial cancer

2.1.1 Incidence and risk factors

Endometrial cancer is the most common malignancy of the female genital tract in industrialized countries. For the general population in those countries an overall cumulative incidence of 1.8/100 women and a cumulative rate of mortality from EC of 0.3/100 women up to 75 years of age have been reported (Torre et al., 2015). In Finland during 2012–2016 the overall cumulative incidence of EC was 1.6/100 women and the cumulative rate of mortality from EC was 0.3/100 women up to 75 years of age, according to the Nordcan database (Danckert et al., 2019). The corresponding mortality-to-incidence ratios of 0.3/1.8 and 0.3/1.6 are in consonance with what is generally known about the relatively good prognosis of EC overall. In women diagnosed with EC a 5-year relative survival rate of 81% has recently been reported in the US (Siegel et al., 2019), and rates of 83% to 85% in the Nordic countries (Danckert et al., 2019). The incidence of EC is increasing globally (Ferlay et al., 2015; Ferlay et al., 2019).

Risk factors of developing EC include older age, obesity, physical inactivity, T2D, metabolic syndrome, genetic predisposition, and hormonal/reproductive factors including early menarche, nulliparity, late-onset menopause and the use of postmenopausal unopposed estrogen therapy or tamoxifen (Ali, 2014; Kalliala et al., 2017; Liao et al., 2014; Meyer, Broaddus, & Lu, 2009; Morice et al., 2016; Raglan et al., 2018; Schmid et al., 2015; Trabert et al., 2015). A systematic review and meta-analysis showed EC risk to be associated with both overweight (body mass index [BMI] 25–29.9 kg/m^2, relative risk [RR] 1.32, 95% confidence interval [CI] 1.16–1.50) and obesity (BMI 30 kg/m^2 or more with RR 2.54, 95% CI 2.11–3.06) (Zhang, Y. et al., 2014). In a recent umbrella review, a 0.1 unit increase in waist to hip ratio resulted in a 1.21-fold risk (95% CI 1.13–1.29) of developing EC (Kalliala et al., 2017). Oral contraceptive use, the levonorgestrel-releasing intrauterine system and cigarette smoking seem to have a protective effect against the development of EC (Ali, 2014; Setiawan et al., 2013; Soini et al., 2014).

Endometrial cancer has traditionally been divided into two pathogenetic/histologic categories with different types of clinical behavior, namely endometrioid (Type I) and non-endometrioid (Type II, including serous and clear-

cell histology) EC (Bokhman, 1983). Of these subtypes, endometrioid tumors represent the majority of ECs (about 80%); they are often low grade (G1-2), preceded by endometrial hyperplasia, and are more strongly associated with the above-mentioned metabolic and estrogen-related risk factors (Ferlay et al., 2015; Setiawan et al., 2013).

2.1.2 Diagnosis and staging

Abnormal uterine bleeding occurs often in the early stage of EC and is the most common symptom of the disease, noted in about 90% of patients. Thus, the majority of ECs are diagnosed at an early stage. In cases of advanced disease, the patient may suffer from abdominal or pelvic pain and abdominal distension (Morice et al., 2016).

The diagnosis is based on pathological assessment of an endometrial biopsy or curettage sample. Clinical pelvic examination and pelvic ultrasonography support the diagnosis (Colombo et al., 2015).

The staging of EC is based on surgery. The international Federation of Gynecology and Obstetrics (FIGO) classification of endometrial cancer staging in 2009 is presented in Table 1 (Pecorelli, 2009). Non-endometrioid EC is diagnosed at an advanced stage more commonly than endometrioid EC. In addition to histological-type classification, ECs are categorized into low-grade (grades 1–2) and high-grade (grade 3) tumors based on the degree of differentiation of cancer cells, according to FIGO recommendations.

Table 1. Staging of endometrial cancer according to FIGO classification (2009).

Stage	Definition
I	Tumor confined to the corpus uteri
IA	No or < ½ myometrial invasion
IB	≥ ½ myometrial invasion
II	Tumor invades cervical stroma but not beyond uterus
III	Tumor with local or regional extension
IIIA	Tumor invades serosa or adnexa, or both
IIIB	Vaginal and/or parametrial involvement
IIIC	Regional lymph node metastasis
IIIC1	Pelvic lymph node involvement
IIIC2	Para-aortic lymph node involvement with or without pelvic lymph node involvement
IV	Tumor invades bladder or bowel mucosa, or distant metastatic disease present
IVA	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases including inguinal lymph nodes, intraperitoneal disease, lung, bone or liver

2.1.3 Treatment and Prognosis

In Finland, the treatment of EC is based on consensus guidelines of the European Society for Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO) and the European SocieTy for Radiotherapy & Oncology (ESTRO) (Colombo et al., 2015). Surgery (removal of the uterus and adnexa) is the mainstay of the treatment. In addition, pelvic and para-aortic lymphadenectomy is performed if the patient is considered to be at a high risk of nodal metastasis, based either on an individual preoperative risk assessment (histology and grade of EC and the presence of deep myometrial invasion in imaging studies) or the results of sentinel node biopsy. Omentectomy is recommended in patients with high-grade serous EC, and women with advanced disease may benefit from debulking surgery.

The need for adjuvant treatment (radiation and/or chemotherapy) depends on the surgical stage (presence of deep myometrial invasion and nodal metastasis) and pathological assessment of the tumor (histology, grade, and presence of lymphovascular invasion), i.e. factors affecting the risk of EC recurrence. Treatment options for advanced/recurrent EC remain limited, with a minority of patients responding to chemotherapy or hormonal therapy and new targeted therapies not yet living up to the expectations placed on them (Fleming, 2015; Lheureux & Oza, 2016).

The prognosis of EC is dependent on the stage of the disease, the histology and grade of the tumor, the presence of lymphovascular invasion and the patient´s age

and comorbidities (AlHilli et al., 2014; Wakayama et al., 2017). In a prospectively studied cohort of US adults, obese women (BMI 30.0–34.9 kg/m^2) were found to have increased mortality from EC (hazard ratio [HR] 2.53, 95% CI 2.02–3.18) compared with normal-weight women (BMI 18.5–24.9 kg/m^2) (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003). A recent review and meta-analysis indicated a 10% rise in BMI to lead to a 9.2% increase in the odds of mortality (all causes) in women with EC (Secord et al., 2016).

Recently, scientific knowledge of EC has been elaborated by the discovery of the genetic/molecular EC subtypes connected to the prognosis of the disease (Suarez, Felix, & Cohn, 2017). The Cancer Genome Atlas (TCGA) categorized EC into four subgroups on the grounds of the mutational burden in the cancer cells, i.e. DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy-number low and copy-number high. The first three subgroups are composed mostly of endometrioid ECs. The prognosis is best in POLE ultramutated EC, intermediate in microsatellite instability hypermutated and copy-number low EC and worse in copy-number high EC, which includes mostly serous ECs and in which tumor protein p53 mutations are commonly found (Cancer Genome Atlas Research Network et al., 2013). Defects in mismatch repair (MMR) genes are often found in the ECs of patients with Lynch syndrome and are connected to poor prognostic indicators (McMeekin et al., 2016). The nuclear protein Ki-67 is a marker of cellular proliferation which has been found to correlate with shorter disease-free survival and a higher risk of distant recurrence in patients with high-risk EC (Di Donato et al., 2018).

The prognosis of EC is generally good because the majority of ECs are diagnosed at an early stage (Morice et al., 2016), leading to a 5-year survival rate of 81% in the US (Siegel et al., 2019) and 83 to 85% in the Nordic countries (Danckert et al., 2019). However, EC patients are often elderly women with several comorbidities and a substantial proportion of them die from other health conditions.

2.2 Type 2 diabetes

2.2.1 Epidemiology and risk factors

The worldwide age-standardized prevalence of diabetes in women (World Health Organization [WHO] standard population) increased from 5.0% in 1980 to 7.9% in 2014. During the same time period, together with population growth and aging, the

estimated number of adults with diabetes rose from 108 to 422 million globally (non-communicable diseases [NCD] Risk Factor Collaboration [NCD]-RisC), 2016b). There are over 500 000 individuals diagnosed with diabetes in Finland, of whom about 75% have T2D. The prevalence of T2D in Finland rose steeply in the beginning of the 21st century (Type 2 diabetes: Current Care Guidelines, 2018). Approximately 310 000 persons (5.7% of the total population) received special reimbursement for ADM in Finland in 2016 (Social Insurance Institution 2016).

Obesity (BMI ≥ 30 kg/m^2) is the most important risk factor of T2D. The global age-standardized prevalence of obesity (WHO standard population) increased from 6.4% to 14.9% in women between 1975 and 2014 (NCD Risk Factor Collaboration [NCD-RisC], 2016a). In a national FINRISK study (from 1972 to 2012) including persons between 30 and 59 years of age, the pooled mean BMI of Finnish women remained stable between 2007 and 2012 after an initial increase to 26.5 kg/m^2, and the prevalence of obesity in 2012 varied between 18% and 26% depending on the region of the country (Borodulin et al., 2015). In addition to obesity, risk factors that predispose individuals to T2D include physical inactivity, dietary factors, alcohol consumption, smoking, genetic susceptibility, an unfavorable gut microbiome, sleep disturbances, depression and low socioeconomic status (Agardh, Allebeck, Hallqvist, Moradi, & Sidorchuk, 2011; Räikkonen, Matthews, & Kuller, 2007; Shan et al., 2015; Wu, Y., Ding, Tanaka, & Zhang, 2014).

2.2.2 Diagnosis and treatment

Type 2 diabetes is diagnosed on the basis of either an elevated level of fasting blood glucose/hemoglobin A1c (HbA1c) or an abnormal result of a 2-hour oral glucose tolerance test (OGTT) (Alberti & Zimmet, 1998; Type 2 diabetes: Current Care Guidelines, 2018) (Table 2). WHO diagnostic venous plasma glucose limits for T2D have changed over the years both for fasting glucose (≥ 8 mmol/l (1980) to ≥ 7.8 mmol/l (1985) to ≥ 7.0 mmol/l (1999)) and for 2-hour glucose in OGTTs (≥ 7.2 mmol/l (1965) to ≥ 11.0 mmol/l (1980) to ≥ 11.1 mmol/l (1985)) (World Health Organization (2006)). A plasma HbA1c value of 6.5% was approved as a cut-off point for diagnosing diabetes in 2011 (World Health Organization (2011)).

Table 2. Venous plasma values for the diagnosis of T2D (according to WHO criteria).

Laboratory test	Diabetes
Fasting blood glucose	≥ 7.0 mmol/l
2-hour blood glucose value in an OGTT	≥ 11.1 mmol/l
A single blood glucose value in a symptomatic patient	> 11.0 mmol/l
HbA1c value	≥ 48 mmol/mol (6.5%)

The aim of treatment of hyperglycemia is to prevent the symptoms and complications (e.g. cardiovascular events, nephropathy, retinopathy) of T2D. Patients with T2D have a 2- to 4-fold risk of cardiovascular events and death compared with the general population (Rawshani et al., 2017). However, in a Swedish study, there was little or no excess mortality in non-smoking patients with T2D if the chosen risk-factor variables were at target limits (glycated hemoglobin, low-density lipoprotein cholesterol, albuminuria and blood pressure) (Rawshani et al., 2018).

Lifestyle modifications such as weight control, physical activity and dietary changes are the basis of treatment of these patients. Metformin, an oral biguanide, is the first-line medication of T2D, which currently in Finland is started at the time of diagnosis if there are no contraindications (Type 2 diabetes: Current Care Guidelines, 2018). In Finland metformin has been in clinical practice since 1967 (Fimea, 2018). Metformin decreases gluconeogenesis in the liver, thus ameliorating hyperglycemia and hyperinsulinemia. Metformin is an inexpensive and usually well-tolerated drug, mild gastrointestinal symptoms being the most common side-effect. Side-effects are related to the dose, the usual dose being 500–3000 mg daily (Inzucchi & Majumdar, 2016; Type 2 diabetes: Current Care Guidelines, 2018).

If the desired blood glucose levels are not reached with metformin treatment only, another type of oral medication is added. Such drugs have different mechanisms of action. Sulfonylureas (SUs) and glinides work by increasing insulin secretion of the pancreatic β cells. The thiazolidinediones (TZDs) are insulin-sensitizers which act through peroxisome proliferator-activated receptors. Incretin-based therapies (dipeptidyl peptidase-4 [DPP-4]) inhibitors and glucagon-like peptide-1 [GLP-1] analogues) increase glucose-dependent insulin secretion and decrease the levels of glucagon. The antidiabetic effects of sodium-coupled glucose cotransporter 2 (SGLT2) inhibitors are mediated by increased urinary secretion of glucose. Insulin is added to the treatment when blood glucose levels remain high in spite of optimal oral medication. Over 50% of patients with T2D need insulin treatment at some stage of their disease. If metformin treatment is contraindicated,

or the patient suffers from difficult side-effects, another form of oral ADM may be used (Inzucchi & Majumdar, 2016; Type 2 diabetes: Current Care Guidelines, 2018).

Medication is also started for hypercholesterolemia and hypertension if the recommended blood lipid and pressure levels are not reached via lifestyle modifications alone. Statins are commonly used as cholesterol-lowering agents to prevent cardiovascular morbidity and mortality in patients with diabetes. Statins are usually well tolerated but can cause elevation of liver enzymes, myopathy, a small increase in the risk of developing diabetes and interactions with certain drugs (Mooradian, 2019; Rutishauser, 2011). Acetylsalicylic acid (100 mg daily) is started for all patients with T2D who have multiple risk factors for or are diagnosed with coronary artery disease and have no contraindications (Mooradian, 2019; Type 2 diabetes: Current Care Guidelines, 2018).

2.2.3 Diabetes, obesity and cancer

The interplay between obesity, diabetes and cancer is complicated and effects may vary with different cancer types (Garcia-Jimenez et al., 2016). A meta-analysis showed a 5 kg/m^2 increase in BMI to be strongly associated with the incidence of endometrial (RR 1.59, 95% CI 1.50–1.68), gallbladder, esophageal and renal cancers in women (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). A large prospective US cohort study showed women with higher BMI to be at an increased risk of death from several cancer types including endometrial, breast, colon and rectum, liver and kidney cancers (Calle et al., 2003).

Patients with diabetes appear to have an increased risk of several cancer types including pancreatic, liver, colorectal, breast and endometrial cancer (Carstensen, Witte, & Friis, 2012; Liao et al., 2014; Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009; Vrachnis et al., 2016). An umbrella review of meta-analyses of observational studies detected evidence of an elevated incidence of cancers of the breast, colorectum and endometrium as well as intrahepatic cholangiocarcinoma in patients with diabetes (Tsilidis, Kasimis, Lopez, Ntzani, & Ioannidis, 2015). Overall mortality is elevated in cancer patients with preexisting diabetes (Barone et al., 2008), but the possible association between diabetes and cancer-related mortality is questionable (Tsilidis et al., 2015). However, an increased risk of death from EC has been recently reported in women with prior diabetes (Nagle et al., 2018).

Obesity, specifically abdominal obesity, and T2D are frequently associated with metabolic disturbances such as insulin resistance and inflammation, which may promote cancer progression (Gallagher & LeRoith, 2015). Moreover, cancer and diabetes share several common risk factors including aging, overweight/obesity, physical inactivity, tobacco smoking and alcohol consumption. Many physiological changes that are linked to diabetes, e.g. hyperglycemia, hyperinsulinemia, elevated levels of insulin-like growth factor 1 and inflammatory cytokines, are also potentially cancer-promoting (Giovannucci et al., 2010; Vrachnis et al., 2016).

The possible associations between different forms of ADM and the risk and prognosis of cancer have been investigated widely. Most types of ADM either increase circulating insulin levels (insulin analogues, SUs, glinides, incretin mimetics) or reduce blood glucose by sensitizing the peripheral tissues to insulin (metformin, TZDs). Alpha glucosidase inhibitors act by slowing down the digestion of complex carbohydrates (Garcia-Jimenez et al., 2016). Previous research has showed metformin use to be associated with a decreased incidence of several cancer types (e.g. liver, pancreatic, colorectal and breast cancer) and improved prognosis (liver and breast cancer) (Bosco, Antonsen, Sørensen, Pedersen, & Lash, 2011; Chen, Lin, Huang, & Wen, 2011; He et al., 2012; Lee, M. S. et al., 2011; Libby et al., 2009; Zhang, P., Li, Tan, Chen, & Wang, 2013). In addition to studies on patients with T2D, some studies have included patients without T2D in their comparison groups. An increased risk of cancer has been observed in patients with diabetes using insulin compared with the non-diabetic population and other patients with diabetes (Carstensen et al., 2012). Mortality from cancer has been found to be increased in patients with initiation of metformin/SU therapy with subsequent insulin use, compared with patients not on insulin (Bowker, Yasui, Veugelers, & Johnson, 2010). A meta-analysis of 265 studies indicated a decreased cancer risk in users of metformin or TZDs, whereas a higher incidence of cancer was seen in users of insulin, SUs or alpha glucosidase inhibitors (Wu, L., Zhu, Prokop, & Murad, 2015). However, in a more recent meta-analysis of observational studies a lower risk of cancer, especially gastrointestinal cancer was reported in users of alpha glucosidase inhibitors compared with other patients with diabetes (Zhao, Wang, Lou, & Shan, 2017).

Observational studies have indicated decreased all-cause mortality among statin users. Also, in statin users, lower incidence, recurrence and/or mortality rates have been detected in connection with several cancer types including endometrial, breast, ovarian, colorectal, hepatocellular and prostate cancer (Haukka, Niskanen, & Auvinen, 2017; Li et al., 2018; Liu et al., 2014; Manthravadi, Shrestha, &

Madhusudhana, 2016; Mei et al., 2017; Pradelli et al., 2013; Shannon et al., 2005; Vogel, Goodman, Li, & Jeon, 2017; Yu et al., 2014). On the other hand, antineoplastic therapies such as use of high-dose glucocorticoids (Harris et al., 2013) and cytotoxic agents (Feng, J. P. et al., 2013; Nan et al., 2003) have been shown to predispose cancer patients to the development of diabetes. Additionally, enhanced glucose uptake by malignant tumors causes an increase in blood glucose levels through hepatic adaptation, whereas more advanced cancers can deplete glucose from the circulation (Garcia-Jimenez et al., 2016).

2.3 Metformin and endometrial cancer

2.3.1 Preclinical studies

Metformin has been demonstrated to inhibit the proliferation and invasion of both endometrioid and non-endometrioid endometrial cancer cells *in vitro* (Cantrell et al., 2010; Sarfstein et al., 2013; Tan et al., 2011). Preoperative metformin treatment has been reported to reduce the expression of the proliferative marker Ki-67 in endometrial samples from women with EC (Sivalingam et al., 2016). In addition, metformin has been shown to sensitize EC cells to the effects of cytotoxic agents (Dong et al., 2012; Hanna et al., 2012) and progestins (Zhang, Z. et al., 2011). Metformin also appears to prevent endometrial changes in breast-cancer patients treated with tamoxifen (Davis et al., 2018).

On a cellular level metformin acts as a pleiotropic metabolic inhibitor. The anticancer effects of metformin therapy on EC cells are thought to be transmitted both directly and indirectly, i.e. directly through activation of 5′ adenosine monophosphate-activated protein kinase (AMPK), affecting divergent downstream molecular targets, e.g. inhibition of mammalian target of rapamycin (mTOR), inactivation of Acetyl CoA carboxylase (ACC), reduction in the transcription factor signal transducer and activator of transcription 3 (STAT3) and an increase in the transcription factor forkhead box protein O1 (FOXO1), and indirectly via decreases in blood glucose and insulin levels (Dowling, Niraula, Stambolic, & Goodwin, 2012; Lee, T. Y. et al., 2018). The intracellular molecular effects of metformin are summarized in Figure 1. The combined result in malignant cells is inhibition of proliferation and cell-cycle progression, promotion of apoptosis, reduction of protein and fatty-acid synthesis as well as a decrease in the secretion of paracrine and endocrine factors promoting cellular proliferation.

2.3.2 Incidence: epidemiological studies

A few cohort studies have been carried out to address the question of the possible relationship between metformin use and the risk of developing EC. A recent meta-analysis of seven studies including 5 293 039 women did not show evidence of an association between metformin use and the risk of EC in the general population (odds ratio [OR] 1.05, 95% CI 0.82–1.35) or in women with diabetes (OR 0.99, 95% CI 0.78–1.26). A high degree of heterogeneity was detected among the studies (I^2 = 90.9%) (Chu et al., 2018).

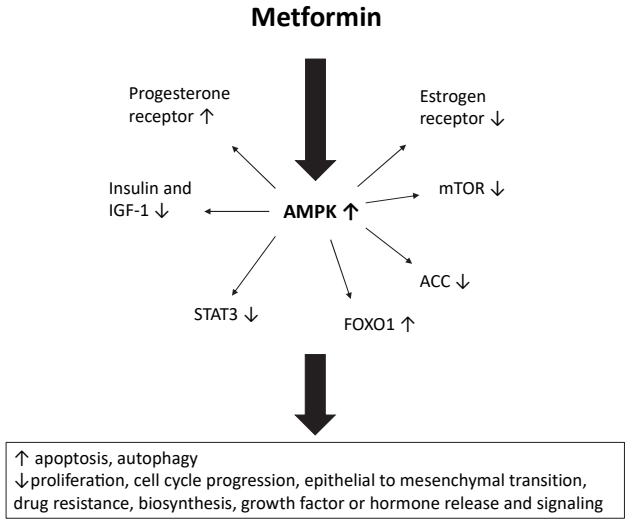


Fig. 1. Direct mechanisms of action of metformin inside the cancer cell.

The results of previous epidemiological studies addressing the associations between metformin use and the incidence of EC are presented in Table 3. All of these studies were included in the aforementioned meta-analysis (Chu et al., 2018). In a case-control study metformin use was not observed to affect the risk of EC either in the whole study population or in the subset of patients with diabetes (OR 0.87, 95% CI 0.63–1.21). The results remained the same when the cumulative medication use (daily defined doses, DDDs) was analyzed separately (Becker, Jick, Meier, & Bodmer, 2013).

In a cohort study with 729 EC patients the risk of developing the disease was similar in patients on metformin compared with SU users. An additional analysis

from the same study including only patients with diabetes yielded comparable results (HR 0.89, 95% CI 0.68–1.17) (Ko et al., 2015).

In a prospective Women´s Health Initiative (WHI) study information on the diagnosis of diabetes, EC and the use of different types of ADM was collected via self-administered questionnaires filled in by the study participants at baseline and every six to 12 months thereafter. No evidence was found for the use of metformin at baseline to be associated with the risk of developing EC, but the number of these cases was low (n = 12). In a subgroup analysis of patients with diabetes, metformin use at baseline was not observed to affect the incidence of EC (HR 0.97, 95% CI 0.60–1.58) (Luo et al., 2014). In contrast, in a Taiwanese cohort study evidence of a reduced EC risk in women with T2D and a history of metformin use was obtained. Additionally, the increasing cumulative use of metformin was observed to be inversely correlated with the risk of EC (Tseng, 2015).

Metformin use was assessed at the time of cohort entry and during follow-up in an Italian nested case-control study with 376 EC patients. A slightly higher incidence of EC was found in women with diabetes using metformin during the follow-up period. A further sensitivity analysis indicated that the excess risk was possibly explained by the higher BMI of metformin users compared with the patients on other types of ADM (Franchi et al., 2017). In none of the above-mentioned studies were endometrioid and non-endometrioid subtypes of EC analyzed separately.

2.3.3 Prognosis: epidemiological studies

A meta-analysis including seven studies and 3923 patients with EC indicated that metformin could have a beneficial effect on overall survival (OS) in women with EC both in the overall study population (HR 0.61, 95% CI 0.48–0.77) and in a subpopulation of patients with diabetes (HR 0.47, 95% CI 0.33–0.67). In addition, a decrease in the risk of EC recurrence was noted among metformin users (HR 0.50, 95% CI 0.28–0.92). No significant heterogeneity was identified in the meta-analysis (Chu et al., 2018).

The results of the previous cohort studies of metformin and the prognosis of EC which were all included in the previously mentioned meta-analysis (Chu et al., 2018) are summarized in Table 4. In one study metformin use at the time of EC diagnosis was associated with an improvement in recurrence-free survival (RFS) and OS but not with the time to recurrence (TTR) in women with diabetes. The authors concluded that metformin use seems to be connected with reduced all-cause

mortality but the possible effects on the prognosis of EC remained uncertain (Ko et al., 2014).

In a cohort of 985 women diagnosed with EC, metformin use was found to be associated with improved OS in women with non-endometrioid but not endometrioid cancer when compared with patients without diabetes. The estimated HR remained basically unchanged when the analysis was limited to patients with diabetes (HR 0.53, 95% CI 0.24–1.16) (Nevadunsky et al., 2014).

The relationship between metformin use and EC prognosis was explored in a cohort of 349 patients with advanced (FIGO stage III–IV) or recurrent EC receiving chemotherapy. In multivariate analysis adjusted for study site, BMI, age, race and FIGO stage, superior OS was observed in metformin users compared with the other women with diabetes (Ezewuiro et al., 2016).

In a cohort including 1303 patients with newly-diagnosed EC, propensity score matching was used to balance the comparison groups as regards potential confounding covariates including age, BMI, pulmonary dysfunction, prior cardiac event/intervention, vascular disease, smoking status, American Society of Anesthesiologists score, EC histology, FIGO grade and stage, residual disease, tumor diameter, lymphovascular/cervical stromal/myometrial invasion, adnexal/serosal involvement, positive peritoneal cytology, operative complexity, extent of lymphadenectomy and adjuvant therapy. When metformin users were compared with the other women with diabetes, no evidence for an association with OS or progression-free survival (PFS) was found (Al Hilli et al., 2016). Mortality from EC and the possible effects of cumulative metformin use were not evaluated in any of the above-mentioned studies. The extensive adjustment for potential confounders could explain the difference in results obtained by Al Hilli et al. compared with the abovementioned studies (Ezewuiro et al., 2016; Ko et al., 2014; Nevadunsky et al., 2014).

In an Austrian study including 465 women with EC, metformin use was not observed to be associated with RFS, OS or EC-related mortality. The results remained unchanged in a subgroup analysis including only women with endometrioid EC (Seebacher et al., 2016).

2.4 Statins and endometrial cancer

2.4.1 Preclinical studies

Statins have been demonstrated to exert anti-proliferative (simvastatin, lovastatin) and anti-metastatic (simvastatin) effects on EC cells in preclinical studies (Kato et al., 2010; Schointuch et al., 2014). Additionally, lovastatin has been shown to have a synergistic pro-apoptotic impact on ovarian cancer cells together with the cytotoxic agent doxorubicin (Martirosyan, Clendening, Goard, & Penn, 2010).

Statins inhibit HMG-CoA reductase, the key enzyme in the cholesterol synthesis pathway, leading to a decrease in mevalonate and isoprenoid levels. The mevalonate pathway is up-regulated in several types of cancer including p53-mutated breast cancer. The possible antitumoral effects of statins are pleiotropic and thought to be mediated both through mevalonate-dependent and -independent mechanisms. The resulting effects of statins on cancer cells are antiproliferative, anti-invasive and pro-apoptotic (Bathaie, Ashrafi, Azizian, & Tamanoi, 2017; Iannelli et al., 2018; Kobayashi et al., 2018; Matusewicz, Meissner, Toporkiewicz, & Sikorski, 2015). There is some evidence that lipophilic statins (e.g. atorvastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, pitavastatin) might potentially be more anticancerous than their hydrophilic counterparts (pravastatin, rosuvastatin) which have more hepato-selective activity (Kato et al., 2010; Manthravadi et al., 2016). The anti-cancerous molecular pathways affected by statins are summarized in Figure 2.

Table 3. Risk of developing EC in metformin users (adjusted results from previous cohort studies).

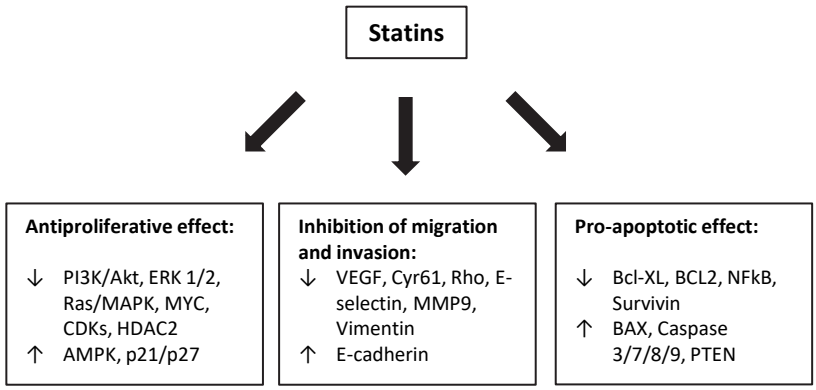
Study	Design	Period and country	Number of patients	Patients with T2D (%)	Patients on metformin (%)	Cumulative dose	Follow-up time, years	Number of ECs	EC risk
Becker et al. 2013	Retrospective case-control study	1995–2012 UK	17 878	1087 (6.1)	632 (3.5)	Yes	Mean 13	2554	HR[1] 0.86, 95% CI 0.63–1.18
Ko et al. 2015	Retrospective cohort study	2000–2011 USA	541 128	272 411 (50.3)	456 838 (84)	NA	Median 1.2	729	HR 1.09, 95% CI 0.88–1.35
Luo et al. 2014	Prospective cohort study	1993–2010 USA	88 107	4247 (4.8)	529 (0.6)	NA	Mean 11	1241	HR 1.64, 95% CI 0.92–2.91
Tseng 2015	Retrospective cohort study	1998–2009 Taiwan	478 921	478 921 (100)	193 005 (40.3)	Yes	NA	2885	HR 0.68, 95% CI 0.61–0.74
Franchi et al. 2017	Retrospective nested case-control study	2002–2012 Italy	7861	7861 (100)	5877 (74.8)	Yes	Mean 7.3	376	HR[1,2] 1.30, 95% CI 1.00–1.70

[1] Based on the study design, the comparative parameters to be estimated were indeed hazard ratios (HRs) in spite of the authors calling them odds ratios (ORs), [2] For metformin use during follow-up, NA = not applicable

Table 4. Prognosis of EC in metformin users (adjusted results from previous retrospective cohort studies).

Study	Period and country	Number of patients	Patients with diabetes (%) / on metformin[1] (%)	Analysis by EC subtype	Median follow-up time, years	EC-specific mortality	Prognosis of EC
Ko et al. 2014	2005–2010 USA	1495	363 (24.3) / 200 (13.4)	NA	2.8	NA	RFS[2] HR 1.8, 95% CI 1.1–2.9, OS[3] HR 2.3, 95% CI 1.3–4.2 in metformin non-users, TTR[4] HR 1.12, 95% CI 0.6–2.2
Nevadunsky et al. 2014	1999–2009 USA	985	250 (25.4) / 114 (11.6)	Endometrioid / non-endometrioid	3.3	NA	Endometrioid EC OS HR 0.79, 95% CI 0.31–2.00, non-endometrioid EC OS HR 0.54, 95% CI 0.30–0.97
Ezewuiro et al. 2016	1992–2011 USA	349	58 (16.6) / 31 (8.9)	NA	3.1	NA	OS HR 0.42, 95% CI 0.23–0.78
Al Hilli et al. 2016	1999–2008 USA	1303	277 (21.3) / 116 (8.9)	NA	4.3/5.2[5]	NA	OS HR 0.61, 95% CI 0.30–1.23, PFS HR 1.06, 95% CI 0.34–3.30
Seebacher et al. 2016	1995–2011 Austria	465	87 (18.7) / 46 (9.9)	Endometrioid / non-endometrioid	NA	Yes	OS HR 0.9, 95% CI 0.69–1.2, EC-related mortality HR 1.18, 95% CI 0.7–1.9, RFS HR 1.2, 95% CI 0.8–1.7

[1] At the time of diagnosis (or recurrence in Ezewuiro et al.) of EC, [2] recurrence free survival, [3] overall survival, [4] time to recurrence, [5] patients with diabetes/patients without diabetes, NA = not applicable



PI3K/Akt = phosphoinositide 3-kinase/Akt, ERK 1/2 = Extracellular signal-Regulated Kinase 1/2, Ras/MAPK = Ras/Mitogen Activated Protein Kinase, CDK = Cyclin-Dependent Kinase, HDAC2 = Histone Deacetylase 2, AMPK = AMP-Activated Protein Kinase, VEGF = Vascular Endothelial Growth Factor, Cyr61 = Cysteine-rich angiogenic inducer 61, MMP9 = Matrix Metalloproteinase 9, Bcl-XL = B-cell lymphoma-extra large, BCL2 = B-Cell Lymphoma 2, NFkB = Nuclear Factor kappa-light-chain-enhancer of activated B cells, BAX = BCL2-Associated X protein, PTEN = Phosphatase and tensin homolog

Fig. 2. The anti-cancerous cellular signal transduction pathways affected by statins.

2.4.2 Incidence: epidemiological studies

A meta-analysis of randomized controlled trials and observational studies involving 9517 EC patients did not find adequate evidence for an association between statin use and the risk of EC (Yang et al., 2017). Most of the previous studies addressing statins and cancer risk have included several different cancer types.

Studies on statin use and the risk of EC are summarized in Table 5. A Danish register-based case-control study of 5382 patients diagnosed with EC did not show a connection between ever use of statins and the incidence of EC. The results remained essentially unchanged when the duration/intensity of statin use and the histological subtype of EC were considered (Sperling, Verdoodt, Friis, Dehlendorff, & Kjaer, 2017). In line with these results, a Finnish record-linkage study indicated no evidence for an association between statin use and EC risk in the general population (Haukka et al., 2010). These findings were consistent with the results of a WHI-based cohort study of statins and the incidence of EC in which statin use was analyzed as a time-dependent variable (Desai et al., 2018). On the other hand, a reduced EC risk in statin users (over one year before EC diagnosis) was reported

in an Israeli study involving both ovarian and endometrial (n = 215) cancer cases (Lavie, Pinchev, Rennert, Segev, & Rennert, 2013).

2.4.3 Prognosis: epidemiological studies

A recent meta-analysis including 5923 women with EC showed a positive impact of statin use on both OS (HR 0.80, 95% CI 0.66–0.95) and mortality from EC (HR 0.69, 95% CI 0.61–0.79) (Li et al., 2018).

The adjusted results of previous observational studies of statin use and the prognosis of EC are presented in Table 6. A register-based cohort study of 2987 elderly (65 years or older) EC patients showed no evidence of improvement in OS regardless of the histological EC subtype when post-diagnostic statin use was analyzed as a time-dependent variable (Yoon, Goodman, Rimel, & Jeon, 2015). Comparable results concerning post-diagnostic statin use and all-cause and cancer-specific mortality of EC patients (n = 3085) were reported in a population-based cohort study carried out in the UK (Sanni et al., 2017). In contrast, an Israeli study showed improved OS in patients using statins only after EC diagnosis (Lavie et al., 2013). However, the result could have been affected by bias because several possible confounders were unknown in the study and selection bias could be present when considering starting statin medication after EC diagnosis.

In addition to the above, the results of other cohort studies have indicated possible favorable effects of statins on the prognosis of EC patients. In a cohort study in which statin use was recorded at the time of EC diagnosis, a reduction in mortality from EC was seen in patients with non-endometrioid EC. Interestingly, there seemed to be an even greater survival advantage when statin and aspirin were used concurrently (HR 0.25, 95% CI 0.09–0.70) (Nevadunsky et al., 2015). In agreement with that, a beneficial effect of statin use (recorded at the time of EC diagnosis) on PFS and OS of hyperlipidemic patients with high-risk (non-endometrioid or grade 3 endometrioid) EC has been observed (Feng, C. H. et al., 2016). In a Danish register-based study with 6694 EC patients, an inverse association was found between EC mortality and both post-diagnostic and continuing (pre- and post-diagnostic, HR 0.70, 95% CI 0.53–0.92) statin use. The associations between post-diagnostic statin use and EC mortality persisted in connection with both the endometrioid and non-endometrioid subtype of EC (Sperling et al., 2018).

Table 5. The risk of developing EC in statin users (adjusted results from previous cohort studies).

Study	Design	Period and country	Number of patients	Patients with diabetes (%)	Patients on statins (%)	Cumulative dose	Mean follow-up time, years	Number of ECs	Analysis by EC subtype	EC risk
Sperling et al. 2017	Retrospective case-control study	2000–2009 Denmark	77 509	3675 (4.7)	7639 (9.9)	Yes	NA	5382	Endometrioid / non-endometrioid	HR[1] 1.03, 95% CI 0.94–1.14
Haukka et al. 2010	Retrospective record-linkage study	1996–2005 Finland	473 302	NA	236 651 (50.0)	Yes	8.8	1721	NA	HR[1] 1.05, 95% CI 0.95–1.15
Desai et al. 2018	Prospective cohort study	1993–2012 USA	94 018	NA	6653 (7.1)[2]	NA[3]	NA	1377	Endometrioid	HR 0.91, 95% CI 0.76–1.08
Lavie et al. 2013	Retrospective case-control study	2003–2010 Israel	430	NA	167 (38.8)	NA[3]	10.8	215	NA	HR[1] 0.48, 95% CI 0.26–0.89

[1] Based on the study design, the comparative parameters to be estimated were indeed hazard ratios (HRs) in spite of the authors calling them odds ratios (ORs), [2] At baseline, [3] Duration of statin use assessed, NA = not applicable

Table 6. The prognosis of EC in statin users (adjusted results from previous retrospective cohort and case-control studies).

Study	Period and country	Number of patients	Patients with diabetes (%)	Patients on statins (%)	Statin use	Cumulative dose	Follow-up time, years	Analysis by EC subtype	EC-specific mortality	Prognosis of EC
Yoon et al. 2015	2007–2010 USA	2987	1130 (38)[1]	1598 (53.5)	Postdiagnostic	NA[2]	From 1 to 4	Endometrioid / non-endometrioid	NA	Hazard of death: endometrioid EC HR 0.92, 95% CI 0.70–1.20, non-endometrioid EC HR 0.92, 95% CI 0.65–1.29
Sanni et al. 2017	1998–2014 UK	3058	NA	1134 (37.1)	Postdiagnostic	Yes	Mean 6.1	NA	Yes	Cancer-specific mortality HR 0.83, 95% CI 0.64–1.38, all-cause mortality HR 0.91, 95% CI 0.77–1.09
Lavie et al. 2013	2003–2010 Israel	274	NA	143 (52.2)	Postdiagnostic	NA[2]	NA	NA	NA	OS HR 0.45, 95% CI 0.23–0.87
Nevadunsky et al. 2015	1999–2009 USA	983	251 (26)	220 (22.4)	At the time of EC diagnosis	NA	Median 3.3	Endometrioid / non-endometrioid	Yes	Non-endometrioid EC cancer-specific mortality HR 0.63, 95% CI 0.40–0.99
Feng et al. 2016	1995–2014 USA	199	51 (26)	50 (25.1)	At the time of EC diagnosis	NA	Median 2.6	High risk ECs	Yes	PFS HR 0.47, 95% CI 0.23–0.95, OS HR 0.42, 95% CI 0.20–0.87

Study	Period and country	Number of patients	Patients with diabetes (%)	Patients on statins (%)	Statin use	Cumulative dose	Follow-up time, years	Analysis by EC subtype	EC-specific mortality	Prognosis of EC
Sperling et al. 2018	2000–2013 Denmark	6694	874 (13)	1208 (18.0)[3]	Pre- and postdiagnostic	Yes	Median 4.5	Endometrioid / non-endometrioid	Yes	EC mortality HR[3] 0.61, 95% CI 0.48–0.77

[1] Diabetes or high glucose, [2] Duration of statin use assessed, [3] Postdiagnostic statin users, NA = not applicable

3 Aims of the present study

The prevalence of T2D is increasing in Finland and worldwide (NCD Risk Factor Collaboration [NCD-RisC], 2016). Women with diabetes face an elevated risk of EC (both endometrioid and non-endometrioid) which is often aggravated by concomitant obesity and metabolic syndrome. Different forms of ADM and statins are commonly used in this population but their impact on the risk and prognosis of EC has not been widely studied.

The results of preclinical and epidemiological studies have suggested potential anticancer effects of both metformin and statins. However, previous epidemiological studies have several limitations. Important information about medication use including the dose, cumulative amount, duration and temporal relationship to EC diagnosis has been missing. The duration of diabetes has often been unknown. Moreover, in studies carried out to investigate the association between ADM and/or statin use and the prognosis of EC, the endpoint has usually been death from all causes omitting cause-specific mortality.

This study was conducted to obtain more reliable information about the relationship between the use of metformin, other forms of ADM, and statins, and the incidence and prognosis of EC in women with T2D. In our study we utilized a nationwide diabetes database, FinDM, which is linked to high-quality data from the Drug Reimbursement Register and the Finnish Cancer Registry.

More specifically, the present study was aimed at obtaining valid and precise answers to the following research questions:

1. Do women with T2D who use metformin or statins have a lower risk of endometrioid EC?
2. Is the prognosis of endometrioid EC improved in pre-diagnostic metformin users compared with patients with T2D using other types of ADM?
3. Is the incidence of or mortality from non-endometrioid EC reduced in women with T2D using metformin or statins?

4 Material and methods

4.1 Data sources

4.1.1 Finnish diabetes database

All studies were based on data from FinDM, a Finnish individual-level diabetes database combining information from several nationwide registers to identify all persons with diabetes in Finland between 1964 and 2011 (Sund & Koski, 2009). Data linkage between different registers is made on the basis of the personal identification codes unique to each resident of Finland.

Patients with diabetes are entered in the database either at the time of receiving their first reimbursement for any form of ADM based on the records of the Drug Reimbursement Register of the Social Insurance Institute (Social Insurance Institution 2019) or when diabetes diagnosis is encoded either in the Hospital Discharge Register of the National Institute for Health and Welfare (THL 2016) or in the Cause of Death Register maintained by Statistics Finland (Statistics Finland 2019). Inclusion in FinDM is based solely on medication data for approximately half of the patients with T2D, on diagnosis of T2D in hospital records for less than 10% and on death certificates for under 1%. The rest of the patients are entered in FinDM through combined data from more than one of these sources (Sund & Koski, 2009). Patients with diet-controlled T2D who are treated solely in an outpatient setting are not included in FinDM and thus the duration of T2D of the individual patients can only be estimated.

The patients are then categorized as having type 1 (primarily insulin-dependent) or type 2 diabetes according to the type of purchases of ADM. A patient with regular purchases of insulin and none of the types of ADM that stimulate pancreatic insulin secretion (SUs, sitagliptin, vildagliptin, repaglinide, nateglinide or exenatide) is classified as having type 1 diabetes. A patient who has more purchase-years of oral ADM than insulin or purchases of the above-mentioned types of ADM that increase insulin secretion by the pancreas is categorized as having T2D. In addition, FinDM data is linked to data from the Finnish Cancer Registry (Pukkala et al., 2018). FinDM data linkages are presented in Figure 3.

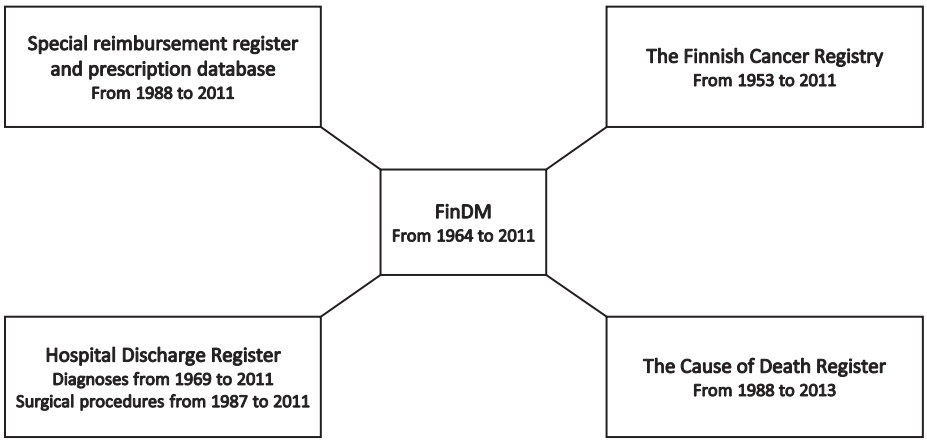


Fig. 3. Data linkages of the FinDM database.

4.1.2 The Drug Reimbursement Register

In Finland patients with diabetes and certain other diseases are entitled to receive reimbursement for their medication. Individually linked data about reimbursed medication has been reliably recorded in the Drug Reimbursement Register since 1994. Information about the amount and date of purchase of all forms of ADM, statins and other types of reimbursed medication are included in the register.

4.1.3 The Hospital Discharge Register

The Hospital Discharge Register contains information about diagnoses (International Classification of Diseases, ICD-10 [World Health Organization (2016)]) documented in hospital records in inpatient (from 1969) and outpatient settings (from 1998) as well as data about surgical procedures performed in hospitals since 1987 (NOMESCO Classification of Surgical Procedures [Nordic Centre for Classifications in Health Care 2010]). The dates of visits are also included in the register.

4.1.4 The Finnish Cancer Registry and the Cause of Death Register

The Finnish Cancer Registry holds information on over 95% of all cancer cases (solid tumors) in Finland since 1953 (Leinonen, Miettinen, Heikkinen, Pitkaniemi, & Malila, 2017). Data on the date of diagnosis, stage and histology (International

Classification of Diseases for Oncology-3, ICD-O-3 [Fritz, 2000]) of cancer are recorded in the FCR. Information from the FCR is linked at regular intervals to the Finnish Population Information System maintained by the Population Register Centre (Population Register Centre 2018), holding data on the vital status, date of death, emigration and the official place of residence of Finnish citizens.

The Cause of Death Register contains information about dates and causes of deaths (both cancer-related and other causes according to ICD-10) of Finnish citizens. These data are individually linked to FinDM data up to 2013.

4.2 Cohort selection

There was a total of 244 322 women identified in the FinDM database resident in Finland with either prevalent T2D at the beginning of 1996 or incident diabetes diagnosed after that until 31 December 2011. To perform the selected exclusions needed for the constitution of cohorts for each study, individually linked register data from the Drug Reimbursement Register, the Hospital Discharge Register, the FCR and the Cause of Death Register were utilized.

4.2.1 The incidence of endometrial cancer (Studies I and III)

Women who were 40 years or older and diagnosed with T2D between 1 January 1996 and 31 December 2011 were identified from the FinDM database. Those diagnosed with EC prior to cohort entry were excluded. Furthermore, women who developed EC during the first year after the diagnosis of T2D were excluded, because it is possible that the enhanced medical surveillance following newly diagnosed diabetes could result in an increased discovery of occult malignancies in the first year after diagnosis (Carstensen et al., 2012). Women with a history of hysterectomy were removed from the cohort (data available from 1987). Prior use of systemic hormone replacement therapy (HRT) was used as an exclusion criterion to eliminate the impact of HRT on the risk of developing EC (data available from 1994). After applying these exclusions, a total of 92 366 women constituted the final study cohort. The cohort selection flow chart of Studies I and III (non-endometrioid EC incidence cohort) is presented in Figure 4.

In addition to the full-cohort study, nested case-control analyses were conducted, in which up to 20 randomly sampled controls were matched for age and duration of T2D (± 182 days) for each of the women in the cohort diagnosed with endometrioid (Study I) or non-endometrioid (Study III) EC during the follow-up

period. Controls were chosen amid those who were alive and at risk of developing EC (no history of hysterectomy) at the date of EC diagnosis of the case.

4.2.2 Mortality of endometrial cancer patients (Studies II and III)

For Study II, women diagnosed with endometrioid EC (ICD-O-3 codes C54.1/C54.9 plus M-8380/3) from 1 January 1998 to 31 December 2011 were identified from the FinDM database. Patients diagnosed with non-endometrioid EC (serous, clear cell, or mixed carcinoma), EC of unknown histology, leiomyosarcomas, carcinosarcomas and endometrial stromal sarcomas were excluded from the cohort. A history of prior cancer, except for non-melanoma skin cancers, was an exclusion criterion. The estimated duration of TD2 had to be at least 180 days before the diagnosis of endometrioid EC for the patient to be included in the cohort. The final study cohort consisted of 1215 women. The flow chart of Study II is presented in Figure 5.

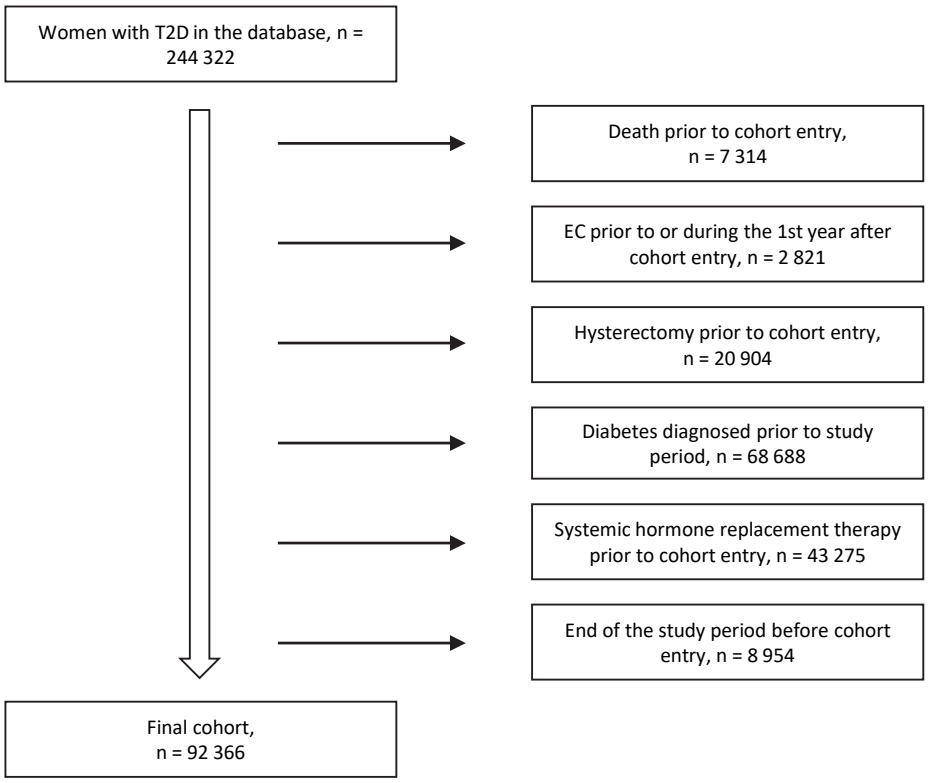


Fig. 4. Flow chart of the EC incidence cohort (Studies I and III).

The cohort-selection process in Study III (non-endometrioid EC mortality cohort) was similar to that in Study II, except that women diagnosed with non-endometrioid EC (ICD-O-3 codes M-8260/3, M-8441/3, M-8460/3, M-8310/3, M-8010/3, M-8000/3, M-8140/3) were included in the cohort, excluding patients with endometrioid EC. The final study population consisted of 105 women. The flow chart of Study III (mortality cohort) is presented in Figure 6.

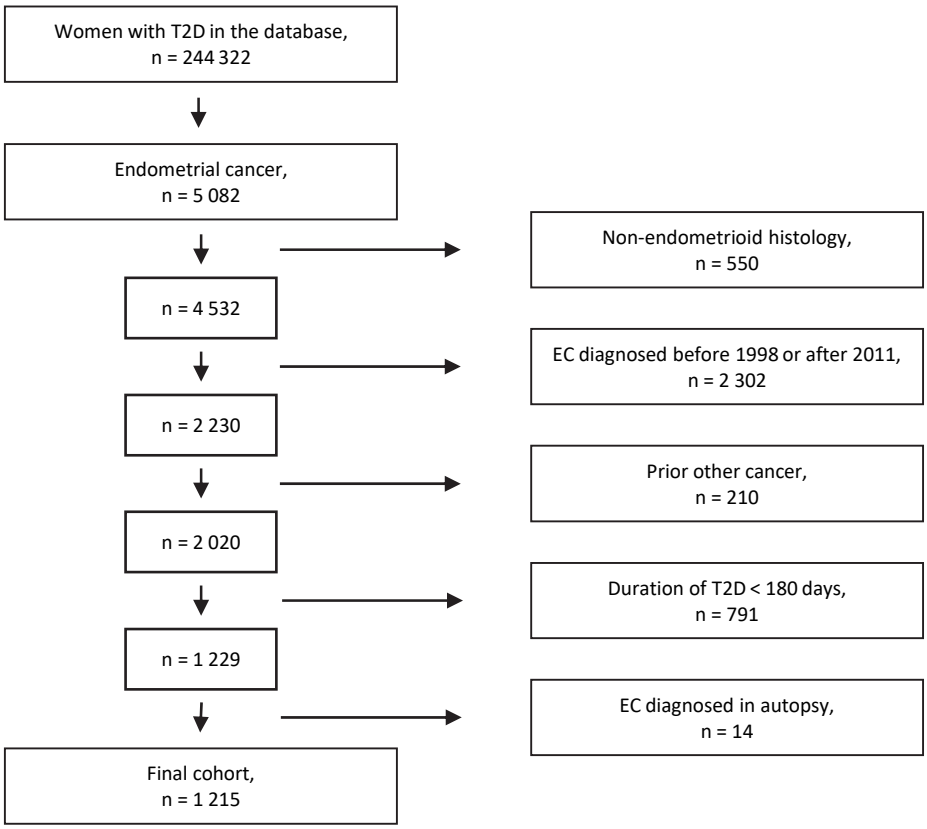


Fig. 5. Flow chart of the endometrioid EC mortality study cohort (Study II).

4.3 Methods

4.3.1 The incidence of endometrial cancer (Studies I and III)

Exposure to ADM was analyzed in three groups: metformin, other types of oral ADM, and insulin. In addition, statin use was estimated in a distinct category (classification by Anatomical Therapeutic Chemical [ATC] codes is shown in Table 7). Exposure to all types of medication was defined as beginning 365 days after its first purchase date to prevent the risk of bias through reverse causality. In both nested case-control analyses and the full-cohort analysis cohort members were defined as being exposed to a particular medication from this date to the end of the

individual follow-up time (ever/never exposed). Use of different types of ADM and statins was analyzed as a time-varying variable.

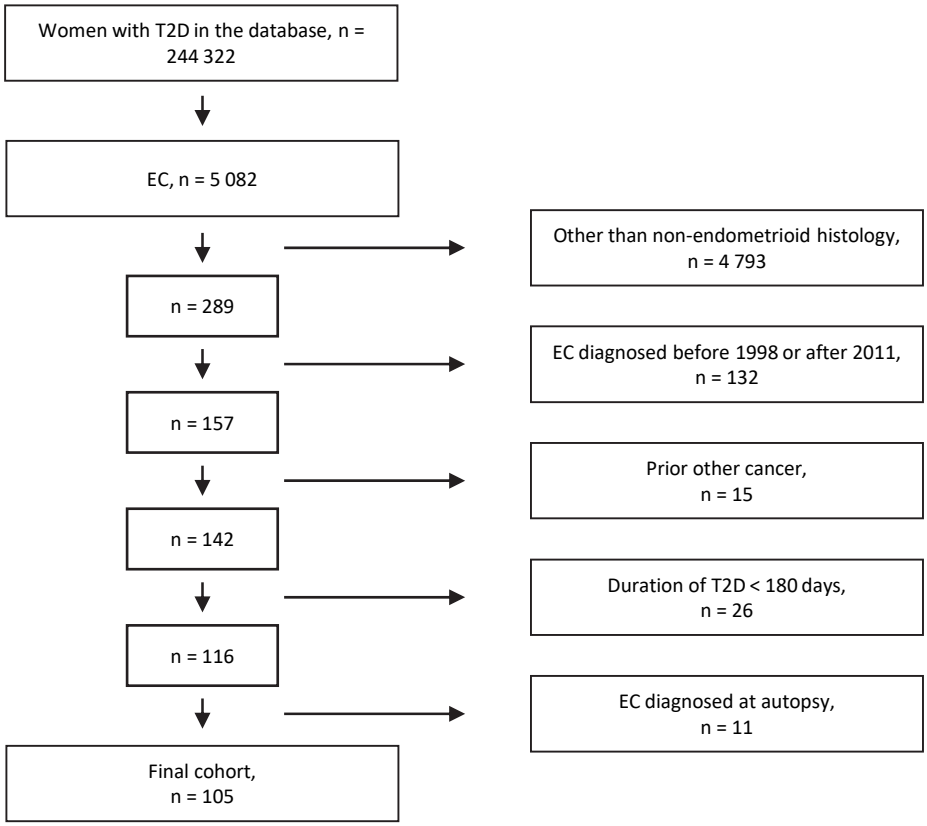


Fig. 6. Flow chart of the non-endometrioid EC mortality cohort (Study III).

Table 7. ATC codes for types of medication under study (different forms of ADM and statins).

Subgroup	ATC code
Metformin	A10BA02
Other types of oral ADM	
Sulfonylurea	A10BB01-A10BB12
Sulfonylurea	A10BB31
Alpha glucosidase inhibitors	A10BF01-03
Thiazolidinedione	A10BG01-A10BG03
Dipeptidyl peptidase-4 inhibitor	A10BH01-A10BH06

Subgroup	ATC code
Dipeptidyl peptidase-4 inhibitor	A10BH51
Guar gum	A10BX01
Glinide	A10BX02-A10BX03
Glinide	A10BX08
GLP-1 agonist	A10BX04
GLP-1 agonist	A10BX07
GLP-1 agonist	A10BX10
GLP-1 agonist	A10BX13
Amylin analogue	A10BX05
Gliflozin	A10BX09
Gliflozin	A10BX11-A10BX12
Other	A10BX06
Combination other oral ADM	A10BD04
Combination other oral ADM	A10BD06
Combination other oral ADM	A10BD09
Combination other oral ADM	A10BD12
Combination other oral ADM	A10BD19
Combination metformin and other types of oral ADM	
	A10BD02-A10BD03
	A10BD05
	A10BD07-A10BD08
	A10BD10-A10BD11
	A10BD13-A10BD18
Insulin	
	A10AB01-A10AB06
	A10AB30
	A10AC01-A10AC04
	A10AC30
	A10AD01-A10AD06
	A10AD30
	A10AE01-A10AE06
	A10AE30
	A10AE56
Statin	
Simvastatin	C10AA01
Lovastatin	C10AA02
Pravastatin	C10AA03
Fluvastatin	C10AA04
Atorvastatin	C10AA05
Serivastatin	C10AA06
Rosuvastatin	C10AA07
Pitavastatin	C10AA08

Subgroup	ATC code
Simvastatin combination	A10BH51
Simvastatin combination	C10BA02
Simvastatin combination	C10BA04
Simvastatin combination	C10BX01
Simvastatin combination	C10BX04
Lovastatin combination	C10BA01
Pravastatin combination	C10BA03
Pravastatin combination	C10BX02
Atorvastatin combination	C10BA05
Atorvastatin combination	C10BX03
Atorvastatin combination	C10BX06
Atorvastatin combination	C10BX08
Rosuvastatin combination	C10BA06
Rosuvastatin combination	C10BX05
Rosuvastatin combination	C10BX07
Rosuvastatin combination	C10BX09
Ezetimibe[1]	C10AX09
Ezetimibe and statin combination	C10BA02
Ezetimibe and statin combination	C10BA05-C10BA06

[1] In mortality analysis only

Furthermore, in the nested case-control analyses of Study I, cumulative use of ADM and statins was evaluated as the total amount of daily defined doses (DDDs) (World Health Organization [2018]) purchased by individual patients throughout the follow-up period.

4.3.2 Mortality of endometrial cancer patients (Studies II and III)

Pre-diagnostic ADM use was evaluated in the following patient categories: 1) metformin only, 2) other oral ADM only, 3) metformin plus other oral ADM, 4) insulin at any time, and 5) no ADM. In addition, in Study III the use of statins was assessed in two groups, users and non-users (for ATC codes, see Table 7). In ADM groups 1–3 and statin users the minimum duration of medication use was set at 180 days. Hence the data on patients with metformin and/or other types of oral ADM use for 1–179 days (n = 42 in Study II, n = 2 in Study III) were left out from the results. Those who had at least one purchase of insulin were allocated to group 4.

Exposure to medication was analyzed during the period of three years prior to diagnosis of EC, beginning from the date of first purchase and ending 90 days after the last purchase, or at the date of EC diagnosis if this occurred earlier.

In Study II, the cumulative use of metformin was assessed during the period of three years preceding the diagnosis of EC as DDDs purchased.

4.4 Follow-up

4.4.1 The incidence of endometrial cancer (Studies I and III)

Follow-up of each cohort member began at the diagnosis of T2D and ended at the date of EC diagnosis, hysterectomy for another indication, commencement of systemic HRT, death or 31 December 2011, whichever came first. The duration of T2D and the use of ADM and statins were assessed from the diagnosis of T2D, but follow-up concerning diagnosis of EC began at 40 years of age.

4.4.2 Mortality of endometrial cancer patients (Studies II and III)

Follow-up of each patient started at the date of EC diagnosis and ended at death, emigration, or 31 December 2013, whichever came earliest. Data concerning follow-up were acquired from the FCR, which each year receives information about the dates and causes of death (both cancerous and noncancerous causes) of each individual patient from the Cause of Death Register. The personnel of the Finnish Cancer Registry consider the official causes of death of each patient with cancer, and conclude if the patient died from a certain type of cancer or some other reason (Pukkala et al., 2018). Based on these conclusions, deaths were allocated in the following groups: (1) deaths from EC, and (2) deaths from other causes. In Study II deaths from other causes were further classified as follows: (1) deaths from other cancer (ICD-10 codes C00–C97), (2) deaths from cardiovascular diseases (ICD-10 codes I00–I99), and (3) deaths from other causes (all the other ICD-10 codes).

4.5 Statistical methods

For the incidence of EC (Studies I and III) SAS/STAT® software version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA) was used to preprocess the register data. The following data transformations, statistical analysis and figures were conducted in R environment versions 3.3.0 (Study I) and 3.3.2 (Study III) (R Core Team, 2017).

In the full-cohort analysis a Poisson regression model was utilized to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the incidence of EC in relation to the use of metformin, other types of ADM and statins (Clayton & Hills, 1993). In addition, a multiple Poisson regression model including age, duration of T2D and ever use of other forms of medication (ADM and statins) as confounders was used, wherein the effects of current age and duration of T2D were presumed to follow the piecewise constant hazards pattern over selected intervals (Results, Tables 8 & 13).

In nested case-control analyses conditional logistic regression was used to estimate analogous HRs with 95% CIs concerning the use at any time of different forms of ADM and statins (Keogh & Cox, 2014). The HRs were adjusted for age, duration of T2D and ever use of other types of medication (ADM and statins). Lexis tools in the Epi package were used to create a person-period file in which the individual follow-up time of each cohort member was concurrently divided into appropriate categories of age, duration of T2D, and time-varying medication use status (Carstensen, Plummer, Läärä, & Hills, 2017). The Poisson regression model was fitted by means of the glm function for the full-cohort analysis and the conditional logistic regression model by using the clogit function of the survival package on the nested case-control data (Therneau, 2015). An interaction term was included in the conditional logistic regression model used in the case-control analyses to evaluate the possible joint effect of metformin and statin use.

The reason behind conducting nested case-control analyses in addition to the full-cohort study was that the method is of a more straightforward design when estimating cumulative medication use. Concerning the incidence of endometrioid EC (Study I), a separate model was used to obtain estimates of the effects of cumulative use of different types of ADM and statins. The cumulative dose was defined by the tertiles of the total amounts of DDDs purchased.

Data on mortality from EC (Studies II and III) were analyzed by using SPSS version 24 (IBM Corp., Armonk, NY, USA) and R environment versions 3.4.1 (Study II) and 3.3.0 (Study III) software (R Core Team, 2017). Mortality from EC and other causes was examined in the chosen ADM and statin groups by means of the Aalen–Johansen estimator of cumulative incidence function for competing risks (Putter, Fiocco, & Geskus, 2007). Cox proportional hazards models were utilized to adjust for the impact of year, age and stage at diagnosis of EC and the duration of T2D, and HRs with 95% CIs were approximated from these models.

4.6 Ethical aspects

All studies were conducted after FinDM received approval from the Ethics Committee of the National Institute for Health and Welfare (30 January 2014, reference number 609) to use the confidential individual-level data from the above-mentioned nationwide registers. The data contained in FinDM is saved according to Finnish data protection legislation.

The data linkages between FinDM and the other registers were based on the patients´ personal identity numbers. However, the research personnel received anonymized data, in which the recognizable personal identity codes had been changed into unidentifiable codes.

5 Results

5.1 Metformin, other forms of antidiabetic medication, statins and the risk of endometrioid endometrial cancer (Study I)

The total follow-up in the cohort covered 503 937 person-years at risk, with a mean follow-up time of 5.5 years. In total, 590 women had a diagnosis of endometrioid EC during the follow-up period. The incidence of EC varied by age, being highest among women aged between 65 and 69 years. The incidence of EC was increased in women in whom the duration of T2D was over eight years, compared with those with a shorter duration of the disease. Of the cohort members, 87% used some type of ADM during the follow-up period. Of the 590 women diagnosed with EC, 411 (70%) had used metformin at some time, 351 (60%) had used other forms of oral ADM and 270 (46%) had used statins (Table 8). In the nested case-control analyses the most commonly used forms of oral ADM other than metformin, based on the numbers of ever-users included sulfonylureas (n = 6301, 94%) and thiazolidinediones (n = 579, 9%). The most frequent statins were simvastatin (n = 4296, 69%), atorvastatin (n = 2159, 35%) and fluvastatin (n = 1307, 21%).

Table 8. Distribution of person-years at risk in the cohort, numbers of cases and their matched controls, and the unadjusted incidence rates of endometrioid EC by age, duration of T2D and ever-use of medications under study. Controls (up to 20 per case) were individually matched for age and duration of T2D for each case (Study I).

Variable	Subgroup	Person-years	Cases, n (%)	Controls, n (%)	Incidence[1] (95% CI)
Age (years)					
	40–44	11 222	4 (0.7)	79 (0.7)	35.6 (13.4-95.0)
	45–49	18 145	5 (0.8)	107 (0.9)	27.6 (11.5-66.2)
	50–54	25 159	28 (4.7)	545 (4.6)	111.3 (76.8-161.2)
	55–59	33 529	42 (7.1)	847 (7.2)	125.3 (92.6-169.5)
	60–64	43 572	67 (11.4)	1321 (11.2)	153.8 (121.0-195.4)
	65–69	55 902	94 (15.9)	1909 (16.2)	168.2 (137.4-205.8)
	70–74	77 105	99 (16.8)	1987 (16.9)	128.4 (105.4-156.4)
	75–79	91 366	128 (21.7)	2532 (21.5)	140.1 (117.8-166.6)
	80–84	81 070	82 (13.9)	1631 (13.8)	101.1 (81.5-125.6)
	85–89	47 495	29 (4.9)	627 (5.3)	61.1 (42.4-87.9)
	90–106	19 373	12 (2.0)	207 (1.8)	61.9 (35.2-109.1)
Duration of T2D (years)					
	1–<3	160 744	175 (29.7)	3569 (30.3)	108.9 (93.9-126.3)
	3–<5	118 799	138 (23.4)	2736 (23.2)	116.2 (98.3-137.3)
	5–<8	120 018	135 (22.9)	2657 (22.5)	112.5 (95.0-133.2)
	8–<16	104 377	142 (24.1)	2830 (24.0)	136.0 (115.4-160.4)
Medication					
Metformin	Ever	321 349	411 (69.7)	7671 (65.1)	127.9 (116.1-140.9)
	Never	182 588	179 (30.3)	4121 (34.9)	98.0 (84.7-113.5)
Other oral ADM	Ever	266 793	351 (59.5)	6342 (53.8)	131.6 (118.5-146.1)
	Never	237 145	239 (40.5)	5450 (46.2)	100.8 (88.8-114.4)
Insulin	Ever	58 963	91 (15.4)	1449 (12.3)	154.3 (125.7-189.5)
	Never	444 974	499 (84.6)	10343 (87.7)	112.1 (102.7-122.4)
Any ADM	Ever	417 730	523 (88.6)	9805 (83.1)	125.2 (114.9-136.4)
	Never	86 208	67 (11.4)	1987 (16.9)	77.7 (61.2-98.7)
Statin	Ever	235 758	270 (45.8)	5993 (50.8)	114.5 (101.6-129.0)
	Never	268 179	320 (54.2)	5799 (49.2)	119.3 (106.9-133.1)
	Total	503 937	590 (100)	11792 (100)	117.1 (108.0-126.9)

[1] cases/100 000 person-years

The incidence of EC in the selected reference group (age 70–74 years, duration of T2D less than three years, no previous record of ADM use) was 103.2/100 000 person-years. In the multiple Poisson regression model, both "ever use" of both metformin and other forms of oral ADM was associated with an increased risk of

EC compared with never users. The incidence of EC was not found to be different between metformin ever-users and ever-users of other types of oral ADM ever-users (HR 1.00, 95% CI 0.87–1.12). In contrast, use of statins at any time correlated inversely to the incidence of EC (Table 9).

Results of the nested case-control analyses were in line with those of the full-cohort analysis: “ever use” of metformin or other forms of oral ADM was associated with an increased risk of EC. The incidence of EC was not observed to differ between metformin ever-users and ever-users of other forms of oral ADM ever-users (HR 1.00, 95% CI 0.87–1.15). Ever use of statins was inversely related to the risk of EC, while no clear pattern was observed regarding the cumulative use of metformin or statins (Figure 7, Table 9). In an additional analysis, no evidence for an interaction between metformin and statin use was observed.

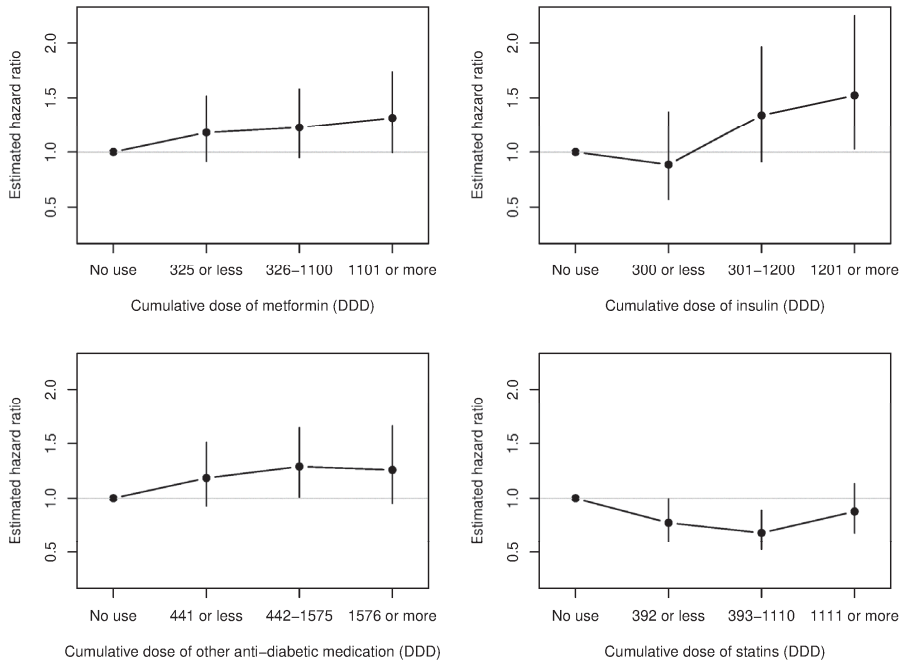


Fig. 7. Estimated HRs (with 95% CIs) of endometrioid EC by cumulative doses of different forms of ADM and statins, adjusted for age, duration of T2D and the use of other medication (Study I).

Table 9. Unadjusted (HR^u) and adjusted (HR^a, HR^c) estimates of HR 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 (Study I).

Ever-use	HR^u [1]	HR^a [2] (95% CI)	HR^c [3] (95% CI)
Other oral ADM	1.31	1.26 (1.06-1.50)	1.25 (1.04-1.50)
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)
Statin	0.96	0.82 (0.70-0.97)	0.78 (0.65-0.94)

[1] unadjusted, [2] adjusted from full cohort data for age, duration of T2D and use at any time of other forms of medication, [3] adjusted from nested case-control data for age, duration of T2D and use at any time of other forms of medication

5.2 Metformin, other forms of antidiabetic medication and mortality from endometrioid endometrial cancer (Study II)

The final cohort consisted of 1215 women with T2D and a diagnosis of endometrioid EC. Of these, 236 (19%) used metformin, 147 (12%) other types of oral ADM, 301 (25%) other types of oral ADM and metformin, 316 (26%) insulin and 173 (14%) had no ADM. Baseline characteristics differed in several aspects between these groups (Table 10). Metformin users were younger than the patients in the other groups. The duration of T2D was shorter in women using metformin or other oral forms of ADM only compared with those using combination treatment, insulin, or no ADM. The mean follow-up time in the cohort was 5.8 years and 196 (16%) women had more than 10 years of follow-up.

During the follow-up period 492 deaths occurred, which resulted in a 10-year unadjusted cumulative mortality rate of 48%. Of the patients, 190 died from EC (10-year mortality 17%). Some variation was seen in the unadjusted mortality from EC when the different ADM groups were compared (13% in metformin users to 20% in users of other types of oral ADM). Mortality from other causes was observed to be lower in metformin users than in all the other ADM groups. In particular, the 10-year unadjusted mortality rate from cardiovascular disease was decreased in the metformin group (8%) compared with the users of other types of oral ADM (20%) (Table 11, Figure 8).

In the Cox proportional hazards model advanced age and higher stage of cancer were associated with increased mortality from EC, but no clear difference was seen between the different ADM groups (Table 12). The estimated HR for mortality from

EC was 0.89 (95% CI 0.52–1.5) when metformin users and users of other forms of oral ADM were compared. However, mortality from other causes of death was observed to be lower in metformin users (HR 0.52, 95% CI 0.31–0.88) when compared with users of other types of oral ADM.

Table 10. Baseline characteristics of the patients in the endometrioid EC mortality cohort according to different ADM groups (Study II).

Variable	Other oral ADM[1]	Metformin[1]	Metformin and other oral ADM[1]	Insulin ever	No ADM	Total
Patients, n (%)	147 (12.1)	236 (19.4)	301 (24.8)	316 (26.0)	173 (14.2)	1215 (100)
Median age at diagnosis (IQR[2]), years	75 (69–81)	68 (61–75)	71 (65–77)	71 (64–78)	71 (63–78)	71 (63–78)
Age, n (%)						
30–59 Years	10 (7)	41 (17)	32 (11)	48 (15)	31 (18)	177 (15)
60–69 Years	32 (22)	85 (36)	98 (33)	94 (30)	44 (25)	363 (30)
70–79 Years	55 (37)	81 (34)	122 (41)	109 (34)	67 (39)	448 (37)
80–98 Years	50 (34)	29 (12)	49 (16)	65 (21)	31 (18)	227 (19)
Median duration of T2D (IQR[2]), years	3.8 (2.2–7.2)	3.0 (1.6–5.3)	6.5 (4.0–9.8)	11.4 (8.3–15.2)	7.6 (4.5–12.2)	6.6 (3.1–11.0)
Stage, n (%)						
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] Interquartile range

Table 11. Mortality from various causes of death during the follow-up period in different ADM groups in the endometrioid EC cohort. The entries are absolute numbers of deaths, and 10-year unadjusted cumulative mortality proportions (Study II).

Cause of death (ICD-10 code)	Other oral ADM[1] n (%)	Metformin[1] n (%)	Metformin and other oral ADM[1] n (%)	Insulin ever n (%)	No ADM n (%)	Total n (%)
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

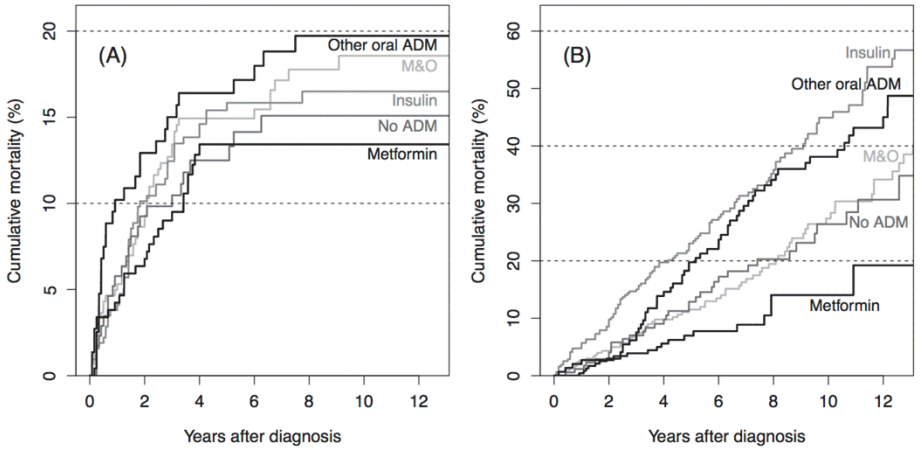


Fig. 8. Cumulative mortality (%) from EC (A) and from other causes of death (B) after diagnosis of endometrioid EC in different ADM groups. The curves are based on unadjusted Aalen–Johansen estimates. Note the different scaling of the vertical axis in (A) and (B). M&O = Metformin and other oral ADM (Study II).

Table 12. Estimated results from Cox proportional hazard models of mortality from endometrioid EC and from other causes of death. The entries are hazard ratios (HRs) and their 95% confidence intervals (CIs) associated with the available prognostic factors. Patients on any oral ADM for less than 180 days were excluded from the analysis (Study II).

Factor	Number of patients	EC HR (95% CI)	Other causes 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 (4.61–13.0)
≥ 85	83	7.78 (3.96–15.3)	15.7 (8.96–27.5)
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	10.3 (7.35–14.5)	1.20 (0.79–1.81)
Unknown	257	2.19 (1.44–3.32)	1.20 (0.91–1.58)
Duration of T2D (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)
ADM			
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

5.3 Metformin, other forms of antidiabetic medication, statins and the incidence and prognosis of non-endometrioid endometrial cancer (Study III)

Incidence. The final cohort consisted of 92 366 women with a total follow-up time of 503 934 person-years at risk and a median follow-up time of 4.6 years. Age range at cohort entry was from 40 to 102 years. Fifty-seven new cases of non-endometrioid EC were observed during the follow-up period. The most common types of histology were serous (n = 27, 47%) and clear-cell (n = 9, 16%) EC. Women who were 85 or older had a higher risk of non-endometrioid EC than women in the other age categories. An increased incidence of EC was detected in the patients with a diagnosis of T2D at least eight years earlier compared with those with a shorter duration of the disease. During follow-up 87% of the patients in the cohort were exposed to some type of ADM. Of the 57 women diagnosed with non-endometrioid EC 38 (67%) were ever-users of metformin, 32 (56%) users of other forms of oral ADM, nine (16%) users of insulin and 20 (35%) users of statins (Table 13). The most commonly used (by number of ever-users in the nested case-control analyses) types of oral ADM other than metformin were SUs (n = 695, 97%). The most frequently used statins were simvastatin (n = 418, 70%), atorvastatin (n = 196, 33%) and fluvastatin (n = 118, 20%).

Table 13. Distribution of person-years at risk in the cohort, numbers of cases and their matched controls, and the unadjusted incidence rates of non-endometrioid EC by age, duration of T2D and ever-use of medications under study. Controls (up to 20 per case) were individually matched for age and duration of T2D for each case (Study III).

Variable	Subgroup	Person-years	Cases n (%)	Controls n (%)	Incidence[1]
Age (years)					
	40–69	187 524	9 (15.8)	188 (16.5)	4.8
	70–74	77 105	12 (21.1)	236 (20.8)	15.6
	75–79	91 366	10 (17.5)	196 (17.3)	10.9
	80–84	81 070	13 (22.8)	251 (22.1)	16.0
	85–102	66 868	13 (22.8)	265 (23.3)	19.4
Duration of T2D (years)					
	1–<3	160 742	13 (22.8)	254 (22.4)	8.1
	3–<5	118 797	11 (19.3)	220 (19.4)	9.3
	5–<8	120 018	13 (22.8)	278 (24.5)	10.8
	≥8	104 377	20 (35.1)	384 (33.8)	19.2
Medication					
Metformin	Ever	321 346	38 (66.7)	754 (66.4)	11.8
	Never	182 588	19 (33.3)	382 (33.6)	10.4
Other oral ADM	Ever	266 791	32 (56.1)	686 (60.4)	12.0
	Never	237 143	25 (43.9)	450 (39.6)	10.5
Insulin	Ever	58 963	9 (15.8)	167 (14.7)	15.3
	Never	444 971	48 (84.2)	969 (85.3)	10.8
Any ADM	Ever	417 726	49 (86.0)	973 (85.7)	11.7
	Never	86 208	8 (14.0)	163 (14.3)	9.3
Statin	Ever	235 758	20 (35.1)	580 (51.1)	8.5
	Never	268 176	37 (64.9)	556 (48.9)	13.8
	Total	503 934	57 (100)	1136 (100)	11.3

[1] Cases/100 000 person-years

In the agreed reference category (age 70–74 years, duration of T2D less than three years, no ADM use) the incidence of non-endometrioid EC was 14 per 100 000 person-years. The risk of non-endometrioid EC was not related to a history of using metformin or other forms of oral ADM in the multiple Poisson regression model. Furthermore, the risk of developing the disease was not seen to differ between ever-users of metformin and those of other types of oral ADM (HR 1.23, 95% CI 0.82–1.85). On the other hand, statin use was linked to a decreased risk of non-endometrioid EC (Table 14).

The nested case–control analyses yielded results that were in line with those of the full-cohort analysis. Ever-use of metformin or other types of oral ADM was not found to be associated with the incidence of non-endometrioid EC. The EC risk was not observed to differ between the ever users of metformin and ever users of other forms of oral ADM (HR 1.20, 95% Cl 0.76–1.89). In agreement with the findings of the full-cohort analysis, statin use was inversely proportional to the risk of developing non-endometrioid EC (Table 14). Furthermore, no evidence for an interaction between metformin and statin use was observed.

Table 14. Unadjusted (HR^u) and adjusted (HR^a, HR^c) estimates of hazard ratios regarding the association between non-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 (Study III).

Ever-use	HR^u [1]	HR^a [2] (95% CI)	HR^c [3] (95% CI)
Other oral ADM	1.14	0.82 (0.47–1.44)	0.76 (0.41–1.39)
Metformin	1.14	1.25 (0.71–2.21)	1.09 (0.59–2.00)
Insulin	1.41	1.24 (0.57–2.68)	1.20 (0.53–2.70)
Statin	0.61	0.53 (0.30–0.93)	0.47 (0.26–0.84)

[1] unadjusted, [2] adjusted from full cohort data for age, duration of T2D and use at any time of other forms of medication, [3] adjusted from nested case-control data for age, duration of T2D and use at any time of other forms of medication

Prognosis. The final cohort consisted of 105 women with T2D who received a diagnosis of non-endometrioid EC. The most frequent histological subtypes were serous (n = 53, 50%) and clear-cell (n = 8, 17%) EC. The patients in the cohort were between 53 and 94 years of age. Baseline characteristics differed between various medication groups. Patients on metformin, and metformin plus other forms of oral ADM were younger compared with the patients in the other ADM groups. Women with metformin only and with other forms of oral ADM only had a shorter duration of T2D (Table 16). Statin users were slightly younger but had a longer history of T2D compared with non-users (Table 15). The most common form of other oral ADM (by number of ever-users in the other oral ADM group) were SUs (n = 11, 92%). Predominantly used subgroups of statins were simvastatin (n = 32, 74%) and atorvastatin (n = 10, 23%).

Table 15. Baseline characteristics of statin users and non-users in the non-endometrioid EC mortality cohort (Study III).

Variable	Statin[1]	No statin	Total
Patients, n (%)	43 (41.0)	62 (59.0)	105 (100)
Median age at diagnosis (IQR[2]), years	73 (67–79)	78 (70–84)	75 (69–82)
Age, n (%)			
< 60	0 (0.0)	4 (6.5)	4 (3.8)
60–69	14 (32.6)	9 (14.5)	23 (21.9)
70–79	19 (44.2)	22 (35.5)	41 (39.0)
≥ 80	10 (23.3)	27 (43.5)	37 (35.2)
Median duration of T2D (IQR[2]), years	11.3 (3.8–15.5)	8.1 (3.3–14.1)	8.4 (3.7–15.4)
Stage, n (%)			
Local	14 (32.6)	23 (37.1)	37 (35.2)
Advanced	23 (53.5)	24 (38.7)	47 (44.8)
Unknown	6 (14.0)	15 (24.2)	21 (20.0)

[1] Duration of medication ≥ 180 days, [2] Interquartile range

A total of 83 deaths was observed in the follow-up period, of which 55 were caused by EC (66%). The cumulative mortality from EC reached 55% and that from other causes over 25% in eight years after EC diagnosis. Some differences could be seen between the medication groups in the unadjusted mortality data (Figure 9), but this probably resulted mainly from chance variation considering the limited group sizes.

Table 16. Baseline characteristics in different ADM groups of the non-endometrioid EC mortality cohort (Study III).

Variable	Other oral ADM[1]	Metformin[1]	Metformin and other oral ADM[1]	Insulin ever	No ADM	Total
Patients, n (%)	12 (11)	21 (20)	26 (25)	26 (25)	18 (17)	105 (100)
Median age at diagnosis (IQR[2]), years	78 (70–84)	73 (66–80)	73 (69–85)	77 (70–81)	77 (72–82)	75 (69–82)
Age, n (%)						
< 60 Years	1 (8.3)	1 (4.8)	1 (3.8)	0 (0.0)	0 (0.0)	4 (3.8)
60–69 Years	2 (17)	7 (33)	6 (23)	6 (23)	2 (11)	23 (22)
70–79 Years	4 (33)	7 (33)	9 (35)	9 (35)	11 (61)	41 (39)
≥ 80 Years	5 (42)	6 (29)	10 (39)	11 (42)	5 (28)	37 (35)
Median duration of T2D (IQR[2]), years	3.5 (1.4–7.8)	3.2 (1.4–4.6)	8.1 (5.4–13)	15 (13–18)	12 (8.2–27)	8.4 (3.7–15)
Stage, n (%)						
Local	6 (50)	8 (38)	8 (31)	10 (39)	5 (28)	37 (35)
Advanced	3 (25)	10 (48)	15 (58)	10 (39)	8 (44)	47 (45)
Unknown	3 (25)	3 (14)	3 (12)	6 (23)	5 (28)	21 (20)

[1] Duration of medication ≥180 days, [2] Interquartile range

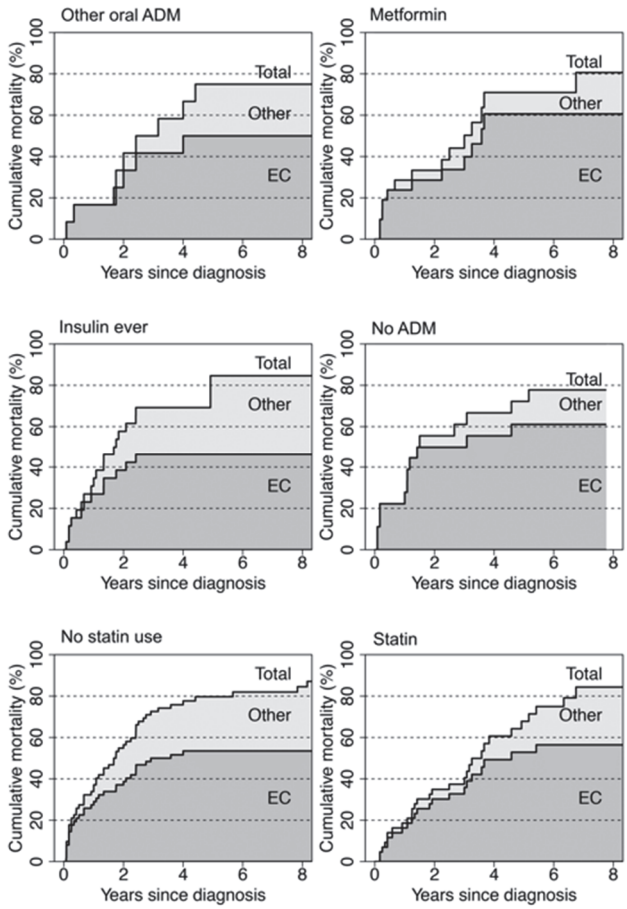


Fig. 9. Cumulative mortality (%) from endometrial cancer (EC) and from other causes of death (Other) after diagnosis of non-endometrioid EC in different medication groups. The curves are based on unadjusted Aalen–Johansen estimates (Study III).

In the Cox proportional hazards model, older age and higher stage were found to be associated with a worse prognosis of non-endometrioid EC, but mortality from EC did not differ between the various ADM groups. No evidence was found for mortality from other causes to be different when the users of metformin and other types of oral ADM were compared. Statin use was correlated with a reduced mortality from non-endometrioid EC (HR 0.41, 95% CI 0.20–0.82) (Table 17).

Table 17. Results from Cox proportional hazards models of mortality from non-endometrioid EC and other causes. The entries are estimated hazard ratios (HRs) and their 95% confidence intervals (CIs) associated with the chosen covariates. Numbers of patients as well as numbers of deaths from non-endometrioid EC and from other causes are presented. Patients on any form of oral ADM or statin for less than 180 days were excluded from the analysis (Study III).

Factor	Number of patients	EC		Other causes	
		Number of deaths	HR (95% CI)	Number of deaths	HR (95% CI)
Age at EC diagnosis (years)					
< 60	4	1	0.57 (0.06–5.98)	0	0 (0–∞)
60–69	23	6	1	7	1
70–79	41	23	2.28 (0.87–5.95)	12	0.83 (0.27–2.61)
≥ 80	37	25	4.18 (1.57–11.17)	9	2.36 (0.61–9.19)
Year of EC diagnosis					
1998–2002	21	8	1	10	1
2003–2007	32	16	1.04 (0.38–2.84)	11	0.91 (0.27–3.02)
2008–2011	52	31	1.29 (0.48–3.47)	7	0.42 (0.11–1.62)
Stage of EC					
Local	37	8	1	14	1
Advanced	47	35	8.73 (3.65–20.89)	9	2.61 (0.84–8.09)
Unknown	21	12	3.89 (1.47–10.30)	5	1.16 (0.35–3.85)
Duration of T2D (years)					
0.5–<3	20	10	1	3	1
3–<6	19	7	0.39 (0.13–1.15)	8	1.77 (0.43–7.30)
6–<12	28	16	0.77 (0.23–2.53)	9	1.75 (0.38–8.12)
12–36	38	22	0.90 (0.24–3.45)	8	0.74 (0.10–5.66)
Medication					
ADM					
Other oral ADM[1]	12	6	1	4	1
Metformin[1]	21	11	1.56 (0.40–6.07)	3	2.09 (0.25–17.59)
Metformin and other oral ADM[1]	26	13	1.03 (0.34–3.11)	10	3.66 (0.92–14.52)
Insulin ever	26	13	0.84 (0.22–3.26)	7	5.98 (0.94–37.98)
None	18	11	1.44 (0.42–4.95)	4	2.43 (0.40–14.81)
Statins[1]					
No	62	34	1	20	1
Yes	43	21	0.41 (0.20–0.82)	8	0.41 (0.12–1.36)

[1] Duration of medication ≥ 180 days

6 Discussion

6.1 Data quality

Reliability and completeness of data is of essential importance in register-based studies. Good coverage of patients with diabetes in FinDM was validated when it was compared with that in a regional diabetes register of the Helsinki Metropolitan area (Sund, Harno, Ranta, & Tolppanen, 2010).

The FCR has been repeatedly demonstrated to hold information on over 95% of cancer cases in Finland (Leinonen et al., 2017; Teppo, Pukkala, & Lehtonen, 1994). Moreover, between 2009 and 2013 the coverage of cancers of the female genital tract in the FCR was estimated to be as high as 97.1%. Furthermore, 99.1% of ECs were morphologically verified and data on only 0.4% of cases were solely based on death certificates (Leinonen et al., 2017).

6.2 Biases in observational cancer studies

Observational studies exploring associations between different types of medication and the risk or prognosis of cancer can be affected by several types of bias. Time-related biases can be particularly present in studies on the incidence of cancer (Klil-Drori et al., 2017; Suissa & Azoulay, 2012; Suissa & Azoulay, 2014). A systematic review and comprehensive bias evaluation of studies addressing the associations between metformin use and cancer risk in patients with T2D showed an unlikely or low risk of bias in only 3/46 of the included studies which did not support a cancer risk-reducing effect of metformin. Moreover, the largest protective effects of metformin were observed in the studies with the highest risk of bias in the definition of metformin exposure (Farmer et al., 2017).

Immortal time bias occurs when exposure to a medication is categorized in a time-fixed manner so that a patient who starts medication during follow-up is thought to use it throughout the whole follow-up time. This can lead to an overestimation of the protective effect of that medication on cancer risk. Immortal time bias can be avoided by treating the exposure to a certain drug as a time-varying variable, as we did in Studies I and III.

Time-window bias results from using time-windows of different lengths between cases and controls when analyzing time-dependent exposures and this can lead to an overestimation of the cancer risk-reducing effect of a medication under

study (Suissa, Dell'aniello, Vahey, & Renoux, 2011). In our case-control analyses of EC incidence we took this into account by matching the cases and controls by age and duration of T2D so that their length of exposure to ADM would be comparable (Studies I and III).

Time-lag bias can become a problem when the associations between medication and the incidence or prognosis of cancer are compared between patient groups who are at different stages of a long-term disease such as diabetes. If the stage or previous treatment of the disease affects the probability of developing cancer or dying from it, the results become biased. In our studies we aimed to minimize time-lag bias by including the entire history of ADM use of the patients in our analysis of EC incidence and by comparing metformin users with users of other oral types of ADM instead of comparing them with the patients on insulin or no ADM.

In ascertainment bias the diagnosis of occult cancers is increased as a result of closer medical surveillance after newly diagnosed diabetes (Johnson et al., 2012). In Studies I and III we diminished this risk by excluding patients who were diagnosed with EC during the first year after receiving diabetes diagnosis.

6.3 Metformin and endometrial cancer (Studies I, II and III)

The incidence of neither EC subtype was found to differ when the ever-users of metformin were compared with the ever-users of other types of oral ADM (Studies I and III). In Study I, metformin use at any time was associated with an increased risk of endometrioid EC compared with no such use. In Study III no evidence was found for the use of metformin at any time to be related to the risk of developing non-endometrioid EC, although the number of cancer cases was low. Thus, we found no evidence to support the hypothesis of an EC risk-reducing effect of metformin (Febbraro, Lengyel, & Romero, 2014). It is notable that the majority of never-users of metformin had used other types of ADM, as less than one fifth of the patients in the case-control analyses had not used any ADM (Studies I and III).

The ever-users of other types of oral ADM were observed to have a higher risk of endometrioid EC compared with never-users (Study I). Since the predominantly used other oral forms of ADM in our cohort were SUs (94.1%), these results are consistent with those of earlier studies suggesting that the use of SUs is related to an increased incidence of cancer (Wu et al., 2015). A trend toward a higher risk of developing endometrioid EC was seen with insulin ever-use (case-control study,

HR 1.22, 95% CI 0.95–1.58) and with increasing cumulative use of insulin. This finding is in line with earlier observations of a cancer-promoting effect of the exogenous use of insulin (Bowker et al., 2010; Carstensen et al., 2012).

In Study II, endometrioid EC-related mortality was not found to be different when metformin users were compared with users of other types of oral ADM in the Cox proportional hazards model. However, mortality from other causes, predominantly cardiovascular diseases, was observed to be lower in the metformin group (adjusted HR 0.52, 95% CI 0.31–0.88). This result is probably influenced by residual confounding associated with unavailable cardiovascular risk factors, many of which are age-related – in our cohort metformin users were younger than the women on other types of oral ADM. Nonetheless, the result is in line with earlier observations of a lower rate of cardiovascular mortality in metformin-treated patients (Selvin et al., 2008). In our study, insulin use was found to be related to an increased risk of mortality from other causes, which could be due to the fact patients with more advanced diabetes have higher rates of cardiovascular complications of the disease (Gamble, Simpson, Eurich, Majumdar, & Johnson, 2010). In Study III, no evidence was found for mortality from non-endometrioid EC or other causes to be different between metformin users and the users of other forms of oral ADM. However, because of low patient numbers, the error margins of the obtained HRs were wide.

Observations of antitumoral effects of metformin at a molecular/cellular level, together with affordable price and good tolerability have evoked the idea of repurposing metformin for the prevention and treatment of different cancer types including EC. Ongoing clinical trials are being carried out to assess the effects of metformin in cases of EC, in combination with other anticancer drugs including carboplatin, paclitaxel, everolimus, letrozole and megestrol acetate (Chae et al., 2016; Febbraro et al., 2014; Irie et al., 2016).

Despite promising preclinical results, most epidemiological studies have not shown evidence for the use of metformin to be associated with the risk of developing EC (Becker et al., 2013; Ko et al., 2015; Luo et al., 2014). The discrepancy between results of preclinical and epidemiological studies may be partly explained by the fact that metformin concentrations used in in vitro models have been well above those seen in clinical use (Dowling et al., 2012). In a Taiwanese study a decreased EC risk in metformin users was reported. However, the prevalence of obesity in the study cohort was less than one percent, while the corresponding rate is around 30% among similar patient groups in Western

countries (Ng et al., 2014). Franchi et al. found metformin use to be connected with an increased incidence of EC, which is in line with our results (Study I). However, this association disappeared when the differences in BMI between the various medication groups were adjusted (Franchi et al., 2017). None of the previous studies have involved analysis of endometrioid and non-endometrioid EC separately. The proportion of patients with diabetes in earlier study cohorts has ranged from five to100 percent and data on the duration of diabetes is often missing. In a study by Luo et al. ADM use was analyzed only at the beginning of follow-up and it was based on self-reported use of medication. In addition, the cumulative amount of ADM use was not analyzed separately (Luo et al., 2014). Neither did Ko et al. (2015) take cumulative ADM use into account, and the median follow-up time was only 1.2 years, predisposing their results to ascertainment bias. Some previous studies may have been influenced by other significant time-related biases (see Section 6.2).

The results of some previous epidemiological studies concerning the association between metformin use and the prognosis of EC have suggested improved overall survival in metformin-treated patients with non-endometrioid histology (Nevadunsky et al., 2014). Metformin use has also been associated with an overall survival benefit in patients with advanced EC (stage III-IV/recurrent), and those on chemotherapy (Ezewuiro et al., 2016). Ko et al. found metformin use to be associated with improved overall survival and recurrence-free survival but not time to recurrence in EC patients (Ko et al., 2014). In contrast, Al Hilli et al. did not observe an association between metformin use and overall survival or progression-free survival in patients with EC when confounding factors were taken into account (Al Hilli et al., 2016). The primary endpoint in the above-mentioned studies was death from all causes, but cause-specific mortality from EC was not analyzed separately. Mortality from non-cancerous causes is common in EC patients, who are generally elderly women with various comorbidities. This is especially true in our cohort of women with T2D, who are at risk of cardiovascular complications of the disease. Furthermore, mortality from other causes is pronounced in cases of endometrioid EC, where the prognosis of cancer itself is better than in the non-endometrioid subtype. Seebacher et al. found no evidence that the use of metformin would be related to overall survival, progression-free survival or cancer-specific mortality in women with EC. However, the number of metformin-treated patients in that study was low (n = 46) (Seebacher et al., 2016).

In addition to the above, earlier studies have been constrained by the lack of information on diagnostic criteria or duration of diabetes, and low numbers of patients. In all studies the use of metformin and other forms of ADM was recorded at the time of diagnosis/recurrence of EC, resulting in missing information about the cumulative dose and duration of medication use (Al Hilli et al., 2016; Ezewuiro et al., 2016; Ko et al., 2014; Nevadunsky et al., 2014; Seebacher et al., 2016). Only Nevadunsky et al. analyzed histological subgroups of endometrioid and non-endometrioid EC separately, and they found improved OS in women with non-endometrioid EC using metformin (Nevadunsky et al., 2014). No association between metformin use and the prognosis of endometrioid EC was found in the study by Seebacher et al., but the number of non-endometrioid EC cases was too small for subgroup analysis. (Seebacher et al., 2016).

6.4 Statins and endometrial cancer (Studies I and III)

In our study statin use was inversely related to the risk of developing both endometrioid (case-control data, HR 0.78, 95% CI 0.65–0.94) and non-endometrioid (case-control data, HR 0.47, 95% CI 0.26–0.84) EC (Studies I and III). Moreover, statin use was observed to be associated with decreased mortality from non-endometrioid EC (HR 0.41, 95% CI 0.20–0.82) but not with mortality from other causes (Study III).

The accumulating evidence of the antitumoral effects of statins, together with their cost-effectiveness and good tolerability makes them a lucrative option to use as preventive and co-treatment agents for different types of cancers (Bathaie et al., 2017; Iannelli et al., 2018). In clinical trials statins have been used in monotherapy settings and in combination with other agents in connection with several cancer types including breast, lung and colon cancer, with encouraging results (Iannelli et al., 2018). A pre-operative window of opportunity trial concerning the effect of atorvastatin on EC cells is currently underway (clinicaltrials.gov 2019).

Only a few epidemiological studies have been conducted to clarify the potential connection between statin use and the risk of EC. Most of them have detected no evidence for an association between statin use and the incidence of EC (Desai et al., 2018; Haukka et al., 2010; Sperling et al., 2017). A large Danish register-based study with 5382 EC patients did not show an association between statin use and the risk of EC. The results were the same when subgroup analysis by histological EC subtype (endometrioid/non-endometrioid) was performed. Compared with our

study population of women with T2D, the prevalence of diabetes in the study was only 8% among EC cases, which could explain the difference between our results (Sperling et al., 2017). In a WHI-based study by Desai et al. no evidence was found for statin use to be related to the risk of developing EC in time-dependent models, and the results remained unchanged for the endometrioid subgroup. However, the number of non-endometrioid EC cases was too small for subtype analysis to be feasible. One weakness of the study was that the data on statin exposure were based on self-reported medication. All EC cases were confirmed by means of a review of medical records (Desai et al., 2018). In agreement with our results, a case-control study by Lavie et al. showed a lower risk of EC after statin use for at least one year. One of the limitations of the study is that data on the risk factors predisposing patients to EC were collected by means of an interview after the diagnosis of EC which increases the risk of recall bias (Lavie et al., 2013).

Statins could have a different influence on EC risk in women with T2D compared with the general population, which could be the reason why our results are not in accordance with those of the majority of previous studies. The anti-cancer potential of different types of statins may also be affected by the pharmacological properties of the drug, e.g. lipid solubility. The most commonly used statins in our case-control analyses exploring the incidence of EC (endometrioid/non-endometrioid, Studies I and III) were (lipophilic) simvastatin and atorvastatin. Interestingly, among the statin drug group, simvastatin has been demonstrated to have an antiproliferative and antimetastatic impact on EC cells *in vitro* (Schointuch et al., 2014).

The results of previous studies on the associations between statin use and the prognosis of EC have been inconsistent, ranging from no association (Sanni et al., 2017; Yoon et al., 2015) to improved OS (Lavie et al., 2013), reduced mortality from EC (Sperling et al., 2018) or from the non-endometrioid subtype only (Nevadunsky et al., 2015), and improved PFS and OS in high-risk EC patients with hyperlipidemia (Feng et al., 2016). The proportion of patients with diabetes in the cohorts was reported in four studies, ranging between 13% and 38% (Feng et al., 2016; Nevadunsky et al., 2015; Sperling et al., 2018; Yoon et al., 2015). Non-endometrioid EC was analyzed separately in the three studies, by Yoon et al. (n = 622), who found no association between post-diagnostic statin use and OS in this patient group (Yoon et al., 2015), Nevadunsky et al. (n = 338) and Sperling et al., both of whom, in line with our results (Study III), observed statin use to be inversely related to cancer-specific mortality from non-endometrioid EC

(Nevadunsky et al., 2015; Sperling et al., 2018). However, in the study by Nevadunsky et al. statin use was defined only at the time of EC diagnosis and data on statin use were unavailable for one fifth of the patients (Nevadunsky et al., 2015). Feng et al. observed superior PFS and OS in hyperlipidemic women with high-risk EC using statins at the time of cancer diagnosis, but no improvement in cancer-specific mortality (Feng et al., 2016). Sanni et al. found no evidence for an association between post-diagnostic statin use and EC prognosis. This result persisted in a sensitivity analysis concerning pre-diagnostic statin use in the year before the diagnosis of EC. A limitation of the study was missing information on the stage of cancer in half of the EC cases (Sanni et al., 2017). The dose–response association between statin use and EC survival was analyzed in two of the studies, with no clear pattern emerging (Sanni et al., 2017; Sperling et al., 2018). Lavie et al. found improved OS in EC patients with post-diagnostic statin use but they did not treat statin exposure as a time-dependent variable, thus leaving a potential for immortal time bias in the results (Lavie et al., 2013).

6.5 Strengths and limitations

One of the major strengths of our study lies in the utilization of a reliable, high-quality nationwide diabetes database including precise information about the types, timing (in relation to EC diagnosis) and cumulative amount (DDDs) of metformin, other types of ADM and statins used during a 15-year time span. In Finland all patients with T2D are diagnosed according to WHO criteria (Alberti & Zimmet, 1998). Data on the duration of T2D are considered to be fairly reliable in FinDM, because all patients are entered in the database when receiving their first reimbursement for any type of ADM, and metformin is recommended to be started at the time of diagnosis of T2D according to national guidelines (Type 2 diabetes: Current Care Guidelines, 2018). Moreover, reliable information about the date of diagnosis and histology of cancer, as well as on causes of death (cancer-related and other causes) was obtained from the FCR. Relatively large cohorts for the analysis of endometrioid EC, incorporating a total of 92 366 women and 590 EC cases regarding the incidence (Study I) and 1215 women as regards mortality from the disease (Study II) constitute another asset of our study. The follow-up times were also relatively long: 5.5 years (mean, Study I), 5.8 years (mean, Study II) and 4.6/2.3 (median, incidence/mortality, Study III) years. Statistical analyses in our

studies were planned carefully to minimize the risk of time-related and other biases which are common in observational studies (see Section 6.2).

One of the limitations in our study is the small number of non-endometrioid EC cases, resulting in relatively wide error margins of the estimated HRs (Study III). Patients with T2D who are treated solely in outpatient primary care outside a hospital setting, and who do not receive any ADM are not entered into FinDM, and thus the exact date of diagnosis of T2D is not available in the database. In addition, categorization of the type of diabetes in FinDM is based on purchases of ADM, which leaves a potential for misclassification. A patient with T2D whose treatment is started with insulin, with no purchases of the types of ADM which stimulate pancreatic insulin secretion, can be falsely classified as having type 1 diabetes. However, this scenario should be rare, because the treatment of T2D is usually started with oral ADM (metformin) and insulin is used in the first-line treatment only temporarily when the patient suffers from difficult symptoms of hyperglycemia (Type 2 diabetes: Current Care Guidelines, 2018). Furthermore, FinDM does not contain information on the BMI of individual patients. In earlier research, metformin users have often been heavier than the other patients with T2D (Currie et al., 2012; Franchi et al., 2017; Ko et al., 2015; Libby et al., 2009), which could bias our results in the direction of a higher incidence of EC in metformin users. The impact of BMI on EC risk may be stronger in connection with the endometrioid subtype compared with non-endometrioid histology (Setiawan et al., 2013).

Another weakness of our study is that we did not have data on the reproductive history, or direct markers of the severity of diabetes (HbA1c, blood glucose/insulin levels) of our cohort members. However, we had information on the duration of T2D and insulin use, which can be considered to be surrogate markers of the severity of diabetes. We did not have access to data on the blood cholesterol levels of the patients using statins. Hysterectomies which were performed before 1987 are not recorded in FinDM, causing a risk that some women with a history of hysterectomy still remain in our EC incidence cohort (Studies I and III). Since the likelihood of hysterectomy is not related to the use of metformin or statins, this should not affect our estimates on the associations between metformin/statin use and the incidence of EC. We were unable to analyze low-grade (grade 1–2) and high-grade (grade 3) endometrioid ECs separately (Studies I and II) or to obtain data on the adjuvant treatments of the EC patients (Studies II and III), because tumor grade and cancer treatment were not recorded in the FCR on a regular basis.

In our study, categorization of patients in the different ADM and statin exposure groups was based on recorded purchases of those drugs. Patients with T2D staying in institutional wards are not reimbursed for their medication, raising the possibility of their being incorrectly classified as no-ADM/no-statin users in FinDM. However, the overall effect of this misclassification on our results should be negligible. One of the limitations considering our results on the association between statin use and the risk and prognosis of EC is the possibility of healthy-user bias, in which the probability of using a certain medication is related to the heath-seeking behavior of the individual. Indeed, a Finnish study of patients with newly-diagnosed diabetes showed statin use to be more frequent among persons with a higher socioeconomic status (Vehko et al., 2013). Furthermore, in the same study the use of lipid-lowering medication increased among women with incident diabetes from 20% to 40% between 2000 and 2006. The same trend was seen in women with coronary heart disease, both preexisting (from 48% to 73%) and coincident with diabetes (from 57% to 75%).

A possible confounder in the estimates of mortality (Studies II and III) is the lack of information on many risk factors connected with mortality from other causes including BMI, smoking, alcohol consumption, typical age-related comorbidities, as well as certain complications of T2D. In Study II, this could have resulted in an overstatement of the beneficial effect on mortality from other causes seen in the metformin group compared with the other oral ADM group, in which the patients were on average older.

7 Conclusions

The following conclusions can be drawn on the basis of the results of this study:

1. We found no evidence to confirm the hypothesis of a beneficial influence of metformin on the risk of endometrioid EC. The risk of developing endometrioid EC was not found to differ between ever-users of metformin and users of other forms of oral ADM. Interestingly, statin use was associated with a decreased incidence of endometrioid EC.
2. Metformin use did not affect the prognosis of endometrioid EC. However, pre-diagnostic metformin use was associated with reduced mortality from other (mainly cardiovascular) causes of death in women diagnosed with T2D and endometrioid EC.
3. Metformin use was not observed to reduce the incidence of or mortality from non-endometrioid EC. However, statin use was associated with a diminished risk and an improved prognosis of non-endometrioid EC. The favorable effect of statins on the prognosis of the rarer, non-endometrioid EC subtype could be explained by the common occurrence of p53 mutations in this cancer type (Kobayashi et al., 2018). However, the results concerning non-endometrioid EC must be interpreted with caution as a result of the small number of EC cases, resulting in wide error margins of the estimated HRs.

8 Future directions

The development of new cancer therapies is expensive and time-consuming, ensuring in the future continuing interest in repurposing existing inexpensive and well-tolerated drugs for the prevention and treatment of cancer. Preclinical studies designed to clarify the molecular-level effects of metformin and statins in cancer cells are needed.

Metformin treatment is used in women with polycystic ovary syndrome, who have an increased risk of endometrial cancer (Trikudanathan, 2015). It would be interesting to study the association between metformin use and the risk of EC in this group of patients.

The National Institute for Health and Welfare is establishing a new national diabetes database which includes information on BMI and other confounding factors, thus increasing the demographic data that can be utilized in future epidemiologic studies involving patients with T2D (Jonsson & Niemi, 2019). Randomized clinical trials of metformin and/or statins as an adjuvant treatment of EC would determine their clinical anti-cancer potential and the combination effect with other anti-cancer therapies.

Original publications

I Arima, R., Marttila, M., Hautakoski, A., Arffman, M., Sund, R., Ilanne-Parikka, P., Kangaskokko, J., Läärä, E., Puistola, U., & Hinkula, M. (2017). Antidiabetic medication, statins and the risk of endometrioid endometrial cancer in patients with type 2 diabetes. *Gynecologic Oncology, 146*(3), 636–641. doi:10.1016/j.ygyno.2017.06.011

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ISBN 978-952-62-2345-2 (Paperback)
ISBN 978-952-62-2346-9 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)