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# The Association of Metformin, Other Antidiabetic Medications, and Statins With the Prognosis of Colon Cancer in Patients With Type 2 Diabetes: A Retrospective Cohort Study

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## Abstract

**Background:** Use of metformin and statins have been associated with improved prognosis of colon cancer (CC) in patients with type 2 diabetes (T2D). We examined the survival from CC in relation to the use of metformin, other oral antidiabetic medications (ADM), insulin, and statins in T2D patients.

**Materials and Methods:** A cohort ( $n = 2252$ ) of persons with pre-existing T2D diagnosed with incident CC between 1998 and 2011 was identified from several Finnish registers. Cox models were fitted for cause-specific mortality rates to obtain adjusted estimates of the hazard ratios (HR) with 95% confidence intervals (CI) in relation to use of ADM and statins before the CC diagnosis. Cox models were also fitted for mortality in relation to post-diagnostic use of the medications treating these as time-dependent exposures, and starting follow-up 1 year after the CC diagnosis

**Results:** Pre- and post-diagnostic metformin use was weakly associated with the risk of CC-related death (HR .75; 95% CI .58-.99, and HR .78; 95% CI .54-1.14, respectively) compared to the use of other oral ADMs. Pre- and post-diagnostic statin use predicted a reduced risk of CC-related death (HR .83; 95% CI .71-.98, and HR .69; 95% CI .54-.89, respectively).

**Conclusion:** Additional evidence was found for use of statins being associated with an improved survival from CC in patients with pre-existing T2D, but for metformin use the evidence was weaker.

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## Keywords

colorectal, malignancy, insulin, survival, mortality

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## Introduction

Colon cancers (CCs) are the fourth most diagnosed cancers worldwide and account for 551 269 deaths globally every year, making CCs the fifth highest cause of cancer deaths.<sup>1</sup> They have been traditionally classified together with rectal cancers (RCs) as colorectal cancers (CRCs), although CC and RC are 2 different disease entities.<sup>2-4</sup>

Type 2 diabetes (T2D) is currently a global pandemic with a prevalence over 450 million cases worldwide.<sup>5</sup> T2D is a risk factor for both the incidence of and mortality from CC.<sup>6-8</sup> This increased mortality may be related to persons with diabetes being diagnosed with cancer at more advanced stages and being treated less intensively when compared to non-diabetic patients.<sup>9</sup> Metformin is the first-line antidiabetic medication used to treat T2D and it has shown multiple preclinically observed anticancer effects.<sup>10</sup> Previous studies<sup>11,12</sup> have also indicated that metformin use is associated with improved survival among CRC patients with T2D.

T2D is a major risk factor for cardiovascular disease (CVD),<sup>13</sup> so patients with T2D are widely prescribed statins, a class of lipid-lowering medications used in the primary prevention of CVD.<sup>14</sup> Statin drugs have also been associated with a reduced overall mortality in CRC patients with T2D, and the benefits of statins have been reported to increase with cumulative exposure.<sup>15</sup> Previous research has demonstrated antitumor effects of statins, and especially of lipophilic statins, *in vitro*.<sup>16,17</sup>

The present study is a retrospective national cohort study that included Finnish persons with type 2 diabetes. Here, we examined the association of survival of CC with the use of metformin, other oral antidiabetic medications, insulin, and statins in persons with T2D. We used a robust study design and multiple high-quality Finnish registers with the aim of uncovering further evidence concerning the hypothesized potential beneficial effects of metformin and statins on CC survival indicated in previous studies. We focused exclusively on CC patients, due to the pathogenetic differences observed between RC and CC.<sup>2-4</sup> We also separately analyzed the left- and right-sided types of CC due to differences in their molecular characteristics and biological backgrounds.<sup>18</sup>

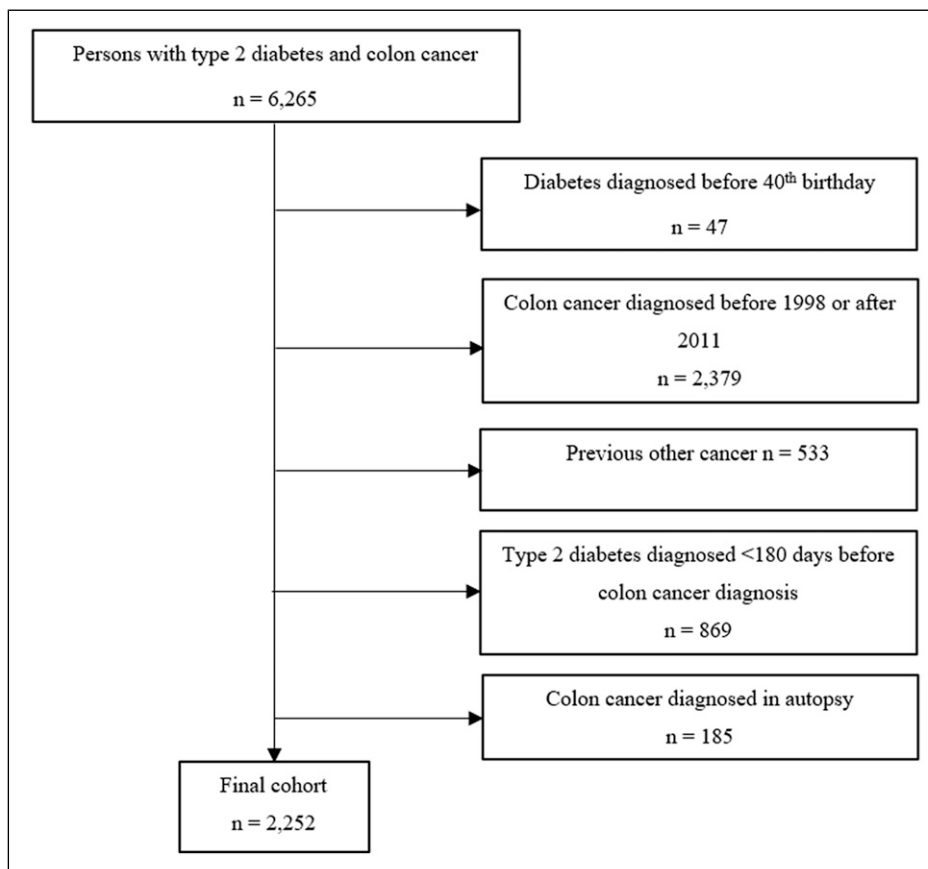
## Materials and Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines on article writing.<sup>19</sup> Data regarding individuals diagnosed with diabetes were acquired from the “Diabetes in Finland”

database (FinDM),<sup>20</sup> which was set up to enable the epidemiological monitoring of diabetes in Finland. This database combines data from multiple registers: the Care Register for Health and the Hospital Discharge Register from the Finnish Institute for Health and Welfare, the Special Reimbursement Register and the Prescription Register from the Social Insurance Institution of Finland, and the Cause of Death Register from Statistics Finland. The Prescription Register contains data about medications prescribed by doctors and reimbursed by the Social Insurance Institution of Finland, so it provides accurate records of purchased drugs since 1994. The diagnosis of diabetes in FinDM is classified using either hospital records (starting in 1969 for inpatients and 1998 for outpatients) or on entitlement to elevated reimbursement for antidiabetic medication (ADM) (since 1964) or a purchase of reimbursed antidiabetic medication. Categorization of type 1 and type 2 diabetes is based mainly on the first reimbursed ADM. This is probably accurate for almost all cases, although a minority of persons with T2D might be classified as having type 1 diabetes due to a prescription for insulin as an acute treatment. Data reliability studies have confirmed that the FinDM shows good coverage against a local register in Southern Finland.<sup>21</sup> Each resident in Finland has a unique personal identity code that is provided at birth or when obtaining citizenship, thereby rendering individuals easily trackable. The size of the study was determined by the available number of eligible patients in the register.

Data on cancer cases were obtained from the Finnish Cancer Registry and linked with FinDM. The Finnish Cancer Registry contains information about almost all cancer cases diagnosed in Finland since 1953, including the date of diagnosis, histology, and morphology.<sup>22</sup> The completeness of the records is estimated to be 96% for solid tumors.<sup>21</sup> The Finnish Cancer Registry receives follow-up data from registers maintained by Statistics Finland, including dates and causes of death. Experts at the Finnish Cancer Registry compare these data to all data available concerning the patient’s cancer and judge whether the death is cancer-related or non-cancer-related. We based our analysis on this judgment.

The cohort selection is presented in the flowchart in [Figure 1](#). We identified 6265 individuals with T2D and CC diagnosis between 1 January 1996 and 31 December 2011. We excluded persons with T2D diagnosed prior to the 40<sup>th</sup> birthday (to minimize the inclusion of hereditary CC cases and T1D cases mislabeled as T2D), persons with CC diagnosed before 1998 or after 2011, persons with another previous cancer diagnosis (except non-melanoma skin cancers ICD-O-3 codes C44 plus M-8090-8095/3, M-8097-8098/3, M-8102/3 and M-8110/3),



**Figure 1.** Flowchart of the cohort selection process.

persons with T2D diagnosed <180 days before the CC diagnosis (inadequate time to assess the effects of T2D and medication use), and CC cases diagnosed at autopsy. Follow-up began after the CC diagnosis. The final cohort contained 2252 persons.

For descriptive analyses and modelling based on pre-diagnostic medications, persons in the cohort were divided into 5 distinct groups according to their ADM usage during the 3 years before the diagnosis of CC: (1) metformin only, (2) other oral ADM only, (3) metformin and other oral ADM, (4) insulin, and (5) no history of regular ADM use. Regardless of the ADM use, the cohort members were also classified into users and non-users of statins. Cumulative medication use was assessed as defined daily doses (DDD) for 3 years prior to the cancer diagnosis. The criterion for oral ADM and statin usage was purchase of the medication for at least 180 days or longer during the 3 years prior to the cancer diagnosis. Purchase periods of ADM or statin under 180 days prior to the diagnosis placed the person in the group of “no history of regular ADM use” or “statin nonuser,” respectively. At least 1 purchase of insulin was sufficient to categorize a patient as belonging to the insulin-users group. Statin use was classified as “yes” if a patient used a statin for at least 180 days. The correctness of personal identity codes, complete name, vital status, possible

date of death, or emigration, as well as the official place of residence before the date of diagnosis, was controlled by regularly linking the data of the Finnish Cancer Registry with the Central Population Register of Finland.<sup>23</sup> Loss to follow-up in these registries is minimal.

In the analyses on the effects of pre-diagnostic use of ADMs, the “other oral ADM only” group was used as the reference group, assuming this to be more comparable to the metformin group than was the “no history of regular ADM use” group. The latter group also includes former diet-controlled patients.

CC was defined as the diagnosis code C18 of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision) and ICD-O-3 (International Classification of Diseases for Oncology) and morphology codes M8000/3, M8010/3, M8140/3, M8210/3, M8260/3, and M8480/3. It includes the following subtypes of CC: cancers of the caecum, appendix, ascending colon, right colic flexure, transverse colon, left colic flexure, sigmoid, and non-defined. Right-sided CC was defined as ICD-10 diagnosis code C18.0-C18.4 and left-sided CC as C18.5-C18.7. C18.9. “Malignant neoplasm of colon, unspecified” is included in the “All colon cancers” analysis, but not in the left-vs right-sided CC analysis.

The stage of CCs was based on the Finnish Cancer Registry's classification as either non-metastasized, metastasized, or unknown. Non-metastasized CCs (stage I–III) include local tumors, tumors that have spread to regional lymph nodes, and tumors that have grown to adjacent tissues but have not metastasized distantly. Metastasized cancers (stage IVA–C) are tumors that have metastasized further than the regional lymph nodes, with or without local advancement to nearby tissues. “Unknown” in this study included CCs with no reliable staging information.

## Statistical Methods

We analyzed the mortality from CC and from other causes of death, respectively, in relation both to the medications used before cancer diagnosis, and to post-diagnostic medications. In the former analyses, the follow-up started on the date of CC diagnosis and ended on the date of death, emigration, or closing of the follow-up on 31 December 2013. The Aalen-Johansen estimator of cumulative incidence function for competing risks was used to describe cumulative mortality from CC and from other causes of death in the different pre-diagnostic ADM groups, as well as among users and non-users of statins. The cause-specific mortality rates were analyzed by the Cox proportional hazard models to obtain estimated hazard ratios (HR) with 95% confidence intervals (CI), adjusting for the confounding effects of age, year, duration of diabetes, and CC stage. Potential differences between the left- and right-sided tumors were assessed by pertinent interaction terms in the models covering all CC patients. A possible nonlinear dose-dependent effect of the medications was assessed by replacing the medication group indicators in the Cox models with cubic spline terms for the total amount of DDDs per medication group. Considering the possibilities that stage at diagnosis could be affected by medication before cancer diagnosis, and that medications could hardly have any effect on metastasized cancers, additional models were fitted, in which stage was not included among the covariates, and in which included were only patients presenting non-localized cancer at diagnosis.

The association between post-diagnostic medication use and mortality from CC and other causes of death, respectively, was analyzed with time-dependent Cox regression models. In these analyses, we only included those patients from the original patient cohort that were still alive and under follow-up on the date, when 1 year had passed since cancer diagnosis. The follow-up also started on that date. The exposure of medication was recorded on a monthly basis starting from the date of CC diagnosis. Exposure to metformin, other oral ADM, and statins, respectively, was each represented as a time-dependent binary indicator variable (use vs non-use) according to the following criteria for being exposed to a given medication at any month: Exposure period of at least 180 days after CC diagnosis was required, and exposure was defined to end 270 days after final purchase of medication.

With regard to insulin, 2 purchases were enough for the person to be categorized as “insulin user” until the end of the follow-up. These time intervals were partly based on the Finnish medical reimbursement system, which encourages 3-month medication purchases. Following variables were included in the model: statin, metformin, other oral ADM and insulin use, sex, stage diabetes duration, current age, and year of diagnosis. Additional analyses were performed on patients with non-metastasized cancer at diagnosis. As we were specifically interested in the contrast between metformin use and use other oral ADMs, we also derived from the pertinent models the point estimates of the hazard ratios (with 95% confidence intervals) associated with this particular contrast.

All statistical analyses were performed with R environment (version 4.1.2).<sup>24</sup> The functions in the “survival” package of R functions were used to compute the Aalen-Johansen estimators of cumulative mortality by cause, to fit the Cox models, and to diagnose possible deviations from the underlying model's assumptions.<sup>24,25</sup> Missing data were encountered only concerning the spread of the cancer, and we labeled these cases as “Unknown” spread.

## Results

The details of the study cohort are presented in [Table 1](#).

A total of 2252 CC cases were collected, with a median follow-up time of 3.1 years and an interquartile range of 1.2 to 6.0 years. Most cancers were diagnosed in the 70–79-year age group (41% of the cases), reflecting the high median age of the study cohort (75 years). Over half of the cases were staged as “metastasized” (52%).

Metformin users were slightly younger, had a shorter diabetes duration, and there were more males and a higher proportion of metastasized cases in that group when compared to the reference group, the users of other oral ADMs.

The median diabetes duration was longer for statin users, and the statin use was more prevalent among males. The most used statins were simvastatin, with 754 users, and atorvastatin, with 389 users ([supplementary Table 1](#)). Both statins are classified as lipophilic statins. The most used other oral ADMs were sulfonylureas, with 279 users that accounted for 91.2% of the other oral ADM group ([supplementary Table 2](#)).

During the follow-up, a total of 1365 deaths occurred in the cohort, with 830 deaths from CC (60.8%) ([Table 2](#)). No large differences were noted in the unadjusted 10-year cumulative mortality from CC between the pre-diagnostic ADM groups: 38% for metformin, 41% for other oral ADM, 39% for metformin and other oral ADM, 40% for insulin, and 41% for no history of regular ADM use ([Figure 2](#)). A clear difference in the 10-year cumulative mortality from CC was found between the users and non-users of statins, at 34% compared to 43%, respectively. No difference was observed in the cumulative mortality from other causes between the medication groups.

In the Cox models for pre-diagnostic medication, metformin use predicted a reduced CC mortality (HR .75; 95% CI .58-.99)

**Table 1.** Characteristics of the study cohort in different antidiabetic medication groups and by statin use based on pre-diagnostic medication use. The entries are numbers (percentages in parentheses) if not otherwise stated.

	Antidiabetic Medication (ADM)					Statin		Total (%)
	Metformin (%)	Other Oral ADM (%)	Metformin and Other Oral ADM (%)	Insulin (%)	No History of Regular ADM Use (%)	Yes (%)	No (%)	
Number of patients	365 (16)	306 (14)	608 (27)	503 (22)	470 (21)	974 (43)	1278 (57)	2252 (100)
Sex								
Male (%)	198 (54)	131 (43)	321 (53)	248 (49)	196 (42)	496 (51)	598 (47)	1094 (49)
Female (%)	167 (46)	175 (57)	287 (47)	255 (51)	274 (58)	478 (49)	680 (53)	1158 (51)
Age groups (years)								
40-59	27 (7)	12 (4)	45 (7)	34 (7)	35 (7)	49 (5)	104 (8)	153 (7)
60-69	113 (31)	43 (14)	152 (25)	120 (24)	107 (23)	260 (27)	275 (22)	535 (24)
70-79	141 (39)	127 (42)	257 (42)	212 (42)	179 (38)	455 (47)	461 (36)	916 (41)
80-100	84 (23)	124 (41)	154 (25)	137 (27)	149 (32)	210 (22)	438 (34)	648 (29)
Median age at colon cancer diagnosis	72	78	75	75	75	75	76	75
Interquartile range	66-80	73-84	68-80	69-81	68-82	68-79	69-82	68-81
Diabetes duration (years)								
.50 ≤ 3	143 (39)	92 (30)	71 (12)	18 (4)	160 (34)	181 (19)	303 (24)	484 (21)
3 ≤ 6	130 (36)	83 (27)	142 (23)	33 (7)	82 (17)	185 (19)	285 (22)	470 (21)
6 ≤ 12	69 (19)	102 (33)	266 (44)	167 (33)	115 (24)	301 (31)	418 (33)	719 (32)
≥ 12	23 (6)	29 (9)	129 (21)	284 (56)	113 (24)	307 (32)	271 (21)	578 (26)
Median	3.6	5.1	7.8	12.9	5.6	8.2	6.6	7.1
Interquartile range	2.2-6.1	2.8-8.3	4.8-11.1	9.2-17.7	1.5-11.5	3.8-13.8	3.1-11.0	3.4-12.2
Stage								
Non-metastasized	127 (35)	106 (35)	191 (31)	179 (36)	157 (33)	369 (38)	391 (31)	760 (34)
Metastasized	199 (55)	132 (43)	323 (53)	268 (53)	255 (54)	499 (51)	499 (51)	1177 (52)
Unknown	39 (11)	68 (22)	94 (15)	56 (11)	58 (12)	106 (11)	209 (16)	315 (14)

**Table 2.** Estimated hazard ratios with 95% confidence intervals related to mortality from colon cancer and from other causes in different sex, year of diagnosis, age, stage, and antidiabetic medication, and statin medication groups during the follow-up for pre-diagnostic medication use. All results are adjusted for the effects of age, year, duration of diabetes, and CC stage.

	Death from Colon Cancer			Death from Other Causes		
	n	Hazard ratio <sup>c</sup>	95% Confidence Interval	n	Hazard Ratio <sup>c</sup>	95% Confidence Interval
<b>Sex</b>						
Female	442	1.00	Reference	283	1.00	Reference
Male	388	1.16	(1.00-1.34)	252	1.48	(1.23-1.77)
<b>Year of diagnosis</b>						
1998-2002	232	1.00	Reference	237	1.00	Reference
2003-2007	294	.87	(.73-1.04)	184	.69	(.56-.85)
2008-2011	304	.83	(.69-1.01)	114	.68	(.52-.89)
<b>Age group (years)</b>						
41-59	60	.83	(.61-1.12)	10	.25	(.13-.48)
60-64	68	.93	(.70-1.25)	23	.47	(.30-.75)
65-69	113	.86	(.67-1.10)	47	.52	(.36-.74)
70-74	144	1.00	Reference	93	1.00	Reference
75-79	154	.83	(.66-1.04)	149	1.55	(1.19-2.01)
80-84	155	1.36	(1.08-1.71)	133	2.83	(2.15-3.72)
85-97	136	1.93	(1.51-2.47)	80	4.21	(3.04-5.83)
<b>Duration of diabetes (years)</b>						
.5-≤3	169	1.00	Reference	102	1.00	Reference
3-<6	178	1.09	(.88-1.35)	94	1.04	(.78-1.38)
6-<12	267	1.05	(.85-1.28)	181	1.17	(.91-1.51)
≥12	216	1.17	(.93-1.47)	158	1.37	(1.03-1.82)
<b>Stage</b>						
Non-metastasized	100	1.00	Reference	254	1.00	Reference
Metastasized	629	5.92	(4.78-7.33)	176	.89	(.73-1.09)
Unknown	101	2.73	(2.06-3.61)	105	.96	(.76-1.21)
<b>ADM<sup>a</sup></b>						
Other oral ADM	125	1.00	Reference	102	1.00	Reference
Metformin	112	.75	(.58-.99)	53	.88	(.62-1.24)
Metformin and other oral ADM	222	.86	(.69-1.08)	143	1.00	(.77-1.31)
Insulin	192	.95	(.74-1.22)	137	1.32	(.98-1.77)
No regular history of ADM <sup>b</sup>	179	.80	(.64-1.02)	100	.80	(.60-1.05)
<b>Statin use<sup>a</sup></b>						
No	533	1.00	Reference	339	1.00	Reference
Yes	297	.83	(.71-.98)	196	1.06	(.88-1.29)

Abbreviation: ADM, antidiabetic medication.

<sup>a</sup>Medication duration >180 days except for insulin which is classified as user or nonuser.

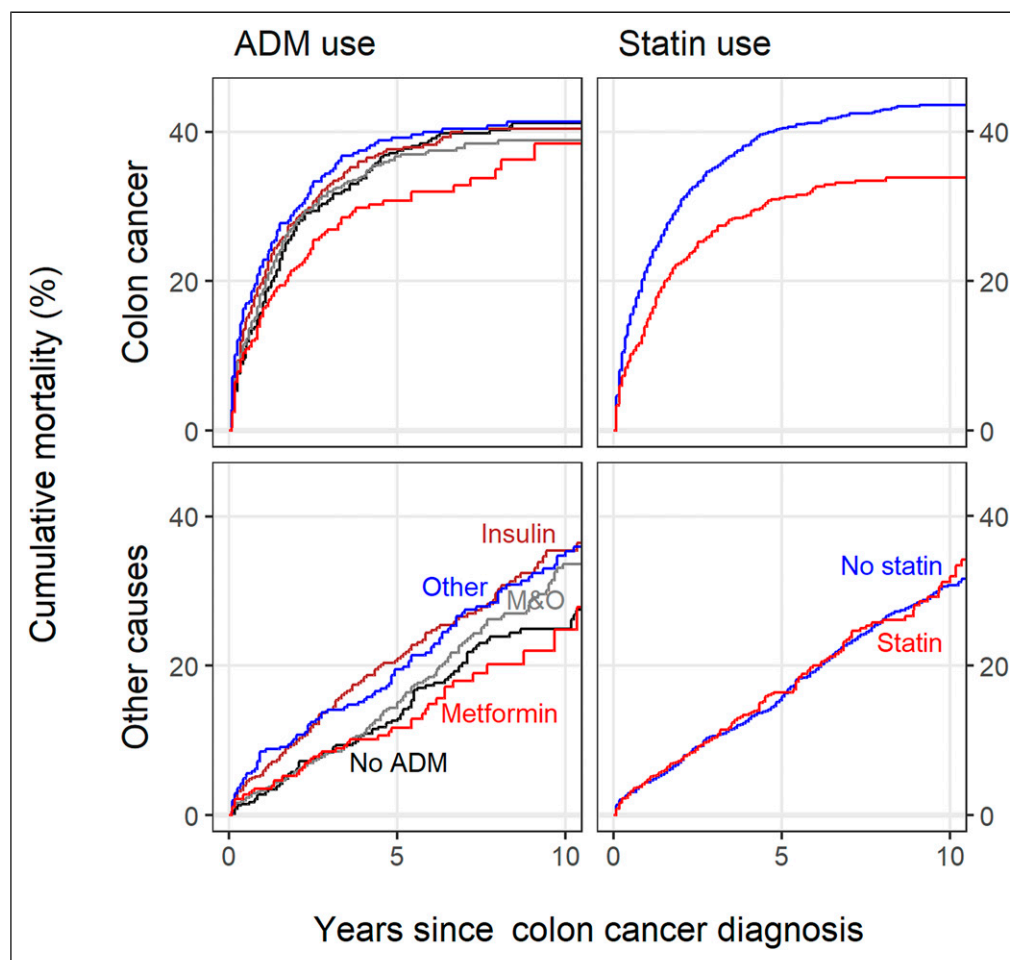
<sup>b</sup>No history of regular ADM use.

<sup>c</sup>Adjusted for the effects of age, year, duration of diabetes, and stage.

when compared to other oral ADM use. Statin use predicted a similar reduction in CC mortality (HR .83; 95% CI .71-.98) when compared to statin nonuse. No evidence was found for an association between insulin use and mortality from CC (HR .95; 95% CI .74-1.22). For other causes of deaths, the results were inconclusive, with wide 95% CIs obtained due to the small number of deaths for metformin use compared to the use of other ADMs (HR .88; 95% CI .62-1.24), as well as for statin use compared to non-use (HR 1.06; 95% CI .88-1.29). Some increased mortality from other causes of death was indicated among the insulin users (HR 1.32 (95%

CI .98-1.77)). The results for the hazard ratios of interest were not different, when stage was left out from the model (data not shown).

When restricted to those patients only, who presented non-metastasized tumor at diagnosed (n = 760), the point estimates of the hazard ratios of interest changed to some degree, but the error margins became substantially wider due to small numbers of cases in this patient group (data not shown). Therefore, no evidence could be found for the associations of the medications with mortality from either cause of being different from the whole original cohort.



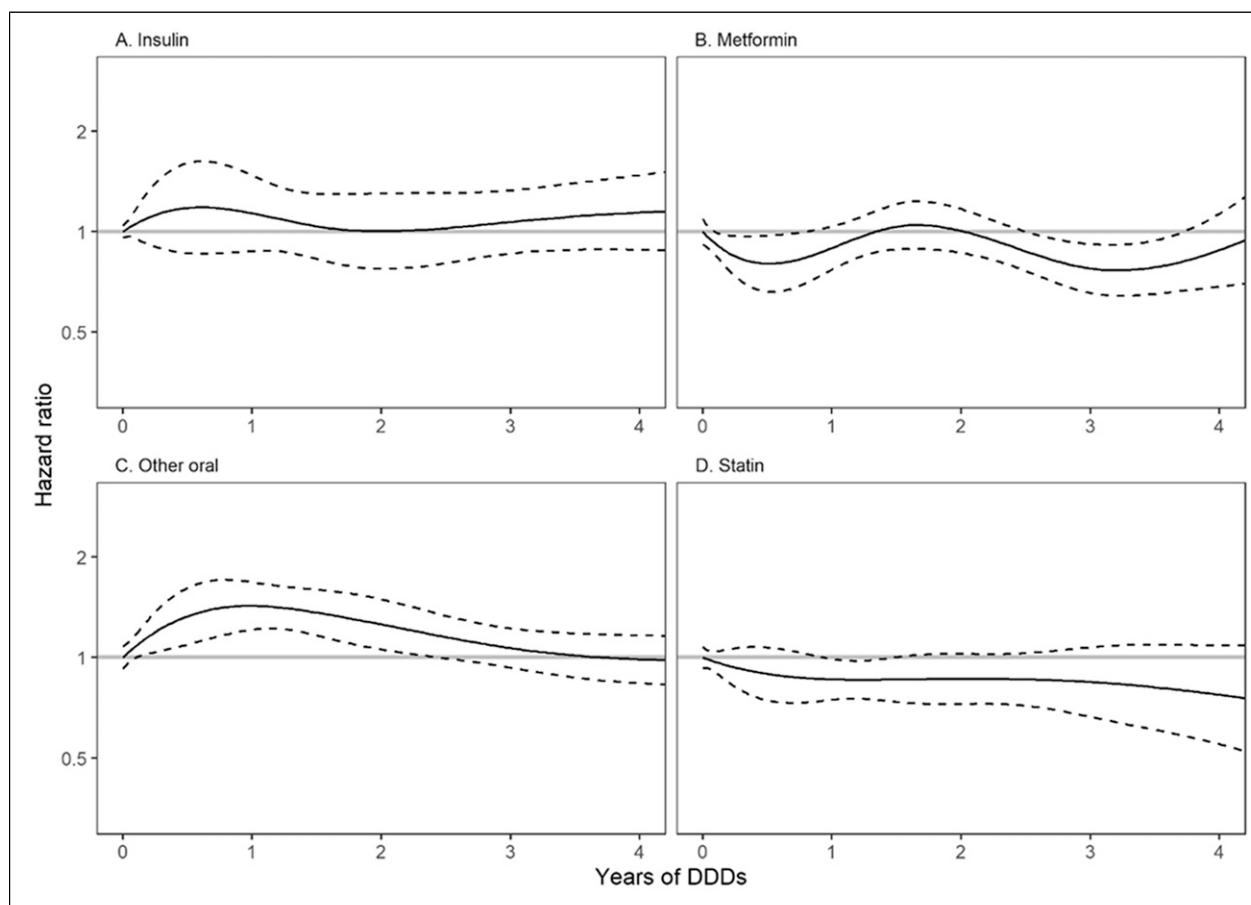
**Figure 2.** Cumulative mortality from colon cancer and from other causes in the different medication groups defined according to pre-diagnostic use. Abbreviations: ADM, antidiabetic medication. Red, metformin, blue, other oral ADM, brown, insulin, gray, metformin and other oral ADM, and black, no history of regular ADM use. Statin: Blue, nonusers; Red, users.

The DDD analysis revealed no clear evidence for an association between the used cumulative amount of any medication and reduced mortality from CC (Figure 3) for pre-diagnostic use. No evidence was discerned for differences between left- and right-sided colon cancers (supplementary Table 3), even after conducting an interaction analysis (data not shown).

Out of the original cohort, 1523 patients survived the first year after the diagnosis of CC. The analyses of mortality in relation to use of post-diagnostic medications comprised these patients only, their follow-up starting 1 year after cancer diagnosis. The results concerning post-diagnostic use vs non-use of the medications of interest with mortality from CC are reported in Table 3. The contrast between use of metformin and that of other oral ADMs, although pointing to the same direction as with pre-diagnostic use, had a wider error margin (HR .78; 95% CI .54-1.14). For post-diagnostic statin use, evidence was found for an association with reduced CC mortality (HR .69; 95% CI .54-.89), concordant with that for pre-diagnostic

use. For other causes of death, use (vs non-use) of metformin, other oral ADM and statin, respectively, appeared to be associated with reduced mortality, while insulin use predicted elevated mortality from these causes (Table 3). The contrast between post-diagnostic use of metformin and that of other oral ADMs appeared more favorable for metformin than in pre-diagnostic use, although inconclusively so (HR .74; .50-1.09). When limiting the analysis to patients with non-metastasized cancer at diagnosis, the point estimates differed somewhat from those above, but the error margins were substantially wider due to small numbers of deaths in this patient group (data not shown). For instance, no discernible contrast between metformin use and use of other oral ADMs was found either in CC mortality (HR .92; 95% CI .34-2.45) or mortality from other causes (HR .96; 95% CI .54-1.70) among these patients. When analyzing the mortality from the 2 causes in relation to cumulative use of any of the medications, no evidence for any monotonic trend could be found (data not shown).





**Figure 3.** Estimated hazard ratios (with pointwise 95% confidence limits) of colon cancer (CC) mortality by cumulative defined daily dose amount of antidiabetic medications and statins during the 3 years preceding CC diagnosis in selected medication groups.

**Table 3.** Hazard ratios with 95% confidence intervals in parentheses, for mortality associated with colon cancer and other causes associated with post-diagnostic medication use.

	Death from CC			Other Cause of Death		
	n*	Hazard Ratio	95% CI	n*	Hazard Ratio	95% CI
Metformin	127	.70	(.55-.89)	92	.54	(.42-.69)
Other oral ADM	118	.89	(.70-1.14)	104	.73	(.57-.93)
Insulin	93	1.12	(.86-1.46)	122	1.23	(.96-1.57)
Statin	93	.69	(.54-.89)	97	.63	(.49-.81)

Abbreviation: CC, colon cancer, ADM, antidiabetic medication, 95% CI, 95% confidence interval.

\*Number of deaths when being exposed to the pertinent medication.

## Discussion

We found some evidence for an association of the use of metformin with a reduced disease-specific mortality after diagnosis of colon cancer (CC) in persons with previously diagnosed type 2 diabetes (T2D) when compared to use of other oral antidiabetic medications (ADM), this evidence being stronger for pre-diagnostic use than post-diagnostic use. No conclusive evidence was discerned for an association of

the use of metformin with mortality from other causes, although the results were compatible with reduced mortality within the limits of the usual error margin. Insulin use was associated with an increased mortality from other causes. Both pre-diagnostic and post-diagnostic statin use appeared to be associated with reduced CC mortality, but mixed results were found for other causes of death.

Previous studies<sup>6-8</sup> have reported elevated disease-specific mortality in CC patients with pre-existing T2D, and some

evidence exists for shared negative prognostic factors,<sup>26</sup> including old age, smoking, diet, physical inactivity, and obesity. The clinical interaction between T2D and CC is complex, as an earlier stage CC might be discovered in persons with comorbidities due to increased contact with the healthcare system that leads to earlier detection and improved survival; however, the treatment might be less intensive.<sup>26</sup>

Improved overall survival and reduced disease-specific mortality in patients with both CRC and T2D has been associated with metformin use in 4 recent meta-analyses<sup>11,12,27,28</sup> and in 1 observational study not included in the meta-analyses.<sup>29</sup> Our results were inconclusive regarding an association of metformin with the mortality from causes other than CC, but the error margin of the HR was wide. Some observational studies concerning metformin and cancer have been criticized for overestimating the effect of metformin due to various biases, including time-window and immortal time biases, and a failure to adjust for baseline disease severity.<sup>30-32</sup> We examined medication use before CC diagnosis; thereby reducing the risk of time-related biases.

One would expect that if any of the medications of interest had any effect on the prognosis of CC cancer, it would be more pronounced in non-metastasized patients. When limiting the analysis to these patients, we were not able to extract any useful statistical information concerning such an effect. Inclusion of localized cases led to a substantial reduction of the number of outcome events implying wide confidence intervals. Another study comparing metformin users to nonusers in stage II-III curatively resected CCs with standard adjuvant therapy found that metformin nonusers had worse outcomes when compared to nondiabetics than metformin users.<sup>33</sup> The study group was similar to ours, although our classification also included stage I cases. Three other studies focusing on post-diagnostic use in all CC stages found either reduced cancer specific mortality,<sup>34</sup> reduced cancer specific mortality in women-only study<sup>35</sup> and no association in a study with similar methodology to ours.<sup>36</sup> A high metformin medication adherence has been associated with reduced cancer specific mortality when compared to low adherence.<sup>37</sup>

Multiple anticancer effects have been reported for metformin *in vitro*.<sup>10</sup> Its main effects are exerted through the reversible inhibition of mitochondrial complex I and the activation of AMP-activated protein kinase (AMPK), although the inhibition of mitochondrial complex I might occur only with suprapharmacological doses.<sup>38,39</sup> Part of the potential anticancer effect of metformin is hypothesized to be mediated through systemic effects, such as reduced blood glucose levels, improved insulin sensitivity, and diminished pro-inflammatory cytokine levels.<sup>40</sup> Direct intracellular effects could include AMPK-dependent cell-cycle arrest, stabilization of p53, and inhibition of the mammalian target of rapamycin (mTOR) pathway.

We could not find any evidence for an association between insulin and disease-specific mortality in CC patients with pre-existing T2D in our study, but an association was detected

between an elevated risk of death from other causes and insulin use. Insulin use has been associated with increased overall mortality in persons with T2D and CRC,<sup>41</sup> and hyperinsulinaemia has been hypothesized to promote cancer growth. Synthetic insulin analogs, and especially those that are long-acting, might have a cancer-promoting effect due to prolonged receptor activation and diverse receptor interactions relative to endogenous insulin.<sup>42</sup>

In our study cohort, the most commonly used other oral ADMs were sulfonylureas. Sulfonylureas have been associated with an increased general cancer mortality,<sup>43</sup> while dipeptidyl peptidase-4 inhibitors might be associated with reduced CRC cancer mortality.<sup>44</sup> No evidence was found in 1 study for an association of thiazolidinediones or sulfonylureas with CRC mortality in persons with T2D.<sup>36</sup>

Pre- and post-diagnostic statin use was found to be associated with reduced cancer-specific mortality in our study, but the evidence with regard to mortality from other causes was inconsistent. This finding regarding CC mortality is consistent with 3 previous studies that investigated persons with CRC and T2D<sup>15,45,46</sup>; 1 of these studies was also conducted among Finnish patients with diabetes<sup>45</sup> but included persons with type 1 and with type 2 diabetes. Three large meta-analyses have found an association between statin use and reduced CRC mortality in the general population,<sup>47-49</sup> whereas 2 clinical trials failed to show any benefit of simvastatin addition to first-line chemotherapy in metastatic, nondiabetic CRC patients.<sup>50,51</sup> We compared statin users to nonusers, as no comparable group taking other lipid lowering medications was available. This introduces the possibility of a healthy user bias, which might affect our results: persons choosing to use a medication are more likely to be health-conscious and have a healthier lifestyle and to seek out healthcare services, thus leading to earlier detection and reduced CC specific mortality and mortality from other causes.

The possible anticancer effects of statins include the inhibition of the cell cycle through multiple proteins involved in that cycle, the induction of cancer cell apoptosis through intrinsic and extrinsic pathways, and the inhibition of cholesterol synthesis.<sup>17</sup> Cancer cells have a higher need for isoprenoids and cholesterol, which makes them more sensitive to the cholesterol-depleting and isoprenoid-depleting effects of statins. Hydrophilic statins accumulate mainly in the liver, whereas hydrophobic statins also penetrate extrahepatic tissue, and thus have a greater anticancer effect. The majority of persons in our cohort used hydrophobic statins.

Cancers of the left- and right-side colon differ in their physiological characteristics and in their genetic basis.<sup>18,52</sup> Their prognosis therefore also differs, and treatment in the metastatic setting also varies.<sup>53</sup> We found no evidence of a difference in the hazard ratios for the various medications between the left and right sides. However, the error margins for the comparisons between the sides were wide. One observational study previously analyzed the effect of sidedness of CC on T2D patients but also found no evidence for a

difference in survival.<sup>30</sup> A subanalysis of the TOSCA clinical trial also revealed no difference between the effect of metformin use on survival and colon cancer sidedness<sup>54</sup> in patients with stage III resected colon cancers, in line with our results.

Our population had a high proportion of metastasized cancers (52%). The proportion was similar in the other large registry study concerning persons with diabetes and cancer conducted in Finland,<sup>31</sup> and in the Finnish general population.<sup>55</sup> This led to our follow-up time being on the shorter end of studies concerning metformin, T2D, and CRC due to the unfavorable prognosis of metastasized CCs. Previous studies concerning diabetes and CC stage at diagnosis have found that persons with diabetes present with a similar stage<sup>56</sup> or less advanced cancers<sup>57</sup> compared to the general population. One possible explanation is that persons with diabetes have more contact with the healthcare system, thus leading to earlier detection.<sup>2,57</sup> We found that medication use and stage at diagnosis were independent and therefore should not affect our results. Asymptomatic patients are rarely screened in Finland, and no routine screening program for CCs was in place during our study period. Therefore, we expect no screening bias in this population.

Six previous studies have assessed the effect of metformin and survival and have classified metformin use dichotomously as either “yes” or “no,” with no information concerning any criteria for metformin use.<sup>11,27,29,45,58,59</sup> Previous studies have used various criteria of the duration of metformin use in the inclusion of patients. We required at least 6 months of medication use for both ADMs and statins during the 3 years prior to the CC diagnosis and for post-diagnostic exposure.

One limitation of our study was the lack of information regarding many relevant prognostic factors, such as BMI and HbA1C, which can indicate the severity of T2D. We only had register data and no information about the socioeconomic status or lifestyle factors, and only limited information about other concomitant diseases. Thus, the possibility remains for residual confounding due to unmeasured factors associated with medication and affecting the prognosis of CC. The Finnish cancer registry contains only sparse data about cancer care and cancer staging, as it labels cases as either “non-metastasized,” “metastasized,” or “unknown.”

The strengths of this study are its large cohort from high-quality registers and a study design that minimizes risk related to several biases. The Finnish registers are comprehensive, and the data are high quality and reliable.<sup>23,60,61</sup> The number of metformin users (365) and statin users (974) in our cohort was reasonable when compared to previous studies concerning antidiabetic medication, statin use, and CRC. We had accurate data on medication use and DDD available. We could adjust for diabetes duration, amount of drug usage, age, and gender. The study cohort represents all persons with type 2 diabetes and all colon cancers in Finland during our study period. We analyzed survival for both left-sided and right-sided CCs separately and had high-quality data that were able to distinguish deaths from CC and from other causes from the Finnish Cancer Registry. We also analyzed post-diagnostic medication use and its association with mortality.

The generalizability of our results is supported by the high-quality data from a nationally representative study population and by a robust study design. However, its generalizability is hindered by the unique qualities of the Finnish healthcare system and population.

## Conclusion

Our findings provide additional evidence that the use of statins, pre-diagnostic or post-diagnostic, is associated with a better prognosis for colon cancer in persons with pre-existing T2D. Weaker evidence of similar direction was observed for the use of metformin.

## Abbreviations

ADM = Antidiabetic medication

CC = colon cancer

CRC = colorectal cancer

CI = confidence interval

CRC = colorectal cancer

VD = cardiovascular disease

DDD = defined daily dose

FinDM = “Diabetes in Finland” database

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A

HR = hazard ratio

ICD-O-3 = International Classification of Diseases for Oncology, 3rd edition

ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision

RC = rectal cancer

STROBE = Strengthening the Reporting of Observational studies in Epidemiology

T2D = type 2 diabetes

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Orion Corporation had no role in the study design; collection, analysis, and interpretation of the data; writing this report; or decision to submit the article for publication.

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## Ethical Approval

“Diabetes in Finland” database has obtained Ethical approval from the Ethics Committee of the National Institute for Health and Welfare (30th of January 2014, proceeding \$609). Data on individual persons in FinDM is stored according to Finnish

data-protection legislation. The data received by the research group were anonymized such that personal identity codes were converted into unidentifiable codes.

### Statement of Human and Animal rights

This article does not contain any studies with human or animal subjects.

### Statement of Informed Consent

Informed consent for patient information to be published in this article was not obtained because this was a registry study.

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### Supplemental Material

Supplemental material for this article is available online.

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