FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Anti-platelet and Anti-coagulant Prescriptions and Breast Cancer Recurrence: a Danish Nationwide Prospective Cohort Study

Research year report

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Preface

The present report is based on a study conducted during my research year at the Department if Clinical Epidemiology, Aarhus University Hospital, Denmark.

First of all, I would like to express my deepest gratitude to my supervisor, Deirdre Cronin Fenton, who have been very supportive and enthusiastic about my project throughout my research year. You have been an outstanding teacher and have given me a great introduction to the world of epidemiological research. You have been patient, welcoming and indispensable throughout the year.

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Abbreviations

ATC	Anatomical Therapeutic Chemical classification system
BCS	Breast-conserving surgery
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRS	Civil Registration System
DBCG	Danish Breast Cancer Group
DNPR	Danish National Prescription Registry
DNRP	Danish National Registry of Patients
ER	Estrogen receptor
ET	Endocrine therapy
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
PY	Person-years
RFS	Recurrence-free survival

Contents

Abstract

Background: Laboratory studies suggest that drugs that inhibit platelets and coagulation impair the growth and dissemination of breast cancer cells. Use of antiplatelet and anticoagulant prescription drugs therefore may improve breast cancer prognosis. We investigated the association of these drugs with breast cancer recurrence.

Methods: We included all women diagnosed with early-stage breast cancer (1996-2008) in the Danish Breast Cancer Group (DBCG) registry. We retrieved information on antiplatelet and vitamin K antagonist (VKA) prescriptions from the National Prescription Registry, and information on breast cancer recurrence from the DBCG. Follow-up began on the breast cancer diagnosis date and continued to breast cancer recurrence, emigration, death, or 31 December 2012, whichever occurred first. We used Cox regression models to estimate hazard ratios (HRs) and associated 95% confidence intervals (95%CI) associating drug exposure with recurrence, adjusting for potential confounders. Antiplatelet and VKA prescriptions were modelled as time-varying exposures lagged by one year. We assessed peri-surgical exposure as drug use within 30 days of breast cancer surgery.

Results: We identified 34,478 patients with 234,706 person-years of follow-up (median=7.1 years), during which 5,355 recurrences were diagnosed. 1,496 (4%) and 1,619 (5%) women received at least one prescription for platelet inhibitors and VKAs, respectively. We observed no evidence of an association between exposure to either platelet inhibitors [$HR_{adjusted}$= 0.88 (95%CI=0.68-1.15)], or VKAs [$HR_{adjusted}$=1.17 (95%CI=0.95-1.44)] and recurrence. However, peri-surgical exposure to platelet inhibitors correlated with a decreased recurrence rate: adjusted $HR_{any\ platelet\ inhibitor}$=0.68, 95% CI=0.47-1.00.

Conclusions: Our study suggests no notable reduction in breast cancer recurrence associated with prescriptions for platelet inhibitors and VKAs. Platelet inhibitor prescriptions around the time of primary surgery correlated with a decreased rate of recurrence.

Dansk resume

Baggrund: Laboratorieforsøg indikerer at lægemidler der hæmmer blodpladerne og koagulationsfaktorerne hindrer vækst og spredning af brystkræftceller. Brugen af pladehæmmende og koagulationshæmmende lægemidler kan derfor potentielt forbedre prognosen blandt brystcancerpatienter.

Metoder: Vi inkluderede alle kvinder med brystkræft på et tidligt stadie (1996-2008) fra Danish Breast Cancer Group (DBCG) registret. Vi hentede information om pladehæmmer og vitamin K antagonist (VKA) lægemiddelrecepter fra det nationale lægemiddelregister, og information om brystcancer tilbagefald fra DBCG. Follow-up begyndte på dagen for brystcancerdiagnosen og fortsatte til det første af brystcancertilbagefald, emigration, død eller 31 december 2012. Vi brugte Cox regressionsmodeller til at estimere hazardratioer (HRs), og tilhørende 95% konfidensintervaller, for sammenhængen mellem lægemiddeleksponering og brystcancertilbagefald, med justering for potentielle confoundere. Pladehæmmende og vitamin K antagonist (VKA) lægemiddelrecepter blev kodet som tidsvarierende eksponeringer med et års forsinkelse. Vi brugte et vindue på 30 dage til at definere eksponering af lægemidlerne i forbindelse med brystcanceroperationen.

Resultater: Vi identificerede 34.478 patienter med 234.706 års samlet follow-up (median=7,1 år), hvor der blev diagnosticeret 5.355 brystcancertilbagefald. 1.496 (4%) og 1.619 (5%) kvinder modtog mindst en recept for hhv. pladehæmmere og VKAer. Vi observerede ikke evidens for en sammenhæng mellem hverken pladehæmmere [$HR_{justeret}$= 0,88 (95%CI=0,68-1,15)], eller VKAer [$HR_{justeret}$=1,17 (95%CI=0,95-1,44)] og brystcancertilbagefald. Til gengæld, fandt vi en nedsat rate af brystcancertilbagefald blandt kvinder eksponeret i forbindelse med deres brystcanceroperation: justeret $HR_{pladehæmmere}$=0,68, 95% CI=0,47-1,00.

Konklusion: Vores studie peger ikke på nogen nævneværdig reduktion I brystcancertilbagefald associeret med receptor for pladehæmmere eller VKAer. Recepter for pladehæmmende medicin givet omkring operationstidspunktet var korreleret med en nedsat rate af tilbagefald.

Introduction

Platelet inhibitors are widely used to prevent occlusive arterial disease.[1-3] Their mechanism of action includes phosphodiesterase inhibition, ADP receptor antagonism and cyclooxygenase inhibition.[4] Vitamin K antagonists (VKAs) prevent recycling of vitamin K resulting in reduced production of coagulation factors,[5,6] thereby decreasing the risk of occlusive venous diseases.

Cell line and animal models show that platelets stimulate tumor growth and dissemination in a number of ways.[4] Platelets can surround circulating tumor cells,[7-11] thereby preventing immune detection, mediating cancer-endothelial cell interaction, and promoting migration through the vasculature and distant metastasis. Platelets also release growth factors creating a pro-angiogenic tumor microenvironment.[12-15] Animal models of several cancer types suggest that inhibiting the P2Y12 receptor, the target of the platelet inhibitor clopidogrel, correlates with decreased invasiveness, higher chemotherapeutic drug dose at the tumor site, and longer survival.[16-19] Drugs that inhibit platelet function, therefore, may prevent tumor dissemination. However, the evidence from epidemiological studies is conflicting.[20-25] Several studies have focused on aspirin, with no clear or consistent association.[20-24] Few have specifically investigated the use of non-aspirin platelet inhibitors and breast cancer prognosis. A recent English study found no association between clopidogrel prescriptions and breast cancer specific mortality.[25] A phase II randomized trial failed to find an association between clopidogrel prescriptions and circulating tumor cells among 42 metastatic breast cancer patients, but included only one month of follow-up.[26]

Preclinical studies in lung and breast tumor models also suggest that warfarin prevents cancer dissemination.[27-31] A 2014 consensus statement highlighted the potential anti-cancer properties of warfarin.[32] However, a review and meta-analysis of five randomized clinical trials of oral anticoagulants in cancer patients without overt venous thromboembolism showed no association with all-cause mortality.[33] However, the studies were small, had limited follow-up, and included patients with metastatic disease so could not estimate the potential effect of oral anticoagulants on cancer recurrence.[34-38] A recent study using data from the Clinical Practice Research Database in the United Kingdom investigated the association of warfarin with cancer specific mortality among patients with breast, colorectal, prostate and lung cancers.[5] While their overall findings showed no association between warfarin prescriptions and cancer specific mortality, the study showed a slight, imprecise reduction in breast cancer specific mortality among users of 12 or more warfarin prescriptions.

Platelet inhibitors and VKAs are known to decrease the risk of mortality due to cardiovascular disease,[39] so the previous studies that assessed mortality rather than recurrence have not facilitated an investigation of the potential effect of the drugs on cancer recurrence. Assessing mortality rather than recurrence may misclassify the potential effect of the drugs on cancer recurrence, which predisposes patients to mortality, with effect of the drugs on mortality through other causes. We therefore conducted a large population-based cohort study examining the association between prescriptions for platelet inhibitors and VKAs and breast cancer recurrence.

Methods

Setting

We conducted a Danish nationwide prospective cohort study using a combination of population-based registries. Since 1968 all residents of Denmark have been registered in the Danish Civil Registration System (CRS).[40,41] The CRS includes information on vital status, emigration status, and a unique 10-digit identification number (the civil personal registration (CPR) number), that allowed us to link each person in the study across five different databases: the Danish Breast Cancer Group (DBCG), the Danish National Prescription Registry (DNPR), the Danish National Registry of Patients (DNRP), the Danish Cause of Death Registry (DCDR) and the CRS.

Source population and data collection

Our study population included all Danish women with an incident diagnosis of non-metastatic invasive breast cancer who were registered in the DBCG between 1996 and 2008. Since 1977, most cases of invasive breast cancer have been reported to the DBCG database.[42] The completeness of the registry increased from 87% in 1986 to 92% in 2013.[43,44] Data on tumor, treatment, and patient characteristics are reported by treating physicians using standardized forms. Patients are examined for recurrence twice a year for the first 5 years after initial surgery, and once a year 5-10 years after diagnosis.[43] Patients presenting with recurrence between examinations are also reported to the registry.[43] We used the DBCG database to ascertain age and menopausal status at diagnosis, World Health Organization (WHO) histological type and grade, lymph node status, tumor estrogen receptor (ER) status, type of primary surgery (mastectomy or breast-conserving surgery), chemotherapy, radiation therapy, endocrine therapy (ET), date and site of recurrence.

We used the DNPR to ascertain prescriptions for exposure drugs and potentially confounding co-prescriptions. For each prescription filled, the DNPR records the drug's Anatomical Therapeutic Chemical (ATC) code, the date the prescription was redeemed, the patient's CPR number, and the strength and quantity of tablets dispensed.[45] We ascertained all prescriptions for the following drugs for members of the study population: anticoagulants (VKAs), platelet inhibitors, simvastatin and hormone replacement therapy (estrogen and progestogen) (see Appendix for drug codes).

We used the DNRP to retrieve information on comorbid disease prevalent at the time of breast cancer diagnosis. Since its establishment in 1977, this registry has registered information about all non-psychiatric hospital admissions in Denmark.[46] Each admission record includes up to 20 different diagnoses, encoded by International Classification of Diseases (ICD) conventions. We pulled out codes necessary for calculation of the Charlson comorbidity index of disease[47].

We used the DCDR to acquire information on breast cancer specific mortality. Since 1970, the DCDR has collected data from death certificates of all Danish citizens. The register holds information on the CPR number, date of death, primary cause of death, and up to four contributory causes of death, coded according to the ICD-10 (ICD tenth revision).[48]

Definitions of analytic variables

Age at diagnosis was divided into three categories (≤59, 60-69 and ≥70) for descriptive purposes and used as a continuous variable in multivariate models. Menopausal status (pre or post) was ascertained at the time of diagnosis from the DBCG. UICC stage was defined according to the TNM classification. Histological grade was defined as low, medium, or high. Estrogen receptor (ER) status and endocrine treatment (ET) were summarized as follows: ER+/ET-, ER-/ET+, ER+/ET+, and ER-/ET-. We defined primary therapy as mastectomy with radiotherapy, mastectomy without radiotherapy, or breast conserving surgery with radiotherapy. We excluded 21 patients who were registered by the DBCG but did not undergo surgery. Adjuvant chemotherapy was defined dichotomously according to indication.

We used two different approaches to account for comorbidity in our analysis. First, we computed the Charlson Comorbidity Index[49] based on all disease categories from the DNRP. Second, we modelled dichotomous indicators for the diseases most likely to be associated with our exposure drugs (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease).

Breast cancer recurrence was ascertained from DBCG and defined as any local, regional, or distant recurrence, or contralateral breast cancer. Subjects were followed from the date of breast cancer surgery until the first of breast cancer recurrence (or mortality), death, or emigration, accrual of ten years of follow-up, or 1 January 2013 (the end of follow-up).

We considered four main exposure groups: VKAs (warfarin and phenprocoumon), platelet inhibitors (clopidogrel, dipyridamole, dipyridamole/aspirin combination therapy, ticagrelor, and prasugrel), exclusive clopidogrel use, and exclusive dipyridamole use. For the exclusive exposure groups, we

removed any patients with prescriptions for platelet inhibitors other than the index drug. We modelled the prescriptions as time-varying exposures (see appendix for detailed description).

We defined longitudinal exposure to platelet inhibitors and VKAs in three ways. First, we defined current use versus non-use for the four medication groups as exposure to one or more prescriptions for the drugs, modelled as a time-varying exposure lagged by one year. Second, to prevent any residual effect former exposure may have in the never exposed group, we modelled current versus former versus never use. The former group comprises person-time among patients who were exposed during follow-up but whose exposed person-time lapsed due to the end of a prescription period (Figure 1). Finally, we defined perioperative exposure as use of the drug in question ±30 days from the date of breast cancer surgery. Our co-medications (aspirin and simvastatin) were coded using the same time varying method lagged by one year. Combination hormone therapy was defined as a baseline covariate.

As a supplementary analysis we estimated drug associations with all-cause mortality and breast cancer specific mortality.

To investigate unmeasured confounding, we made a sub-analysis changing the reference group to VKA users by excluding all patients without prescriptions for VKA's, platelet inhibitors and patients with prescriptions for both.

Statistical methods

We tabulated the frequency and proportion of patients, recurrences, and person-time at risk according to ever / never use of exposure drugs and demographic, tumor, and treatment characteristics. We fit Cox proportional hazards regression models to estimate crude and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (95%CI) for the association between the exposure drugs and breast cancer recurrence, all-cause mortality, and breast cancer specific mortality. We conducted two multivariate analyses. The first based variable selection on a directed acyclic graph[51] (see appendix) and adjusted for age (modelled as a continuous variable), comorbidity (modelled as a categorical variable with 3 groups), aspirin use, and simvastatin use. The second variables were selected *a priori* based on literature search and clinical knowledge and included additional adjustment for age, Charlson score, aspirin, simvastatin, surgery type, menopause, chemotherapy, stage, histology, ER/ET status, and prediagnostic hormone replacement therapy.

All statistical analyses were carried out with STATA 14.0. All statistical tests were two-sided ($\alpha = 0.05$)

Results

We included 34,478 female breast cancer patients diagnosed between 1996 and 2008. Overall 1,697 (4.92%), 1,492 (4.33%), 555 (1.61%), and 786 (2.28%) patients were ever users of VKAs, any platelet inhibitor, exclusive clopidogrel, and exclusive dipyridamole, respectively. The median exposure time for VKAs, clopidogrel and dipyridamole was 1.40, 2.01 and 0.96 years. Compared with non-users, ever users of these drugs were older, more frequently post-menopausal, tended to have higher Charlson Comorbidity Index, and were more likely to also use aspirin and simvastatin (Table 1). Patients prescribed the exposure drugs more often had a history of cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, and/or diabetes (see Table 1). More users of VKAs, dipyridamole, and clopidogrel underwent mastectomy compared with non-users of each drug type. Users of the exposure drugs were less likely to receive chemotherapy than non-users.

Overall, 5,355 (13.1%) patients developed recurrent disease over a median of 7.1 years of follow-up. In crude models, use of any platelet inhibitor, exclusive use of clopidogrel, and exclusive use of dipyridamole showed a potential negative association with breast cancer recurrence. However, multivariable adjustment attenuated these associations: adjusted $HR_{\text{any platlet inhibitor}}$=0.88, 95% CI=0.67-1.15, adjusted $HR_{\text{clopidogrel}}$ =1.06, 95% CI=0.63-1.17, adjusted $HR_{\text{dipyridamole}}$=0.96, 95% CI=0.70-1.31. Compared with non-use, use of VKAs was not associated with breast cancer recurrence in crude and adjusted models: crude HR_{VKA}=1.05, 95% CI=0.85-1.29, adjusted HR_{VKA}=1.16, 95% CI=0.94-1.43 (Table 2).

In analyses of current, former, and never use, we observed a possible negative association between platelet inhibitor prescriptions and breast cancer recurrence: adjusted $HR_{\text{current platelet inhibitor use}}$ = 0.82, 95% CI=0.63-1.07 and adjusted $HR_{\text{former platelet inhibitor use}}$ = 0.63, 95% CI=0.40-0.97 (Table 3). We note similar findings in analyses for exclusive use of clopidogrel and dipyridamole but estimates were imprecise (Table 3).

For exposure in the peri-surgical window (±30 days) we observed a decreased rate of recurrence associated with platelet inhibitor use overall and use of dipyridamole, but less so for clopidogrel: adjusted $HR_{\text{any platelet inhibitor}}$=0.68, 95% CI=0.47-1.00, adjusted $HR_{\text{dipyridamole}}$=0.65, 95% CI=0.42-1.02, adjusted $HR_{\text{clopidogrel}}$ =0.82, 95% CI=0.43-1.60.

Overall, 4,900 patients died with breast cancer as primary cause of death and 8,112 died of any cause during follow-up. We observed no association between platelet inhibitor prescriptions and breast cancer specific mortality, but we note an increased rate of all-cause mortality associated with use of platelet

inhibitors versus non-use: adjusted HR = 1.22, 95% CI =1.07-1.40. VKA prescriptions were positively associated with both all-cause mortality and breast cancer specific mortality: adjusted $HR_{\text{all-cause mortality}}$ = 1.59, 95% CI =1.42-1.78 and adjusted $HR_{\text{breast cancer specific mortality}}$ = 1.45, 95% CI =1.22-1.73.

To evaluate possible effect measure modification we stratified the analyses by age, comorbidity, statin use and aspirin use. We found that the negative association between use of any platelet inhibitor and breast cancer recurrence was most pronounced among women aged 60-69 years (adjusted $HR_{\text{age 60-69}}$ = 0.60, 95% CI: 0.36-0.99). The other strata did not reveal any substantial changes to the estimates.

Finally, compared with VKA users, we observed little evidence of an association between platelet inhibitor prescriptions and breast cancer recurrence: = 0.85, 95% CI: 0.58-1.24.

Discussion

Findings from this large population-based cohort of breast cancer patients suggest little evidence of an association between platelet inhibitor or VKA prescriptions and breast cancer recurrence. These findings remained robust in analyses examining exclusive use of the platelet inhibitors clopidogrel and dipyridamole. We note a reduced rate of recurrence among former users of platelet inhibitors, but estimates were imprecise. An intriguing finding of our study is the reduced rate of recurrence associated with perisurgical use of platelet inhibitors. In analyses of mortality we observed slightly higher all-cause mortality among exposed, however, no association for breast cancer specific mortality.

Previous clinical studies showed no association between VKA use and cancer specific mortality [5,33]. Our study extends this research by using breast cancer recurrence as outcome, adding weight to the argument that VKA use is not associated with breast cancer outcomes. Our results for cancer-specific mortality and platelet inhibitors concur with the English study, which observed no association between clopidogrel prescriptions and breast cancer specific mortality.[25] However, cancer specific mortality may be prone to misclassification, especially among patients with extensive comorbidity. Such misclassification could conceal a protective association between platelet inhibitor use and cancer specific mortality. Accordingly, these patients have higher all-cause mortality. To our knowledge there has only been one trial investigating platelet inhibitors in breast cancer patients.[26] The trial's small size, short follow-up period, and use of circulating tumor cells as an outcome make its null result difficult to compare with our findings. A future trial with longer follow up and recurrence as outcome would be of great interest.

Our observed decreased rate of recurrence associated with peri-operative exposure to platelet inhibitors somewhat concurs with previous research. Studies suggest that the number of circulating tumor cells are increased following breast cancer surgery,[58,59] and that platelet inhibitor therapy during breast cancer needle biopsy may inhibit lymph node metastasis.[60] Thus inhibition of platelets around the time of surgery may contribute to a reduced risk of recurrence. This thought is intriguing, as long term platelet inhibition to prevent cancer recurrence could be suboptimal, due to the risk of bleeding and other side effects. Anti-platelet therapy in a short-term window around the time of surgery, however, may be a potential treatment to prevent the spread of cancer cells.

The protective association between use of any platelet inhibitor and breast cancer recurrence among women aged 60-69 years is intriguing. We do not have a biologic rationale that women in this age group should benefit more from platelet inhibition, however, the exclusion of patients in outlying age categories may remove multimorbid patients that otherwise blur the results.

The validity of our findings relies on several factors. The universal access to high quality healthcare in Denmark ensures a population-based cohort with negligible risk of selection bias. We used the unique personal identification number to crosslink individual-level data across five different health registries with complete follow-up. The DBCG registry contains close to complete information on Danish breast cancer patients and has exceptionally high validity.[43] A study comparing the registry data to medical registries found a positive predictive value of breast cancer recurrence of 99.4%.[52] The DNPR provided prospectively collected prescription data redeemed during follow-up. Although we lacked information on prescription compliance, patients pay a proportion of the cost of their prescriptions, so our estimates are likely to reflect actual drug use. Modelling drug exposure as a time-varying exposure allowed for fluctuations in drug use over time, minimizing the risk of exposure misclassification.[53] Via the network of Danish registries we had access to several important potential confounders, although our crude estimates are largely in line with the adjusted estimates, suggesting minimal confounding. Our DAG suggested that we restrain the analysis to four co-variates (age, comorbidity, statin use and aspirin use), but we note little difference between the model adjusting for these four co-variates and the model adjusting for all co-variates. The only co-variable to make a substantial change in the estimate was simvastatin prescription exposure. We and others note that patients exposed to platelet inhibitors are also more likely to concurrently use statins[25] (table 1) and research indicates that simvastatin prescriptions are negatively associated with breast cancer recurrence.[54,55] The attenuated decreased rate of recurrence associated with platelet inhibitor use after adjustment for simvastatin is therefore expected.

Our study has some limitations. Risk factors for cardiovascular disease, such as obesity, smoking and low physical activity, are not routinely recorded in the Danish registries. These factors may correlate with poorer outcomes in breast cancer patients.[56,57] We therefore included VKA users as a comparison exposure likely to have a similar age, comorbidity, and health behaviour to users of platelet inhibitors[5,25]. We note little change to the effect estimates when using VKA exposure as a reference, suggesting minimal confounding due to these factors. Use of platelet inhibitors is likely to result in frequent healthcare contact. Accordingly, recurrent breast cancer could be detected earlier among exposed patients compared with those unexposed. This could bias the association in a positive direction, but seems unlikely to explain a negative association. However, another concern is the severity of comorbidity among patients exposed to platelet inhibitors. For these patients, breast cancer may not be the most life-threatening issue, so recurrent disease could go undetected. Such bias could contribute towards a decreased rate of recurrence associated with drug use. We note, however, that our associations remain stable even after adjustment for age and comorbidity, and after changing the reference group to VKA users, thus the influence of these sources of bias is likely minimal.

Our study of over 34,000 breast cancer survivors provides little evidence to support a decreased rate of breast cancer recurrence or mortality associated with postdiagnostic platelet inhibitor or VKA use. However, our observed reduction in recurrence rates associated with platelet inhibitor use around the time of surgery is intriguing and necessitates further exploration.

Supplementary

Background breast cancer

Breast cancer is the most prevalent cancer among females with over 4,000 new cases diagnosed in Denmark each year[60]. 1 out of every 9-10 women is diagnosed with breast cancer equalling a lifetime risk of 10%. The average age at diagnosis is 65 years, with 25% aged below 50 years at diagnosis and only 1.5% younger than 35 years. Almost 30% of the patients get recurrent disease within 10 years and the 5 year survival for all types of breast cancer is 85.3%[60]. The disease usually starts with the patient discovering a mass in the breast or through screening programs. All Danish females are offered screening after they turn 50 and meta-analyses have shown reduced mortality among screened breast cancer patients[61]. After the discovery of an unknown mass in the breast all patients go through "triple testing" that consists of: Palpation, radiology (mammography, ultrasound and MRI scan) and fine-needle aspiration.

The majority of breast cancers arise from the epithelial cells of the milk ducts (ca. 80%) and a smaller amount (ca 20%) arise from the milk producing lobules[60,62]. Breast cancer is a complex disease with exposure to hormones playing a major role in its development[63]. Women with dysfunctional ovaries who never receive hormone treatment don't develop breast cancer[63]. Three factors in a female lifetime majorly impact breast cancer incidence: Age at menarche, age at first birth and menopausal status[63]. Breast cancer incidence increased with increased exposure to oestrogen. Genetics also play a role, however, less than 10% of breast cancers can be attributed to genetics[60]. The most well-known gene defect is within the BRCA1-gene. Women who inherit a mutated allele of this gene from either parent have 60-80% life time risk of developing breast cancer[63]. Other factors that influence breast cancer incidence are alcohol use, obesity and a lack of physical activity[60].

Breast cancer treatment can be divided into surgical, endocrine, chemotherapy, radiotherapy and targeted treatment[64]. Primary treatment for breast cancer is removal of the tumor with surgery. The first choice of operation in Denmark is lumpectomy, where only the tumor and some surrounding tissue is removed. If contraindications exist, e.g. inability to achieve microscopic radicality, diffuse malignant disease, or inability to treat the patient with radiotherapy, complete removal of the breast is preformed (mastectomy)[64]. Sentinel lymph node biopsy, where a tracer is used to select the first lymph node receiving drainage from the tumor[65], is used routinely. Mastectomy patients with axillary lymph node metastases and all patients undergoing lumpectomy receive radiotherapy[60]. Adjuvant treatment is individualized based on a number of test. Patients are considered at high risk if they have one of the following characteristics: Primary tumor >10 mm, ductal carcinoma anaplasia level 2-3, lobular carcinoma level 3, hormone receptor negative tumor,

HER2 positive tumor, TOP2A abnormal tumor, axillary metastasis or age < 60 years[60]. High risk patients receive chemotherapy after the surgery. If the tumor is hormone receptor positive, patients are eligible for endocrine therapy[66]. Tamoxifen is guideline endocrine therapy for premenopausal women, while aromatase inhibitors are guideline for postmenopausal women. Prolonged use of tamoxifen up to ten years after diagnosis is now also recommended (Refer to the ATLAS trial). Patients with HER2 positive tumors receive the monoclonal antibody trastuzumab[60].

The most important prognostic factor is tumor size and lymph node status at diagnosis. Other prognostic factors include age, tumor size, metastatic lymph nodes, hormone receptor status, HER2 receptor status and histologic parameters.

Background exposure drugs

Haemostasis involves a complex interplay of different mechanisms to secure a balance between bleeding and clotting in our vascular system[67]. The coagulation system is capable of forming a clot in case of damage to a vessel. Unfortunately, this is not always appropriate. Arterial clotting can result in diseases like heart attack and stroke while venous clotting can cause deep venous thrombosis or pulmonary embolism[63,68].Patients with a suppressed haemostatic system are prone to bleeding, or other serious complications, warranting treatment with platelet inhibitors or anti-coagulants. In this study we investigated drugs that suppress the haemostatic system. These drugs are collectively grouped under the ATC code B01[69] and include: Vitamin K antagonists, Heparins, Platelet aggregation inhibitors, Enzymes, Direct thrombin inhibitors, Direct factor Xa inhibitors and Other antithrombotic agents. While our hypothesis made it interesting to look at all these drugs, we were limited by the number of prescriptions given in our cohort (Table 1).

Table 1. Anti thrombotic drug prescriptions among stage I, II or III breast cancer patients diagnosed in Denmark from 1996-2006.

Category	ATC Code B01A***	Number of prescriptions	Drug (commercial name)
Vitamin K antagonists	A03	44.052	Warfarin (Marevan)
	A04	3.142	Phenprocoumon (Marcoumar)
Heparins	B04	1.917	Deltaparin (Fragmin)
	B10	1.198	Tincaparin (Innohep)

	B05	446	Enoxaparin (Klexane)
	B01	99	Heparin (Ufraktioneret)
Platelet inhibitors	C06	192.731	Aspirin
	C07	35.032	Dipyridamol
	C04	13.848	Clopidogrel
	C30	10.011	Dipyridamol + Aspirin
	C24	244	Ticagrelor
	C22	93	Prasugrel
Direct thrombin inhibitors	E07	1837	Dabigatraneetexilat (Pradaxa)
Direct Factor X_a-inhibitor	F01	338	Rivaroxaban (Xarelto)
		16	Apixaban (Eliquis)
Synthetic pentasaccharide	X05	10	Fondaparinux (Arixtra)

Prescription use is considered exposed follow-up time. We therefore restricted our study to vitamin K antagonists and platelet inhibitors as these were the most frequently used exposure drugs. Platelet inhibitors are used to prevent occlusive arterial diseases.[1-3] In addition to acetylsalicylic acid, two major groups of platelet inhibitors are used in Denmark: phosphodiesterase inhibitors (e.g.: dipyridamole) and thienopyridines (e.g.: clopidogrel).[2,3] The phosphodiesterase inhibitors block platelet uptake of adenosine and inhibit cyclic AMP phosphodieasterase while the thienopyridines act as ADP receptor antagonists.[4] We excluded aspirin as exposure drug in the study because previous research in our study cohort had investigated aspirin and breast cancer recurrence (REF to my paper here).[70] Vitamin K antagonists (e.g. warfarin) prevent recycling of vitamin K resulting in reduced production of the coagulation factors II, VII, IX and X and the coagulation inhibitors protein S and protein C.[5,6] This action prevents the formation of blood clots, particularly at sites with a slow blood flow. The drugs are commonly used to prevent venous clotting in heart disease (e.g., atrial fibrillation), venous disease (e.g., pulmonary embolism), and in patients at high risk of clot formation[2].

Methodological considerations

To investigate our hypothesis, we have chosen a specific study design and statistical method. The goal was to produce as valid and precise estimates of the association between our exposure and outcome as possible. In this section we will discuss the reason behind some of our methodological choices.

Study design

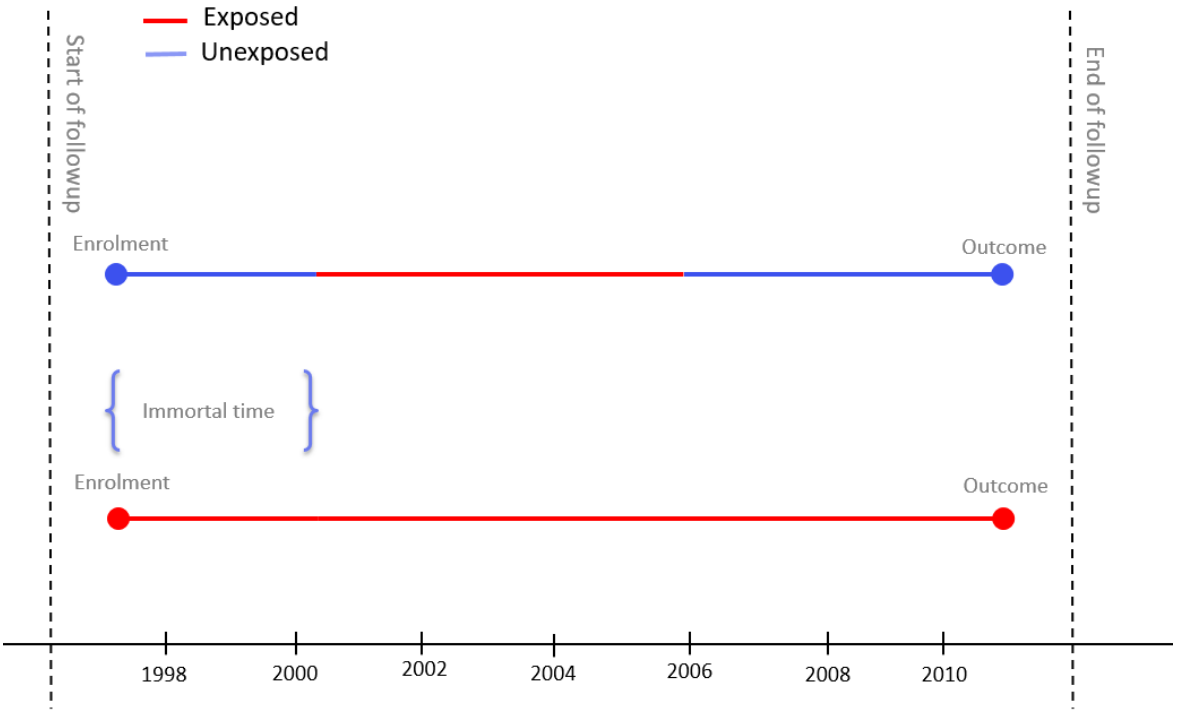
The initial reason to conduct this study was a well-established hypothesis based on different laboratory studies[4,71]. The hypothesis, described in the introduction of this thesis, is that anticoagulant medicine is negatively associated with breast cancer recurrence. We wanted to investigate whether or not this association actually existed in patients. In theory, the best way to test the hypothesis would be through a randomized clinical trial. This method provides the highest validity of evidence and power[72]. It is, however, very difficult, expensive and time consuming to perform a clinical trial[73]. The usual practise is to make multiple observational studies before considering clinical trials. In observational studies, the researcher does not control the exposure. Instead, a cohort is assembled, which consists of a group of people, none of whom has experienced the outcome of interest, but all of whom could experience it[73]. Upon entry into the cohort people are characterized according to exposures of interest that may be associated with the outcome. When observing the cohort over time, the incidence of the outcome is compared among exposed and unexposed.

We designed a nationwide population based cohort study, using data from national population-based registries. Our cohort included all Danish women with an incident diagnosis of non-metastatic invasive breast cancer who were registered in the DBCG registry between 1996 and 2008. All patients were followed from the date of breast cancer surgery until the first of breast cancer recurrence (or mortality), death, or emigration, accrual of ten years of follow-up, or 1 January 2013. This design was made possible by the very high quality and validity[43] of the DBCG registry. This registry is updated after all breast cancer surgeries and annual follow-ups of breast cancer patients in Denmark. The inclusion of all Danish breast cancer patients not only gives us a large population but also a cohort that is very representative of the source population. Via Statistics Denmark, we linked the breast cancer cohort DBCG data to the Danish National Prescription Registry, the Danish National Registry of Patients, the Danish Cause of Death Registry and the Danish Civil Registration System to access exposure information, co-variables and follow-up information. This data linkage allowed us to obtain very detailed individual-level information on a large number of patients. This highlights the scope and strengths of the network of registries in Denmark, which is rarely found outside of Scandinavia, and allows for very high quality observational studies. For these reasons, we concluded that the cohort study design would be very suitable for our study.

Statistical methods

Exposure

We had individual level information on all prescriptions for the drugs included in our study for the patients in the cohort. This information included date of prescription and information on the quantity and strength of the drug prescribed. When converting this data into a measure of exposure you can choose a lot of different methods. The most basic way is to create a dichotomous variable and examine whether or not the patient was exposed in a given time window. You can adjust the amount of drug exposure etc. needed to count as exposed in the study. However, this method has some problems. Exposure to the prescription drugs we investigate is not a one-time event. The number of prescriptions varies hugely between different patients. Making a patient with 14 days of drug exposure contribute with the same amount of time in the exposed group in the survival analysis as a patient with 2 years of drug exposure is very imprecise. Especially if you suspect some kind of dose-response relationship. Another problem is the possibility of immortal person time[74]. Immortal person time refers to a period in follow-up, during which a patient cannot die. In our case, because any outcome results in stop of follow-up, all exposed people would be unable to get any outcomes before the time of their first prescription. Because we would count the entire follow-up as exposed, we would add periods of exposed time, during which the patient would be unable to have a recurrence (figure 2). This would create a bias with a false protective association of the drug against recurrence.



To prevent these problems, we chose to use time varying exposure[75]. In this method, the patients are allowed to change exposure status over time. Each prescription was recoded to a time interval based on quantity of pills, strength of pills, redemption day, and defined daily dose[69]. The time intervals were then aggregated to single exposure intervals, allowing up to a 30-day gap between two prescriptions in a continuous interval. If the gap between two prescriptions exceeded 30 days, or if the patient stopped redeeming prescriptions, their status were changed to the unexposed group. The patients could later re-enter the exposed group if prescriptions resumed. All time intervals where lagged by one year to allow a reasonable etiologic window for an effect of the drug exposure on the outcome in question. Figure 2 illustrates how one patient adds nine different time intervals to the analysis with varying drug exposure.

Figure 2 – exposure coding

startaspirin	1	0	1.287474	1.325804
startsimva	1	1	1.325804	1.643395
endaspirin	0	1	1.643395	1.678987
startaspirin	1	1	1.678987	2.034908
endaspirin	0	1	2.034908	2.05681
endsimva	0	0	2.05681	2.196441
startsimva	0	1	2.196441	3.932238
endsimva	0	0	3.932238	6.896646

Outcome

The outcome of interest in this study is breast cancer recurrence. In an ideal world, a patient would either experience breast cancer recurrence or remain in the cohort from time of inclusion until end of follow-up. However, patients dying, emigrating or otherwise disappearing from the cohort would not be able to experience the outcome. Such events are referred to as "competing risk events"[76]. To prevent follow-up with patients unable to experience recurrence, they were censored after the date of the competing event. Doing this, we assume that the censoring is "non-informative". This refers to the fact that censored patients should be no more or less likely to get recurrence than those who remain in the analysis.

Survival analysis

In this study we measure the time from inclusion until a given outcome. This kind of data is called "survival data". When comparing survival data from two different groups (exposed to the drugs versus non-exposed in our case), in a regression analysis with multiple co-variables, the most commonly used method is the Cox proportional hazards regression[77]. Cox regression assumes that the censoring is independent (as outlined above) and that the rate between the hazards in our exposure groups remain constant over time.

Strengths and limitations

Validity of epidemiological research can be divided into external and internal validity.[73] External validity is the transferability of the results from the study population to the general population. Due to the very strict data collection in our study, we have information on all surgical breast cancer patients in Denmark. This gives very good external validity. Internal validity relies on two types of errors: Random error and systematic error[74]. Random error is a variability in the data that cannot be readily explained. It is heavily influenced by the size of your study population. In this study we are trying to find a difference between two groups. Our ability to find this difference depends on the size of the groups and the size of the difference. A big difference will be easier to detect while a small difference requires a large study population. To help describe the random error in our study, we used confidence intervals. The confidence interval show what estimate range we expect with a certain confidence. We choose 95% confidence, meaning that 95% of the time the estimate would be within that interval.

Error that remains in an infinitely large study is systematic error. Systematic errors can bias the results in a lot of ways. The errors are usually classified as selection bias, information bias or confounding.[74]

Selection bias

Selection bias stems from the procedures used to select the study population and factors that influence participation in the study.[74] The bias arises if the association between exposure and outcome differs between study participants and non-participants. An example is self-selection bias, where people who agree to participate are different to those who don't. They may, for instance, be worrying about symptoms and may therefore be more likely to have the disease in question. This would bias the results because of higher disease prevalence in the study population compared to the source population.

Our study population included all Danish women with an incident diagnosis of non-metastatic invasive breast cancer who were registered in the DBCG registry between 1996 and 2008. The free access to high quality health care in Denmark ensures a well-distributed cohort with negligible risk of selection bias. Since 1977, most cases of invasive breast cancer have been reported to the DBCG database.[42] The completeness of the registry increased from 87% in 1986 to 92% in 2013.[43,44]

Information bias

Information bias may arise if the information collected about the study participants is erroneous[74]. This may lead to a person being placed in the wrong category or "misclassified". The bias can be categorized as differential, if the misclassification varies across other study variables, or non-differential, if the misclassification is constant across all study variables. While differential misclassification can both exaggerate and underestimate an estimate, non-differential misclassification tends to pull the estimate towards null. The two key variables to consider with regard to information bias is exposure and outcome.

Misclassification of exposure

We used the DNPR to gather prospective information on all prescriptions redeemed during follow-up. The fact that all our exposure drugs require prescription and that all redeemed prescriptions are registered greatly prohibits the chance of misclassification. We lacked information on prescription compliance, however patients pay a proportion of the cost of their prescriptions, so our estimates are likely to reflect actual drug use.

Misclassification of outcome

The DBCG registry contains close to complete information on Danish breast cancer patients with exceptionally high validity.[43] A study comparing registry data to medical registries found a positive predictive value of breast cancer recurrence classification to be 99.4%.[54] We therefore find it very unlikely that our study suffers from misclassification of outcome.

Confounding

Confounding is a major point of concern in most observational epidemiologic studies. The simplest definition is that confounding is confusion of effects.[74] In practise, a confounder is typically a co-variable, like sex, age or comorbidity, that influenced the association between exposure and outcome in a way that causes bias. In order to be a confounder, the factor must: be associated with exposure, be associated with outcome and not be a part of the causal chain from exposure to outcome.[73] Contrary to selection bias and information bias, confounding can be controlled both in the study design (by restriction, matching or randomization) and in the statistical analysis (by standardization, stratification and adjustment).[73] Stratification should always be the first method of choice in the analysis[74]. It gives a clear picture of the

association between exposure and outcome in the different strata of the co-variable. The problem with stratification is dilution of the groups, resulting in imprecise estimates. We have used a combination of stratification and adjustment (multivariate regression model) in this study. The stratification showed a particularly strong association in a specific age group (read the discussion in manuscript for more detail).

Clinical perspectives / future

Our study of over 34,000 breast cancer survivors provides little evidence to support a protective effect of general platelet inhibitor use on breast cancer recurrence or breast cancer mortality.

However, we observed a reduction in recurrence rates associated with platelet inhibitor use around the time of surgery. This finding is intriguing, as long term platelet inhibition to prevent cancer recurrence could be suboptimal, due to the risk of bleeding and other side effects. Anti-platelet therapy in a short-term window around the time of surgery, however, may be a potential treatment to prevent spread of cancer cells.

Our results have important implications for future research into the clinical course of other cancers. While our results only showed an imprecise negative association between platelet inhibitors and breast cancer recurrence, it speaks against a positive association between use of the exposure drugs and breast cancer progression.

The decreased rate of recurrence among breast cancer patients who use platelet inhibitors around time of surgery, in theory, may be true for other cancers. Our project may therefore inspire further research on the association of these medicines on the clinical course of other cancers. Future research may also focus on identifying the underlying biological mechanisms of this association.

One of the major problems in this study was limited exposure time. We did show negative associations, however because of limited exposure time, the estimates were imprecise. To overcome this problem, we are conducting a similar study among Danish colorectal cancer patients. If our findings are also evident among colorectal cancer patients, this provides further impetus that anticoagulant medications may have a beneficial role in cancer treatment.

References

1. Altman R, Carreras L, Diaz R, et al. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J*. 1994;308(6921):81-106. Accessed 24 February 2016.

2. Dansk Cardiologisk Selskab. National cardiologisk behandlingsvejledning (national cardiological treatment guidelines). . 2015(www.cardio.dk).

3. Udarbejdet af en arbejdsgruppe nedsat af Dansk Selskab for Apopleksi. Referenceprogram for behandling af patienter med apopleksi og TCI. . 2013.

4. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: A host factor that offers multiple potential targets in the treatment of cancer. *J Cell Physiol*. 2014;229(8):1005-1015. Accessed 24 February 2016. doi: 10.1002/jcp.24539.

5. O'Rorke MA, Murray LJ, Hughes CM, Cantwell MM, Cardwell CR. The effect of warfarin therapy on breast, colorectal, lung, and prostate cancer survival: A population-based cohort study using the clinical practice research datalink. *Cancer Causes Control*. 2015;26(3):355-366. doi: 10.1007/s10552-014-0511-2 [doi].

6. Zacharski LR, Henderson WG, Rickles FR, et al. Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. final report of VA cooperative study #75. *Cancer*. 1984;53(10):2046-2052.

7. Sindelar WF, Tralka TS, Ketcham AS. Electron microscopic observations on formation of pulmonary metastases. *J Surg Res*. 1975;18(2):137-161. Accessed 24 February 2016. doi: 10.1016/0022-4804(75)90010-4.

8. Nierodzik ML, Klepfish A, Karpatkin S. Role of platelets, thrombin, integrin IIb-IIIa, fibronectin and von willebrand factor on tumor adhesion in vitro and metastasis in vivo. *Thromb Haemost*. 1995;74(1):282-290. Accessed 24 February 2016.

9. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer*. 2011;11(2):123-134. doi: 10.1038/nrc3004 [doi].

10. Gay LJ, Felding-Habermann B. Platelets alter tumor cell attributes to propel metastasis: Programming in transit. *Cancer Cell*. 2011;20(5):553-554. doi: 10.1016/j.ccr.2011.11.001 [doi].

11. Nieswandt B, Hafner M, Echtenacher B, Männel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. *Cancer Res*. 1999;59(6):1295-1300. Accessed 1 March 2016.

12. Kuznetsov HS, Marsh T, Markens BA, et al. Identification of luminal breast cancers that establish a tumor-supportive macroenvironment defined by proangiogenic platelets and bone marrow-derived cells. *Cancer Discov*. 2012;2(12):1150-1165. doi: 10.1158/2159-8290.CD-12-0216 [doi].

13. Battinelli EM, Markens BA, Italiano JE,Jr. Release of angiogenesis regulatory proteins from platelet alpha granules: Modulation of physiologic and pathologic angiogenesis. *Blood*. 2011;118(5):1359-1369. doi: 10.1182/blood-2011-02-334524 [doi].

14. Pinedo HM, Verheul HM, D'Amato RJ, Folkman J. Involvement of platelets in tumour angiogenesis? *Lancet*. 1998;352(9142):1775-1777. doi: S0140673698050958 [pii].

15. Roselli M, Mineo TC, Basili S, et al. Vascular endothelial growth factor (VEGF-A) plasma levels in non-small cell lung cancer: Relationship with coagulation and platelet activation markers. *Thromb Haemost*. 2003;89(1):177-184. doi: 10.1267/THRO03010177 [doi].

16. Pandey A, Sarangi S, Chien K, et al. Anti-platelet agents augment cisplatin nanoparticle cytotoxicity by enhancing tumor vasculature permeability and drug delivery. *Nanotechnology*. 2014;25(44):445101-4484/25/44/445101. Epub 2014 Oct 10. doi: 10.1088/0957-4484/25/44/445101 [doi].

17. Wang Y, Sun Y, Li D, et al. Platelet P2Y12 is involved in murine pulmonary metastasis. *PLoS ONE*. 2013;8(11). Accessed 24 February 2016. doi: 10.1371/journal.pone.0080780.

18. Gebremeskel S, Levatte T, Liwski RS, Johnston B, Bezuhly M. The reversible P2Y12 inhibitor ticagrelor inhibits metastasis and improves survival in mouse models of cancer. *Int J Cancer*. 2015;136(1):234-240. Accessed 24 February 2016. doi: 10.1002/ijc.28947.

19. Cooke NM, Spillane CD, Sheils O, O'Leary J, Kenny D. Aspirin and P2Y12 inhibition attenuate platelet-induced ovarian cancer cell invasion. *BMC Cancer*. 2015;15(1). Accessed 24 February 2016. doi: 10.1186/s12885-015-1634-x.

20. Holmes MD, Olsson H, Pawitan Y, et al. Aspirin intake and breast cancer survival - a nation-wide study using prospectively recorded data in sweden. *BMC Cancer*. 2014;14:391-2407-14-391. doi: 10.1186/1471-2407-14-391 [doi].

21. Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin intake and survival after breast cancer. *J Clin Oncol*. 2010;28(9):1467-1472. doi: 10.1200/JCO.2009.22.7918 [doi].

22. Murray LJ, Cooper JA, Hughes CM, Powe DG, Cardwell CR. Post-diagnostic prescriptions for low-dose aspirin and breast cancer-specific survival: A nested case-control study in a breast cancer cohort from the UK clinical practice research datalink. *Breast Cancer Res*. 2014;16(2):R34. doi: 10.1186/bcr3638 [doi].

23. Fraser DM, Sullivan FM, Thompson AM, McCowan C. Aspirin use and survival after the diagnosis of breast cancer: A population-based cohort study. *Br J Cancer*. 2014;111(3):623-627. doi: 10.1038/bjc.2014.264 [doi].

24. Barron TI, Flahavan EM, Sharp L, Bennett K, Visvanathan K. Recent prediagnostic aspirin use, lymph node involvement, and 5-year mortality in women with stage I-III breast cancer: A nationwide population-based cohort study. *Cancer Res*. 2014;74(15):4065-4077. doi: 10.1158/0008-5472.CAN-13-2679 [doi].

25. Hicks BM, Murray LJ, Hughes C, Cardwell CR. Clopidogrel use and cancer-specific mortality: A population-based cohort study of colorectal, breast and prostate cancer patients. *Pharmacoepidemiol Drug Saf*. 2015;24(8):830-840. Accessed 2 May 2016. doi: 10.1002/pds.3807.

26. Roop RP, Naughton MJ, Van Poznak C, et al. A randomized phase ii trial investigating the effect of platelet function inhibition on circulating tumor cells in patients with metastatic breast cancer. *Clin Breast Cancer*. 2013;13(6):409-415. Accessed 2 May 2016. doi: 10.1016/j.clbc.2013.08.006.

27. Bobek V, Kovarik J. Antitumor and antimetastatic effect of warfarin and heparins. *Biomed Pharmacother*. 2004;58(4):213-219. doi: 10.1016/j.biopha.2003.11.007 [doi].

28. Paolino M, Choidas A, Wallner S, et al. The E3 ligase cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. *Nature*. 2014;507(7493):508-512. doi: 10.1038/nature12998 [doi].

29. Bobek V. Anticoagulant and fibrinolytic drugs - possible agents in treatment of lung cancer? *Anticancer Agents Med Chem*. 2012;12(6):580-588. doi: ACAMC-EPUB-20120131-028 [pii].

30. Battinelli EM, Markens BA, Kulenthirarajan RA, Machlus KR, Flaumenhaft R, Italiano JE,Jr. Anticoagulation inhibits tumor cell-mediated release of platelet angiogenic proteins and diminishes platelet angiogenic response. *Blood*. 2014;123(1):101-112. doi: 10.1182/blood-2013-02-485011 [doi].

31. Hejna M, Raderer M, Zielinski CC. Inhibition of metastases by anticoagulants. *J Natl Cancer Inst*. 1999;91(1):22-36.

32. Kakkar AK, Macbeth F. Antithrombotic therapy and survival in patients with malignant disease. *Br J Cancer*. 2010;102 Suppl 1:S24-9. doi: 10.1038/sj.bjc.6605602 [doi].

33. Akl EA, Vasireddi SR, Gunukula S, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database Syst Rev*. 2011;(6):CD006466. doi(6):CD006466. doi: 10.1002/14651858.CD006466.pub3 [doi].

34. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet*. 1994;343(8902):886-889.

35. Daly L. The first international urokinase/warfarin trial in colorectal cancer. *Clin Exp Metastasis*. 1991;9(1):3-11.

36. Zacharski LR, Henderson WG, Rickles FR, et al. Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. final report of VA cooperative study #75. *Cancer*. 1984;53(10):2046-2052.

37. Maurer LH, Herndon JE,2nd, Hollis DR, et al. Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: A cancer and leukemia group B study. *J Clin Oncol*. 1997;15(11):3378-3387.

38. Chahinian AP, Propert KJ, Ware JH, et al. A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the cancer and leukemia group B. *J Clin Oncol*. 1989;7(8):993-1002.

39. Sorensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol*. 2000;95(9):2218-2224. doi: S0002-9270(00)01040-6 [pii].

40. Pedersen CB. The danish civil registration system. *Scand J Public Health*. 2011;39(7):22-25. Accessed 26 February 2016. doi: 10.1177/1403494810387965.

41. Schmidt M, Pedersen L, Sorensen HT. The danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi: 10.1007/s10654-014-9930-3 [doi].

42. Jensen AR, Storm HH, Møller S, Overgaard J. Validity and representativity in the danish breast cancer cooperative group - A study on protocol allocation and data validity from one county to a multi-centre database. *Acta Oncol*. 2003;42(3):179-185. Accessed 25 February 2016. doi: 10.1080/02841860310000737.

43. Moller S, Jensen MB, Ejlertsen B, et al. The clinical database and the treatment guidelines of the danish breast cancer cooperative group (DBCG); its 30-years experience and future promise. *Acta Oncol*. 2008;47(4):506-524. doi: 10.1080/02841860802059259 [doi].

44. Kvalitetsindikatorrapport for brystkræft 2014 - Landsdækkende klinisk kvalitetsdatabase for brystkræft. . 2014.

45. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The danish national prescription registry. *Scand J Public Health*. 2011;39(7):38-41. Accessed 25 February 2016. doi: 10.1177/1403494810394717.

46. Lynge E, Sandegaard JL, Rebolj M. The danish national patient register. *Scand J Public Health*. 2011;39(7):30-33. Accessed 25 February 2016. doi: 10.1177/1403494811401482.

47. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383. Accessed 18 April 2016. doi: 10.1016/0021-9681(87)90171-8.

48. Sundhedsdata-styrelsen. Dødårsagsregisteret - tal og analyse. . 2014.

49. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383.

50. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. Accessed 10 May 2016.

51. Camara O, Kavallaris A, Nöschel H, Rengsberger M, Jörke C, Pachmann K. Seeding of epithelial cells into circulation during surgery for breast cancer: The fate of malignant and benign mobilized cells. *World J Surg Oncol*. 2006;4. Accessed 25 April 2016. doi: 10.1186/1477-7819-4-67.

52. Katharina P. Tumor cell seeding during surgery-possible contribution to metastasis formations. *Cancers*. 2011;3(2):2540-2553. Accessed 25 April 2016. doi: 10.3390/cancers3022540.

53. Ljung R, Sennerstam R, Mattsson F, Auer G, Lagergren J. Anticoagulant medication at time of needle biopsy for breast cancer in relation to risk of lymph node metastasis. *Int J Cancer*. 2014;135(1):238-241. Accessed 25 April 2016. doi: 10.1002/ijc.28671.

54. Hansen S, Andersen E, Andersen KW, Mouridsen HT. Quality control of end results in a danish adjuvant breast cancer multi- center study. *Acta Oncol*. 1997;36(7):711-714. Accessed 23 March 2016.

55. Stricker BHC, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. *Eur J Epidemiol*. 2010;25(4):245-251. Accessed 24 March 2016. doi: 10.1007/s10654-010-9451-7.

56. Ahern TP, Lash TL, Damkier P, Christiansen PM, Cronin-Fenton DP. Statins and breast cancer prognosis: Evidence and opportunities. *Lancet Oncol*. 2014;15(10):e461-8. doi: 10.1016/S1470-2045(14)70119-6 [doi].

57. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after diagnosis of breast cancer and survival: A population-based cohort study. *Epidemiology*. 2015;26(1):68-78. Accessed 4 July 2016. doi: 10.1097/EDE.0000000000000189.

58. Egan KM, Stampfer MJ, Hunter D, et al. Active and passive smoking in breast cancer: Prospective results from the nurses' health study. *Epidemiology*. 2002;13(2):138-145. Accessed 16 June 2016. doi: 10.1097/00001648-200203000-00007.

59. Kushi LH, Doyle C, McCullough M, et al. American cancer society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62(1):30-67. Accessed 16 June 2016. doi: 10.3322/caac.20140.

60. https://www.sundhed.dk. Lægehåndbogen. . 2016.

61. Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: A summary of the evidence for the U.S. preventive services task force. *Ann Intern Med*. 2002;137(5 I):347-360. Accessed 19 May 2016.

62. Nayak MK, Singh SK, Roy A, Prakash V, Kumar A, Dash D. Anti-thrombotic effects of selective estrogen receptor modulator tamoxifen. *Thromb Haemost*. 2011;106(4):624-635. doi: 10.1160/TH11-03-0178 [doi].

63. Dan Longo, Anthony Fauci, Dennis Kasper, Stephen Hauser, J. Jameson, Joseph Loscalzo. Harrison's principles of internal medicine. . 2012(18 edition).

64. Danish breast cancer group: Http://Www.dbcg.dk/. .

65. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997;349(9069):1864-1867. Accessed 23 May 2016. doi: 10.1016/S0140-6736(97)01004-0.

66. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31000 recurrences and 24000 deaths among 75000 women. *Lancet*. 1992;339(8784):1-15. Accessed 23 May 2016.

67. Jens P. Kampmann, Kom Brøsen, Ulf Simonsen. Basal og klinisk farmakologi. . 2011(4. udgave).

68. Professor Parveen Kumar, Michael Clark. Kumar and clarks clinical medicine eighth edition. . 2012 Elsevier Ltd.

69. Pro.medicin.dk. . 2016(Extensive information and guidelines on drug treatment).

70. Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, et al. Low-dose aspirin, non-steroidal anti-inflammatory drugs, selective COX-2 inhibitors and breast cancer recurrence. *Epidemiology*. 2016. Accessed 28 April 2016. doi: 10.1097/EDE.0000000000000480.

71. Bambace NM, Holmes CE. The platelet contribution to cancer progression. *J Thromb Haemost*. 2011;9(2):237-249. Accessed 24 February 2016. doi: 10.1111/j.1538-7836.2010.04131.x.

72. Svend Juul. Epidemiologi og evidens. . 2012;2. udgave.

73. Robert H. Fletcher, Suzanne W. Fletcher, Grant S. Fletcher. Clincal epidemiology - the essentials. . 2014(fifth edition).

74. Kenneth J. Rothman. Epidemiology - an introduction. . 2012(2. edition).

75. Fisher LD, Lin DY, eds. *Time-dependent covariates in the cox proportional-hazards regression model.* ; 1999Annual Review of Public Health; No. 20.

76. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer*. 2004;91(7):1229-1235. Accessed 6 June 2016. doi: 10.1038/sj.bjc.6602102.

77. Betty R. Kirkwood, Jonathan A.C. Sterne. Essential medical statistics. . 2003.

Tables

TABLE 1. Baseline characteristics of stage I, II or III breast cancer patients diagnosed in Denmark from 1996-2006 by antithrombotic treatment.

	Vitamin K antagonists				Dipyridamol				Clopidogrel			
	Ever use		Never use		Ever use		Never use		Ever use		Never use	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at diagnosis (years)												
≤59	408	24	17,979	53	193	21	17,979	54	184	26	17,988	53
60-69	624	37	10,238	30	381	41	10,131	30	274	39	10,238	30
≥70	358	39	5,551	16	358	38	5,436	16	243	35	5,551	16
Charlson comorbidity score												
0	976	58	26,624	81	446	48	27,223	81	377	54	27,223	81
1	374	22	3,447	11	266	29	3,659	11	162	23	3,659	11
2	197	12	1,722	5	113	12	1,830	5	89	13	1,830	5
>=3	150	9	988	3	107	11	1,065	3	73	10	1,065	3
Menopausal status at diagnosis												
Pre	167	10	9,515	29	65	7	9,617	29	63	9	9,619	28
Post	1,530	90	23,251	71	867	93	23,914	71	637	91	24,144	72
Specific comorbidities												
Myocardial infarction	59	3	356	1	39	4	376	1	90	13	325	1
Congestive heart failure	162	10	270	1	29	3	403	1	28	4	404	1
Peripheral vascular disease	89	5	511	2	52	6	548	2	53	8	547	2
Cerebrovascular disease	182	11	955	3	308	33	829	2	103	15	1,034	3
Metastatic solid tumor, leukemia or Lymphoma	21	1	346	1	14	2	353	1	few	few	360	1
Diabetes	110	6	798	2	66	7	842	3	57	8	851	3
Connective tissue disease	89	5	789	2	36	4	842	3	30	4	819	3
UICC stage												
I	604	36	12,362	38	340	37	12,618	38	287	41	12,679	38
II	778	46	14,788	44	456	49	14,788	44	321	56	14,930	44
III	288	17	5,854	17	124	13	5,854	17	83	12	5,895	17
(Missing)	27	2	261	1	11	1	261	1	10	1	262	1
Axillary Lymph node positive												
Yes	791	47	17,297	53	421	45	15,855	47	300	43	15,976	53
No	905	53	15,485	47	511	55	17,691	53	401	57	17,801	47

Primary Tumor size (mm)												
<20 mm	920	54	19,298	59	536	58	19,682	59	440	63	19,778	59
20-50mm	708	42	12,074	37	367	39	12,415	37	240	34	12,542	37
>50mm	68	4	1,409	4	29	3	1,448	4	21	3	1,456	4
Histologic grade												
Low	1345	79	26,766	82	749	81	27,362	82	584	84	27,527	82
Moderate	195	12	3,594	11	120	13	3,669	11	71	10	3,718	11
High	154	9	2.259	7	61	7	2,352	7	43	6	2.370	7
(Missing)												
ER/adjuvant ET status												
ER-/ET-	278	16	6,414	20	152	16	6,540	19	120	17	6,572	19
ER+/ET-	382	23	8,192	25	202	22	8,372	25	189	27	8,385	25
ER+/ET+	985	58	17,021	52	549	59	17,457	52	372	54	17,457	52
ER-/ET+	low	low	199	1	low	low	199	1	low	low	199	1
(Missing)	46	3	955	3	23	2	978	3	36	2	978	3
Type of primary surgery												
Mastectomy	800	47	11,535	35	468	50	11,867	35	295	42	12,040	36
Mastectomy+RT	272	16	6,926	21	139	15	7,059	21	113	16	7,085	21
BCS + RT	625	37	14,320	44	325	35	14,620	44	293	42	14,652	43
Adjuvant chemotherapy received												
No	1,375	81	21,562	66	788	85	22,362	66	575	82	22,362	66
Yes	322	19	11,219	34	144	15	11,415	34	126	18	11,415	34
Pre-diagnosis exposure to Hormone replacement therapy												
No	908	54	19,284	59	454	49	19,738	59	333	48	19,859	59
yes	789	46	13,497	41	578	51	13,808	41	368	52	13,818	41
Drug exposures during study period												
Aspirin (high and low doses)	866	51	26,521	81	148	16	27,239	81	132	19	27,255	81
No	831	49	6,260	19	784	84	6,307	19	560	81	6,522	19
yes												
Simvastatin	1,072	63	26,287	80	337	36	27,022	81	138	20	27,221	81
No	625	37	6,494	20	595	65	6,524	19	563	80	6,556	19
yes												

Table 2. Association between antithrombotic treatment and breast cancer recurrence among stage I, II or III breast cancer patients diagnosed in Denmark from 1996-2006.

	No.	%	Average exposure time (years)	No. of recurrences	Total Person years at risk	Crude Hazard ratio (95% conf. interval)	Adjusted model 1 (95% conf. interval)	Adjusted model 2 (95% conf. interval)
Never users	31,490	91.33	0	5139	213,555	1	1	1
Vitamin K antagonists	1,697	4.92	1.40	93	3,977	1.05 (0.85-1.29)	1.16 (0.94-1.43)	1.13 (0.92-1.40)
Any platelet inhibitor	1,492	4.32	1.43	58	3,581	0.74 (0.58-0.96)	0.88 (0.67-1.15)	0.89 (0.68-1.16)
Only clopidogrel	555	1.16	0.96	15	815	0.86 (0.52-1.43)	1.06 (0.63-1.75)	1.11 (0.66-1.85)
Only dipyridamol	786	2.27	2.09	41	2,296	0.82 (0.60-1.12)	0.96 (0.70-1.31)	0.95 (0.70-1.31)

Model 1: Based on DAG: Adjusted for age, comorbidity, post-diagnostic simvastatin and post-diagnostic aspirin use.

Model 2: Adjusted for all covariables in Table 1

Table 3. Breast cancer recurrence associations according to current, former, never, and perioperative drug exposures.

	No.	No. of recurrences	Total Person-years at risk	Crude Hazard ratio (95% conf. interval)	Adjusted Hazard ratio[1] (95% conf. interval)
Any platelet inhibitor					
Never	32,986	5277	230,415	1	1
Current	1,492	58	3,581	0.74 (0.57-0.96)	0.87 (0.67-1.14)
Former	876	20	1,769	0.58(0.37-0.90)	0.66 (0.42-1.03)
Perioperative exposure	381	29	2,038	0.58 (0.40-0.84)	0.68 (0.47-1.00)
Only clopidogrel					
Never	33,777	5,328	233,044 (7.1)	1	1
Current	555	15	822 (7.7)	0.86 (0.52-1.43)	1.05 (0.63-1.76)
Former	394	13	880 (8)	0.76 (0.44-1.31)	0.90 (0.52-1.57)
Perioperative exposure	98	9	537	0.68 (0.35-1.31)	0.82 (0.43-1.60)
Only dipyridamol					
Never	33,546	5,307	231,716 (7.1)	1	1
Current	786	42	2,321 (7)	0.82 (0.60-1.12)	0.95 (0.70-1.31)
Former	382	7	709 (8.7)	0.51 (0.25-1.08)	0.57 (0.27-1.19)
Perioperative exposure	289	22	1563	0.57 (0.38-0.87)	0.65 (0.42-1.02)
Vitamin K antagonists					
Never	34,092	5,207	227,856	1	1
Current	1,696	92	3,943	1.05 (0.85-1.28)	1.16 (0.94-1.43)
Former	1,409	54	2,873	0.91 (0.69-1.19)	0.96 (0.74-1.27)
Perioperative exposure	496	53	2,530	0.86 (0.66-1.13)	0.97 (0.73-1.27)

1: Based on dag: Adjusted for age, comorbidity, post-diagnostic simvastatin and post-diagnostic aspirin

Table 4. All cause and breast cancer specific mortality of breast cancer patients exposed to platelet inhibitor prescriptions.

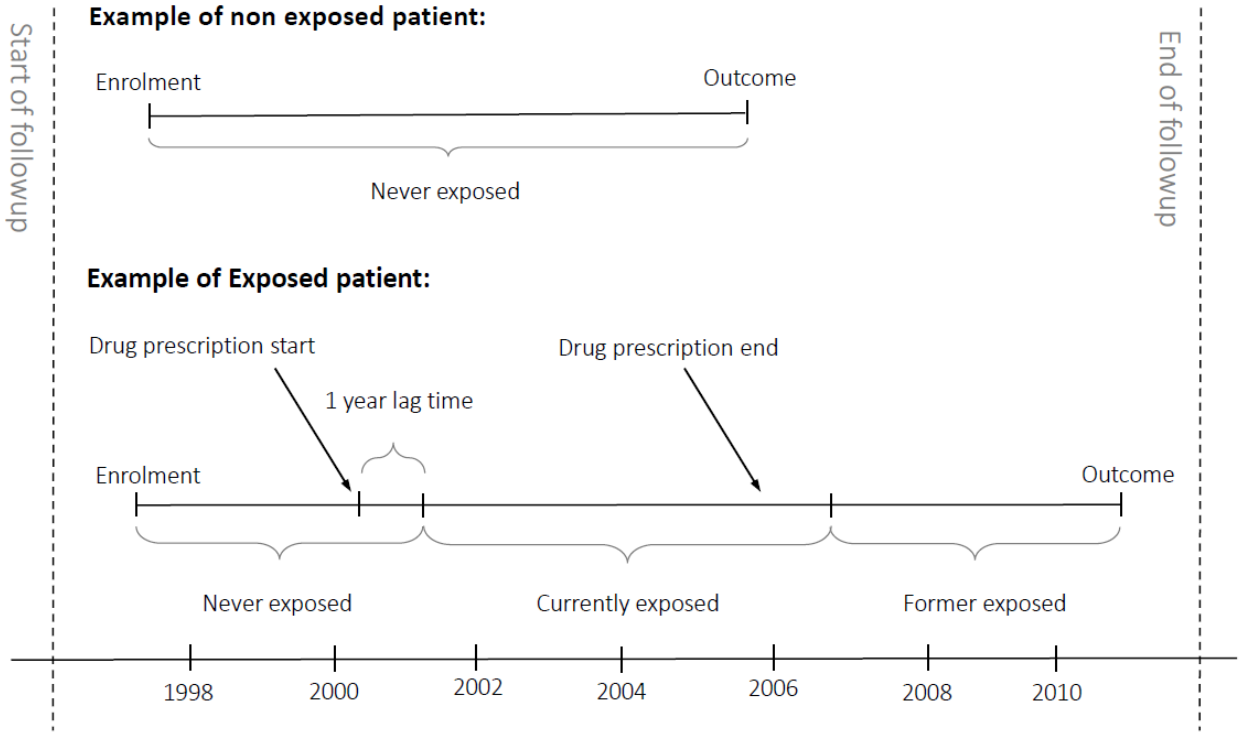
	All cause Mortality	Adjusted[1]	Breast cancer specific mortality[2]	Adjusted[1]
Any platelet inhibitor				
Never	1	1	1	1
Current	1.97 (1.73-2.24)	1.22 (1.07-1.40)	1.04 (0.83-1.30)	1.00 (0.80-1.27)
Former	1.83 (1.52-2.20)	1.20 (0.99-1.45)	1.24 (0.93-1.65)	1.19 (0.89-1.60)
Perioperative exposure	1.89 (1.58-2.25)	0.98 (0.81-1.17)	0.90 (0.65-1.24)	0.78 (0.57-1.10)
Only clopidogrel				
Never	1	1	1	1
Current	1.74 (1.31-2.30)	1.23 (0.93-1.63)	0.51 (0.27-1.00)	0.55 (0.29-1.07)
Former	1.63 (1.23-2.14)	1.13 (0.85-1.48)	1.10 (0.72-1.69)	1.14(0.74-1.76)
Perioperative exposure	1.53 (1.04-2.23)	0.87 (0.60-1.28)	0.55 (0.25-1.23)	0.52 (0.23-1.24)
Only dipyridamol				
Never	1	1	1	1
Current	2.29 (1.95-2.62)	1.37 (1.18-1.60)	1.38 (1.08-1.76)	1.30 (1.01-1.70)
Former	2.11 (1.61-2.76)	1.36 (1.04-1.79)	1.47 (0.96-2.23)	1.33 (0.87-2.03)
Perioperative exposure	1.98 (1.63-2.42)	1.00 (0.81-1.21)	1.00 (0.70-1.42)	0.85 (0.60-1.23)
Vitamin k Antagonists				
Never	1	1	1	1
Current	2.39 (2.14-2.67)	1.59 (1.42-1.78)	1.60 (1.35-1.90)	1.45 (1.22-1.73)
Former	2.54 (2.24-2.89)	1.86 (1.63-2.10)	2.14 (1.80-2.56)	1.97 (1.66-2.35)
Perioperative exposure	2.63 (2.30-3.01)	1.60 (1.39-1.84)	1.41 (1.12-1.78)	1.23 (0.97-1.55)

1: Based on dag: Adjusted for age, comorbidity, post-diagnostic simvastatin and post-diagnostic aspirin

2: Using primary cause of death

Figures

Figure 1: Illustration of different followup groups



Appendix

ATC codes for drugs

We retrieved prescription information on full Anatomical Therapeutic Chemical (ATC) cores, and the date and quantity dispensed for relevant drugs.

Exposure drugs:

Category	**ATC Code**	**Number of prescriptions**	**Drug**
Vitamin K antagonists	B01AA03	44.052	Warfarin
	B01AA04	3.142	Phenprocoumon
Platelet inhibitors	B01AC06	192.731	Aspirin
	B01AC07	35.032	Dipyridamol
	B01AC04	13.848	Clopidogrel
	B01AC30	10.011	Dipyridamol + Aspirin
	B01AC24	244	Ticagrelor
	B01AC22	93	Prasugrel

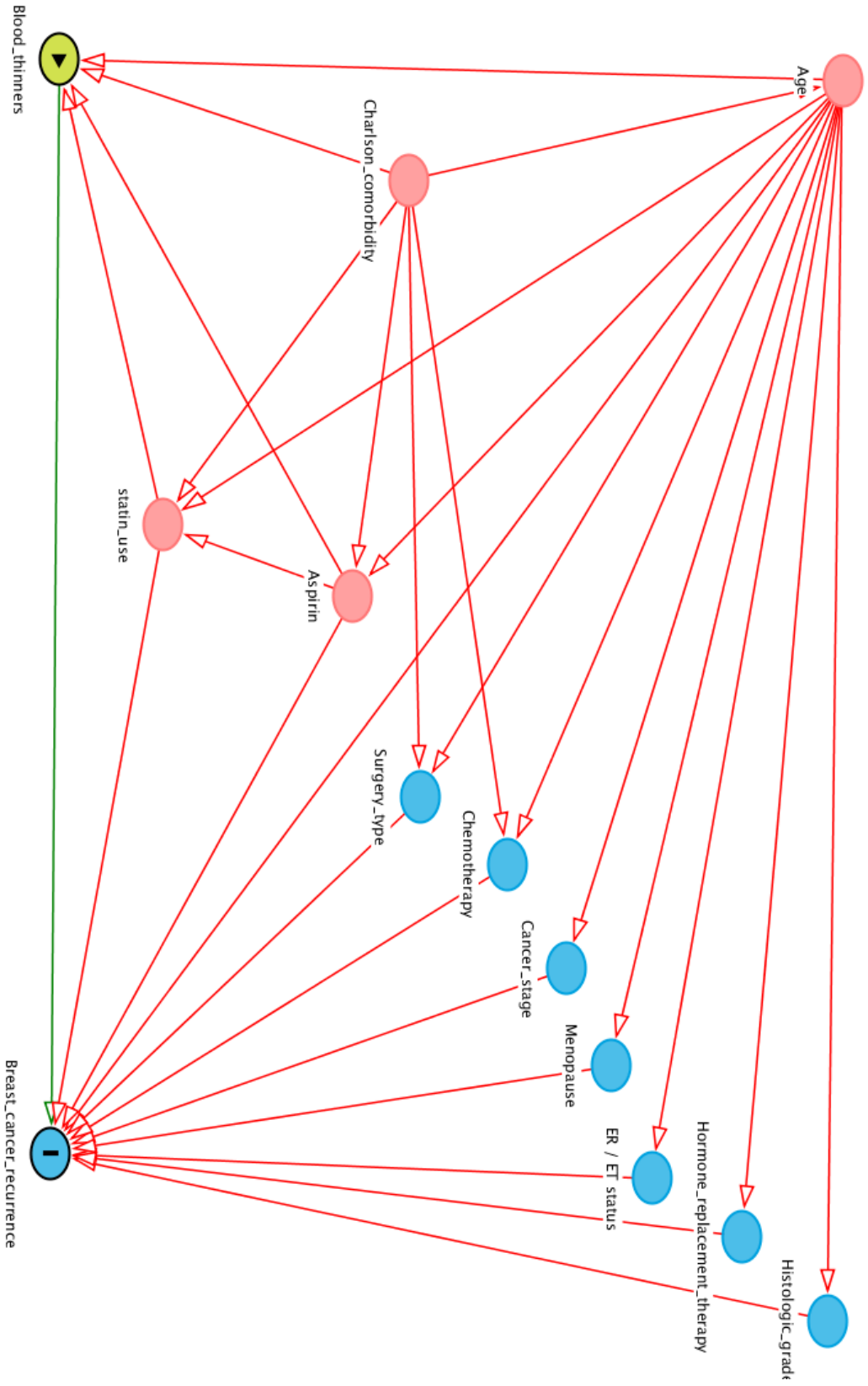
Potential confounder drugs:

Drug	ATC codes
Simvastatin	C10AA01
Hormone replacement therapy	G03C; L02AA; G03F; G03H; G03D

Coding of prescriptions

We modelled the prescriptions as time-varying exposures. Each prescription was recoded to a time interval based on quantity of pills, strength of pills, redemption day, and defined daily dose[69]. The time intervals were then aggregated to single exposure intervals, allowing up to a 30-day gap between two prescriptions in a continuous interval. If the gap between two prescriptions exceeded 30 days, or if the patient stopped redeeming prescriptions, their status was changed to the unexposed group. The patients could later re-enter the exposed group if prescriptions resumed. All time intervals were lagged by one year to allow a reasonable etiologic window for an effect of the drug exposure on the outcome in question.

Directed acyclic graph



Charlson Comorbidity index

Charlson comorbidity category	ICD8	ICD10	score	Comorbidity groups
Myocardial infarction	310	121;122;123	1	Myocardial infarction
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	150; Il 1.0; 113.0; 113.2	1	Congestive heart failure
Peripheral vascular disease	440; 441; 442; 443; 444; 445	170; 171; 172; 173; 174; 177	1	Vascular disease
Cerebrovascular disease	430-438	160-169; G45; G46	1	Cerebrovascular disease
Dementia	290.19; 293.09	F00-F03; F05.1; G30	1	-
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1	Chronic pulmonary disease
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1	-
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1	-
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1	Liver disease
Diabetes type 1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1	Diabetes types 1 & II
Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; El 1.1; E11.9	1	
Hemiplegia	344	G81; G82	2	-
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	112; 113; N00-N05; N07; N11; N14; N17-N19; Q61	2	-
Diabetes with end organ damage typel	249.01-249.05; 249.08	E10.2-E 10.8	2	Diabetes w/organ damage
type2	250.01-250.05; 250.08	E11.2-E11.8	2	
Any tumor	140-194	C00-C75	2	Any other cancer
Leukemia	204-207	C91-C95	2	Any other cancer
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2	Any other cancer
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B 15.0; B 16.0; B 16.2; B 19.0; K70.4; K72; K76.6; 185	3	Liver disease
Metastatic solid tumor	195-198; 199	C76-C80	6	Any other cancer
AIDS	079.83	B21-B24	6	-